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Lung-heart clinical crosstalk in the course of COPD exacerbation

Interakcja kliniczna układu oddechowego i układu krążenia u pacjentów leczonych z powodu zaostrzenia POChP

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Abstract

Introduction: COPD exacerbation is a life-threatening condition with acute dyspnoea caused by respiratory or circulatory distress. The significance and co-presence of lung hyperinflation, bronchial obstruction, and changes in haemodynamics in the course of COPD exacerbation treatment have not been well described yet in course of a single study.

Our aim was to evaluate the influence of COPD exacerbation treatment on bronchial obstruction, pulmonary hyperinflation, and possible changes of right and left ventricle haemodynamics in relation to the patient's clinical status.

Material and methods: A total of 40 patients (90% males), 67 ± 8 years old, with COPD were assessed pre- and post-exacerbation treatment by the following: respiratory function tests, transthoracic echocardiography, 6MWT, endothelin-1 (ET-1) and NT-proBNP serum concentrations, and MRC scale.

Results: A significant decrease in RV%TLC (%) and mean pulmonary artery pressure (PAPmean) [mm Hg] was observed: pre -RV%TLC: 64.3 ± 9.0; post-RV%TLC 60.6 ± 11.1; $p = 0.03$; pre-PAPmean: 41.2 ± 11.2; post-PAPmean: 39.1 ± 12.1; $p = 0.029$, coupled with a significant increase of FEV_1 [L]-preFEV_1: 1.0 ± 0.4, post-FEV_1: 1.2 ± 0.5; $p < 0.001$. A trend for reduced right ventricle systolic pressure (RVSP) [mm Hg]: pre-treatment: 44.5 ± 12.9; post-treatment: 36.3 ± 14.3; $p = 0.068$ and ET-1 [fmol/ml]: pre-treatment: 1.7 ± 2.8; post-treatment: 1.3 ± 1.9; $p = 0.076$, but not for NT-proBNP was noticed. Improvement of both, 6MWT [m]: pre-treatment: 294 ± 132; post-treatment: 415 ± 102; $p < 0.001$ and MRC [pts.]: pre-treatment: 3.3 ± 0.8; post-treatment: 1.8 ± 0.9; $p < 0.001$, were noticed. 6MWT correlated with RV%TLC ($p < 0.05$; $r = –0.46$; $r = –0.53$; respectively) and FEV_1 ($p < 0.05$; $r = 0.55$; $r = 0.60$, respectively) on admission as well as on discharge. There was no such correlation with RVSP or PAP_{mean}.

Conclusions: Pulmonary hyperinflation and bronchial obstruction may be reduced by effective COPD exacerbation treatment and are accompanied by clinical improvement.

The mPAP reduction observed in the course of treatment was not correlated with the results of 6MWT and MRC score.

Key words: COPD exacerbation, dyspnoea, pulmonary hyperinflation, pulmonary hypertension, bronchial obstruction, 6-minute walk test

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Streszczenie

Wstęp: Zaostrzenie POChP jest stanem zagrożenia życia, któremu towarzyszy duszność wtórna do przeciążenia układów oddechowego i/lub krążenia. Jak dotąd w pojedynczym badaniu nie określono istotności klinicznej zmian hiperinflacji, obturacji i wydolności układu krążenia w przebiegu leczenia zaostrzenia POChP.

Celem badania była ocena wpływu leczenia zaostrzenia POChP na nasilenie obturacji oskrzeli, rozdęcia płuc, oraz na zmianę stanu hemodynamicznego chorych leczonych z powodu zaostrzenia POChP.

