



Dynamic hyperinflation during exercise in patients with precapillary pulmonary hypertension

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Received 30 July 2011; accepted 31 October 2011

Available online 18 November 2011

KEYWORDS

Pulmonary hypertension;
Exercise;
Dynamic hyperinflation

Summary

Background: Patients with pulmonary arterial hypertension often present with a mild obstructive lung pattern, however, the functional consequences are not known.

Methods: We analysed flow volume loops during exercise in 61 patients with precapillary pulmonary hypertension (PH) (age 55 ± 14 years) in comparison with 21 patients with COPD (60 ± 12 years), 39 patients with pulmonary fibrosis (58 ± 11 years) and 38 healthy controls (HC) (39 ± 15 years). Inspiratory capacity (IC) was measured at rest, and during maximum exercise (max).

Results: HC exhibited a stable IC of 3.0 ± 0.9 l at rest, and at max. A reduction in IC of 2.6 ± 0.8 l at rest to 2.0 ± 0.7 l at max was observed in patients with COPD. Patients with PH exhibited a significant reduction in IC from 2.3 ± 0.6 l at rest to 2.1 ± 0.6 l at max, while patients with pulmonary fibrosis exhibited a stable IC of 1.8 ± 0.6 at rest and 1.7 ± 0.6 l at max. In patients with PH, a weak negative correlation was drawn between the change in IC (%) and peak $\dot{V}O_2$ ($r = -0.29$, $p = 0.01$), as well as with PVR ($r = -0.27$, $p = 0.02$).

Conclusion: Patients with PH demonstrate a characteristic change in IC during exercise, which might contribute to impaired exercise tolerance.

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Introduction

Precapillary pulmonary hypertension (PH) is a disease characterised by progressive pulmonary vascular and right

ventricular dysfunction, leading to impaired exercise tolerance.¹ Additionally, patients with PH without preexisting obstructive or interstitial lung disease exhibit a change in airway function and breathing mechanics. A mild obstructive

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pattern in pulmonary function tests has been described in patients with pulmonary arterial hypertension (PAH), as well as chronic thromboembolic pulmonary hypertension (CTEPH).