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Materiał i metody: Do badania włączono 40 pacjentów w wieku 67 ± 8 lat (90% mężczyzn) hospitalizowanych z powodu zaostrzenia POChP. Chorych badano przed i po zakończeniu leczenia z zastosowaniem: badań czynnościowych układu oddechowego, echokardiografii przezklatkowej, sześciominutowego testu marszowego, stężeń Endoteliny-1 i NT-proBNP w surowicy krwi oraz skali mMRC.
Wyniki: W trakcie leczenia zaobserwowano istotne zmniejszenie rozdęcia płuc: przed-RV%TLC: 64,3 ± 9,0; po-RV%TLC 60,6 ± 11,1; p = 0,03;, zmniejszenie obturacji FEV_1[L] przed FEV_1: 1,0 ± 0,4, po-FEV_1: 1,2 ± 0,5; p < 0,001; oraz obniżenie średniego ciśnienia w tętnicy płucnej (PAPmean) [mm Hg]: przed-PAPmean: 41,2 ± 11,2; po-PAPmean: 39,1 ± 12,1; p = 0,029. Zaobserwowano trend do zmniejszenia skurczowego ciśnienia w prawej komorze serca (RVSP) [mm Hg]: przed-RVSP: 44,5 ± 12,9; po-RVSP: 36,3 ± 14,3; p = 0,068 oraz stężenia ET-1 [fmol/ml]: przed- ET-1: 1,7 ± 2,8; po-ET-1: 1,3 ± 1,9; p = 0,076, lecz nie NT-proBNP. Zaobserwowano wydłużenie dystansu 6MWT: przed: 294 ± 132; po-leczeniu: 415 ± 102; p < 0.001; oraz zmniejszenie duszności: przed-MRC: 3,3 ± 0,8; po-MRC: 1,8 ± 0,9; [pkt.] p < 0,001. Dystans 6MWT i wynik testu MRC korelowały z RV%TLC (p < 0,05; odpowiednio r = –0,58; r = 0,51), lecz nie z RVSP czy PAP_{mean}.
Wnioski: W trakcie leczenia zaostrzenia POChP obserwuje się zmniejszenie rozdęcia płuc i obturacji oskrzeli. Koreluje to ze zmniejszeniem duszności i poprawą wydolności wysiłkowej. Zaobserwowane w trakcie leczenia obniżenie mPAP nie koreluje z wydłużeniem dystansu 6MWT czy nasileniem duszności mierzonym za pomocą skali mMRC.

Słowa kluczowe: zaostrzenie POChP, duszność, rozdęcie płuc, nadciśnienie płucne, obturacja oskrzeli, 6 minutowy test marszowy
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Introduction

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of mortality worldwide [1]. In most subjects, symptoms and mortality are respiratory and/or cardiovascular dependent. More over, dynamic hyperinflation in COPD is associated with poor cardiovascular response to exercise [2]. COPD acute exacerbations are determined not only by lung function impairment but also frequently by cardiovascular deterioration [3]. That is why simultaneous analysis of both systems should be performed when assessing patients with COPD exacerbation. Although COPD staging is based on FEV_1 [4], it has been accepted that lung hyperinflation has a greater impact on dyspnoea and exercise intolerance than does decrease of FEV_1 [5]. Static hyperinflation is caused by distal airway collapsing on exhalation and subsequent air trapping. It can result in an increase in the RV%TLC ratio, if total lung capacity (TLC) exceeds normal values. In patients with COPD, during exercise, dynamic hyperinflation not only increases expiratory flow limitation, but also has haemodynamic consequences resulting from more rapid, shallow breathing and progressive reduction in dynamic lung compliance. That explains both exercise intolerance and gas exchange disturbances [6]. Dynamic hyperinflation is not present in all COPD patients [7, 8]. It appears when oxygen demand increases. In most severe COPD stages hyperinflation may develop on mild exercise [9], and this results in inspiratory capacity (IC) decline and dyspnoea.

Pulmonary hypertension (PHT), defined as mean pulmonary artery pressure (PAP_{mean}) ≥ 25 mm Hg, is considered as a frequent and serious COPD complication [10]. Pulmonary artery pressure (PAP) may increase with COPD exacerbation and it has a predictive value for decreased survival [11]. According to the European Respiratory Society/European Society of Cardiology (ERS/ESC guidelines) [10], PHT in COPD patients might not only be secondary to hypoxaemia, but also to left heart disease. Concentration of NT-proBNP is an independent predictor of poor prognosis in patients treated for heart failure [12], but may also have some predictive value in COPD exacerbation [13]. It has been proven that endothelin-1 (ET-1) concentration is increased in COPD patients, but its levels are not PHT-dependent [14]. ET-1 levels also increase in the course of COPD exacerbation, but no correlation with the severity of PHT has been found [15].

The purpose of this study was to examine the relationship between exercise capacity and dyspnoea with respiratory function parameters, echocardiographic indexes of cardiac function, and trends of serum markers related to cardiac decompensation in patients undergoing COPD exacerbation treatment.

Material and methods

The study complied with the principles of the Declaration of Helsinki. The protocol was approved by the Ethics Committee of the Medical University. All patients gave their written informed consent.

Study population

Forty-three patients were screened. Those with COPD exacerbation definition according

to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [4], who met all inclusion criteria and were free of exclusion criteria (40 patients 67 ± 8 years, 90% males), took part in the study and were admitted to the Pulmonology Department. Inclusion criteria were as follows: 1) COPD exacerbation with indications for hospitalization (GOLD, Anthonisen- criteria) [4, 16], 2) age > 40 years, and 3) smoking status ≥ 20 pack-years, LVEF within normal values, and no valvular heart diseases.

Exclusion criteria were as follows: 1) chronic/ /acute pulmonary disease other than COPD, 2) PHT other than secondary to COPD, diagnosed with the use of the European Society of Cardiology guidelines for the diagnosis and treatment of pulmonary hypertension [10], 3) hereditary AT-1 deficiency, 4) acute cardio-vascular incident, and 5) pregnancy.

Patients were treated and discharged according to current GOLD guidelines with the use of bronchodilatators, oxygen, systemic steroids, antibiotics, and deep vein thrombosis prophylaxis [4]. Seven (17.5%) of the most severe COPD patients were treated with noninvasive positive pressure ventilation (NIV), and patients with obstructive sleep apnoea (OSA) were treated with CPAP. Coexisting diseases were treated according to previous treatment plans and adequate guidelines. Sixteen patients with the most severe COPD stage were already on and were maintained on home oxygen treatment after hospitalisation.

Study design

The study was designed and performed as a prospective cohort study with no control group. All tests were performed between 7.00 AM and 1.00 PM during the first day and repeated during the last day of hospitalisation. After collecting fasting blood samples, patients took part in respiratory functional tests. Subsequently, 6MWT was performed. Transthoracic echocardiography (TTE) was performed within one day from admission and repeated ± one day from discharge.

Pulmonary function testing

Pulmonary function tests were performed with the use of diagnostic system MasterLab Jeager (Wuerzburg, Germany) including spirometry (to confirm COPD diagnosis and to asses disease severity) [4, 17]), body plethysmography (to measure hyperinflation) indices [18]), and DLCO [19], but thoracic gas volumes obtained at diffusion measurement were not included in the final results because of the high possibility of gas misdistribution in patients with severe COPD exacerbation.

Transthoracic echocardiography

Patients were screened for PHT with the use of TTE, according to current ERS/ESC recommendations [10], by one cardiologist blinded to all other patient data. Results considered indicative for pulmonary hypertension were RVSP > 35 mm Hg [20], and $PAP_{mean} \geq 25$ mm Hg. Standard TTE was performed using Toshiba APILO, (Japan) and transducer PST-30BT with continuous Doppler with frequency of 3 MHz.

Pulmonary artery systolic pressure (PASP) was indirectly calculated according to the equation:

$$PASP = 4v^2 + RAP$$

PASP — systolic pressure in right ventricle (RVSP) in the absence of pulmonary artery stenosis.

v — maximal velocity of tricuspid regurgitation jet

RAP — Right atrial pressure: estimated from the diameter and inspiratory collapse of the inferior vena cava [21].

Additionally, PAPmean was calculated with the use of the Mahama equation because the tricuspid regurgitation jet is often difficult to visualise in COPD patients.

$$PAPmean = 79 — (0.45 \cdot Act)$$

AcT — pulmonary artery valve flow acceleration time

PAPmean — mean pulmonary arterial pressure calculated with a use of the Mahama equation

TAPSE — tricuspid annular plane systolic excursion was assessed by a cardiologist blinded to other treatment results.

Exercise capacity and dyspnoea

Six-minute walk test (6MWT) with continuous oxygen saturation monitoring was performed to assess physical capacity [22]. 6MWT was performed without oxygen supplementation. To assess dyspnoea, the MRC scale was used [23].

Blood tests

Basic blood tests required for in-ward COPD exacerbation treatment were performed in the certified laboratory. Serum samples for ET-1 and NT-proBNP measurement were frozen at –78°C, immediately after being collected and subsequently measured by ELISA kits (*Biomedica Gmgh*) according to the manufacturer`s protocol in all patients.

Statistical analysis

Statistical evaluation was performed using software package Statistica 6.0 (StatSoft Inc,

Table 1. Characteristics of the included patients

	Value	Unit
Number of participants included	40	[n]
GOLD I*	1; 2.5	[n]; (%)
GOLD II*	12; 30	[n]; (%)
GOLD III*	11; 27.5	[n]; (%)
GOLD IV*	16; 40	[n]; (%)
Presence of hyperinflation**	24; 60	[n]; (%)
Age	67 ± 8; (45–80)	[years]
Sex (M/F)	4/36; 10/90	[n]; (%)
Smoking history***	43; (20–100)	[pack-years]
Hospitalization time***	13; (4–40)	[days]
BMI	27.8 ± 5.7; (17.3–39.8)	[kg/m^2]

*GOLD guidelines — at discharge
**Static hyperinflation on admission: ITGV > 140%N, and RV%TLC > 140%N
***Medians and ranges

Table 2. Spirometry results

Parameter	n	Mean	Median	Minimum	Maximum	Standard deviation	p
Pre-IC [L]	39	1.7	1.6	0.8	2.8	0.5	p = 0.4
Post-IC [L]		1.8	1.8	0.4	3.6	0.7	
Pre-VC IN [L]	40	2.3	2.2	1.1	3.5	0.6	p = 0.002
Post-VC IN[L]		2.6	2.5	1.0	4.6	0.7	
Pre-FEV_1 [L]	40	1.0	1.1	0.5	2.0	0.4	p < 0.001
Post-FEV_1 [L]		1.2	1.1	0.2	3.1	0.5	
Pre-FVC [L]	40	2.1	2.0	0.7	3.2	0.6	p = 0.001
Post-FVC [L]		2.4	2.4	0.6	4.8	0.7	
Pre-FEV_1%FVC (%)	40	50.3	49.4	26.9	75.8	11.3	p = 0.3
Post-FEV_1%FVC (%)		51.2	50.3	31.8	95.1	12.4	

Statistically significant differences ($p < 0.05$) and ↓ or ↑ points direction of changes

Tulsa, Oklahoma). Kolmogorov-Smirnov test was used to test variables for normal distribution. Student's t-test and Wilcoxon test were used to determine pre-post differences. Spearman rank correlation test was used to evaluate correlations between variables. $P < 0.05$ was accepted as statistically significant.

Results

Forty patients with a mean age of 67 ± 8 years represented by 90% males with COPD exacerbation were studied. Hyperinflation [intra thoracic gas volume (ITGV) > 140%N and residual volume percentage total lung capacity (RV%TLC) > 140%N] was present in 60% of the 40 subjects included in the study. Most of the patients were GOLD stage III and IV [4]. Patient's characteristics are summarised in Table 1.

Pulmonary function tests

The results of spirometry and plethysmography are presented in detail in Tables 2 and 3. Effective exacerbation treatment resulted in airway patency improvement (FEV_1-improvement) (Table 2). Significant changes were noticed in most spirometric variables studied but not in IC. A significant reduction of post-treatment RV%TLC value was noticed (Table 3). A significant increase in diffusion capacity calculated for alveolar volume (DLCO/VA) [mmol/min/kPa/l] was noticed in the subgroup of primarily

Table 3. Body plethysmography and DLCO results

Parameter	n	Mean	Median	Minimum	Maximum	Standard deviation	p
Pre-Rtot[kPa × s/l]	38	0.8	0.7	0.3	2.2	0.4	p = 0.5
Post-Rtot[kPa × s/l]		0.8	0.6	0.2	3.9	0.6	
Pre-ITGV [L]	38	5.3	5.2	2.6	11.0	1.4	p = 0.5
Post-ITGV [L]		5.2	5.1	2.4	7.8	1.3	
Pre-RV%TLC (%)	38	64.3	63.4	44.5	81.9	9.0	p = 0.03
Post-RV%TLC(%)		60.6	64.0	27.8	81.5	11.1	
Pre-TLC [L]	38	6.9	6.9	4.6	11.9	1.4	p = 0.66
Post- TLC [L]		7.0	7.0	2.9	10.0	1.5	
Pre-RV [L]	38	4.5	4.5	2.4	9.8	1.3	p = 0.37
Post- RV [L]		4.3	4.4	1.1	7.2	1.4	
Pre-DLCO/VA [mmol/min/kPa/L]	38	1.1	1.1	0.4	2.4	0.5	p = 0.24
Post-DLCO/VA [mmol/min/kPa/L]		1.2	1.2	0.5	2.4	0.5	

Statistically significant differences ($p < 0.05$) and ↓ or ↑ points direction of changes

Table 4. Transthoracic echocardiography results

Parameter	n	Mean	Median	Minimum	Maximum	Standard deviation	p
Pre-Right ventricle [mm]	8	28.6	28.0	21.0	38.0	5.0	p = 0.03
Post-Right ventricle [mm]		26.9	25.1	21.0	37.0	4.0	
Pre-RV FAC% (%)	11	55.3	57.0	27.0	72.0	13.3	p = 0.06
Post-RV FAC% (%)		56.2	55.0	41.0	79.0	10.5	
Pre-RV/LV ratio in 4C	11	0.8	0.7	0.5	1.3	0.3	p = 0.3
Post-RV/LV ratio in 4C		0.8	0.7	0.6	1.1	0.1	
Pre-TAPSE [mm]	6	15.2	17.0	8.0	21.8	4.6	p = 0.07
Post-TAPSE [mm]		17.5	17.8	10.4	24.6	3.7	
Pre-RVSP [mm Hg]	4	44.5	46.0	26.0	63.5	12.9	p = 0.07
Post-RVSP [mm Hg]		36.3	39.0	9.8	58.5	14.3	
Pre-VCI diameter [mm]	10	20.7	19.9	14.8	28.0	3.9	p = 0.08
Post-VCI diameter [mm]		20.0	21.1	11.0	26.6	4.7	
Pre-PAP mean (Mahama) [mm Hg]	11	41.2	40.1	22.0	61.0	11.2	p = 0.03
Post-PAP mean (Mahama) [mm Hg]		40.1	43.0	16.0	61.0	13.0	
Pre-LVEF% (%)	10	53.2	55.0	29.0	63.0	9.9	p = 0.7
Post-LVEF% (%)		54.9	58.0	27.0	66.0	10.2	

Statistically significant differences ($p < 0.05$) and ↓ or ↑ points direction of changes

hyperinflated COPD subjects only: (pre-treatment: 0.95 ± 0.35; post-treatment: 1.02 ± 0.36; p = 0.014), but not in the entire group (pre-treatment: 1.13 ± 0.47; post-treatment: 1.18 ± 0.46; p = 0.2).

Transthoracic echocardiography

We aimed to perform TTE in all patients, but reliable results as predicted [24] could have been obtained pre and post treatment only in about 25% of cases, depending largely on the patient's clinical condition and decreased echocardiographic window caused by emphysema. The results of TTE are presented in Table 4. Successful treatment was associated with a significant decrease of PAPmean. The trend of decreased RVSP and increased tricuspid annular plane sys-

Table 5. Exercise capacity and dyspnoea indices

Parameter	n	Mane	Median	Minimum	Maximum	Standard deviation	p
Pre-6MWT [m]	39	294	310	10	550	132.1	$p < 0.001$
Post-6MWT [m]		415	440	120	610	102.1	
Pre-treatment-SaO_2min-6MWT (%)	38	83	86	48	96	10.8	$p = 0.001$
Post-treatment-SaO_2min-6MWT (%)		87	89	67	96	7.5	
Pre-MRC [points]	40	3.3	3.5	2.0	4.0	0.8	$p < 0.001$
Post-MRC [points]		1.8	2.0	0.0	4.0	0.9	

Statistically significant differences ($p < 0.05$) and ↓ or ↑ points direction of changes

tolic excursion (TAPSE) was noticed (Table 4), but post-treatment values of both indices were still outside the normal range (Table 4). No changes in left ventricle ejection fraction were observed. Post -treatment RVSP values were higher ($p < 0.05$) in the subgroup of COPD patients with concomitant obstructive sleep apnoea syndrome.

Exercise capacity and breathlessness

The results of 6MWT and dyspnoea scales are presented in Table 5. Significant improvement of exercise capacity (6MWT) and clinical symptoms (MRC scale) were noticed post-treatment. Not only distance, but also minimal saturation during 6MWT was significantly higher after treatment, compared with baseline (Table 5).

Blood tests

There was a trend for reduction of ET-1 concentrations [fmol/ml] in the course of treatment: (pre-treatment: 1.7 ± 2.8; post-treatment: 1.3 ± 1.9; $p = 0.076$; $n = 38$), but no changes in NT-proBNP levels [fmol/ml] were noticed: (pre-treatment: 17.5 ± 38.9; post-treatment: 12.8 ± 18.6; $p = 0.3$; $n = 38$). Mean NT-proBNP concentration was in the lower range of normal values (normal value = 0-640 fmol/mL). There were no differences in resting oxygenation based on arterialised capillary blood gases SaO_2 (%): pre-SaO_2: 88.7 ± 8.5, post-SaO_2: 91 ± 5.4; $p = 0.1$, PO_2 [mm Hg]: pre-PO_2: 58.5 ± 13.5; post-PO_2: 62 ± 11; $p = 0.2$. Except for a significant reduction in CRP concentrations [mg/L]: (pre-treatment: 29.6 ± 38.1; post-treatment: 9.0 ± 12.9; $p = 0.004$), no significant changes in other routinely assessed blood parameters were noticed.

Correlations

Significant correlations between spirometric (IC) and plethysmographic (RV%TLC) markers of hyperinflation, and both, dyspnoea and exercise capacity were observed. 6MWT and MRC scales correlated with IC on admission ($p < 0.05$; $r = 0.51$; $r = –0.53$, respectively) as well as on discharge ($p < 0.05$; $r = 0.55$; $r = –0.57$, respectively). Also 6MWT and MRC scales correlated with RV%TLC both, on admission: ($p < 0.05$; $r = –0.46$; $r = 0.41$, respectively) and on discharge: ($p < 0.05$; $r = –0.53$; $r = 0.51$, respectively).

IC correlated with FEV_1 both, on admission, and on discharge ($p < 0.05$; $r = 0.6$; $r = 0.72$, respectively). Also RV%TLC correlated with FEV_1 on admission and on discharge ($p < 0.05$; $r = –0.74$; $r = –0.69$, respectively). FEV_1 correlated with 6MWT on admission and discharge ($p < 0.05$; $r = 0.55$; $r = 0.60$, respectively).

No correlations between PHT indices (RVSP, PAP-mean, ET-1, NT-proBNP) and 6MWT distance or MRC scale were noticed.

Discussion

According to the authors' best knowledge, this is the second study, after the report of Blankenburg et al. [25], in which changes of exercise capacity (6MWT) were assessed at the beginning and at the resolution of severe COPD exacerbation. However, only in our study were these parameters additionally referred to hyperinflation and PAP. 6MWT turned out to be a safe tool in evaluating the severity of COPD exacerbation, often more informative and easier to perform than pulmonary functional tests [17–19] or TTE [24]. The above-presented increase of post-treatment exercise capacity and simultaneous decrease of dyspnoea may both be explained by the reduced dynamic and static lung hyperinflation, as well as reduced bronchial obstruction. Although, according to GOLD guidelines, there is no need to perform lung function tests on discharge [4], the authors found it clinically useful to perform at least spirometry. This is supported by observed

major FEV_1 increase and its positive correlation with 6MWT distance and negative correlation with MRC score. The findings are in agreement with Stevenson et al. [26], indicating that the resolution of COPD exacerbation is related to increased values of operating lung volumes (FEV_1, IC). Moreover, in our study we found that a relatively small, but significant improvement in RV%TLC (–4%) and FEV_1 (+200 mL) may be accompanied by major (+121 m) improvement in 6MWT result, which is much higher than generally accepted as clinically significant [27, 28]. Another possible explanation for positive correlation of FEV_1 and exercise is the fact that significant improvement of FEV_1 is usually not observed in stable COPD. The minimal oxygen saturation during 6MWT in our study was significantly higher after treatment, when compared with baseline values. These data are of importance as they indicate that increased exercise tolerance was due to respiratory improvement and not due to the doctor forcing the patient to march faster or due to the patient's learning potential [28]. As expected, IC has not revealed the degree of hyperinflation, whereas RV%TLC, as one of the most accurate methods of measuring hyperinflation, could reflect static hyperinflation changes [27, 29]. That is why, in contrast to what was previously established [30], in the authors' opinion, COPD exacerbation itself is not enough to induce dynamic lung hyperinflation. The results of the study suggest that during the first phase of COPD exacerbation (hospital treatment) the reduction of dyspnoea at rest is probably caused by a decrease in lung volume (RV% TLC) and increase in bronchial patency (FEV_1). The results obtained in our study indirectly suggest that small changes in static hyperinflation (RV%TLC) are probably followed by much more significant changes in lung volumes that accompany physical exertion and are responsible for better post-treatment exercise tolerance.

In our study we decided not to conduct pulmonary function tests directly after 6MWT because most of the patients had severe post-exercise dyspnoea. We therefore assumed that obtaining reliable pulmonary post-exercise function test results in those patients would be impossible [17–19].

Data on pulmonary haemodynamics in the course of COPD exacerbation are sparse. Although we lack direct proof, on the basis of our results we can speculate that effective COPD exacerbation treatment and symptom relieve is associated with reduced risk of developing dynamic hyperinflation on exercise and, in turn, less pronounced compression of pulmonary capillaries by hyperinflated lungs [31]. According to our best knowledge, this is the first study that shows that standard COPD exacerbation treatment [4] decreases mPAP. There were no differences in resting oxygenation based on arterialised capillary blood gases. The observed post-treatment PAPmean and RVSP reduction were independent of dyspnoea, exercise capacity, and blood gasses, which might be the result of oxygen supplementation [32]. In the study by Weitzenblum et al. [33] changes of right heart haemodynamics were observed during an episode of peripheral oedema. However, an episode like this could also have been related to right ventricle decompensation, independent of COPD exacerbation. According to the authors' best knowledge, this is also the first study in which 6MWT and pulmonary hyperinflation were analysed in relation to TTE and laboratory biomarkers of right and left heart function in the course of COPD exacerbation treatment. The analysis of correlations between cardiac and pulmonary parameters was conducted because of high coincidence of COPD and cardio-vascular diseases [3, 4, 34]. As expected, the number of patients reliably examined by TTE was much smaller than those who were able to perform pulmonary function tests (Tables 2–4) [24]. This might partially explain why the significant reduction of PAPmean was accompanied only by a trend for reduced RVSP. According to pulmonary hypertension guidelines [10] and as suspected, moderately increased PAP on admission was found and then was partially reduced by the exacerbation treatment [4] (Table 4). Similarly to Hanaoka et al. [33], but engaging a larger number of patients, we showed that PAP increases during COPD exacerbation. The results of both studies raise the unresolved question of whether there is a need for a larger study with pulmonary artery pressure PAP assessed by right heart catheterisation (RHC). On the basis of our study, it is impossible to determine the exact role of different mechanisms causing PHT in the course of COPD exacerbation. Similarly to Bacakoğlu et al. [14], the authors have observed that ET-1 concentration decreases in the course of COPD exacerbation treatment, but no correlation between its levels and PHT values were found. This might be explained by ET-1 probably being secreted and metabolised mainly in the pulmonary vascular bed wall [35]. Left heart insufficiency, one of the major causes of secondary PHT [10], was not a reason for PHT in our study (Table 4) as the LVEF was within normal range in most patients in the studied group [12]. The results

are not in agreement with Stolz et al. [36], who revealed that BNP levels are elevated during COPD exacerbation. This discrepancy might be explained by the fact that in the study by Stolz et al. [37] blood was collected directly on admission and again at follow-up after hospitalisation. Also, in the study by Stolz et al. [37] most patients were not assessed with TTE on admission, which makes the coincidence of right and/or left heart decompensation on BNP levels quite possible.

The main limitation of the study is the relatively small number of patients with TTE assessment, which results from a weak acoustic window typical for patients with COPD. The authors are fully aware that TTE assessment of PAP is only a screening tool. However, it was more ethical to perform TTE than RHC, especially when taking into account that there are no recommendations for PHT-specific treatment in patients with COPD exacerbation [10].

Conclusions

The results of our study suggest that COPD exacerbation induces static lung hyperinflation in about two-thirds of patients. Pulmonary hyperinflation and bronchial obstruction may be reduced by standard GOLD-COPD exacerbation treatment and are associated with improvement of exercise tolerance and dyspnoea reduction.

COPD exacerbation and its treatment change right, but not left, ventricle haemodynamics. Pulmonary artery pressure reduction is probably independent of clinical improvement. 6MWT may be a useful test in the assessment of patients treated for COPD exacerbation.

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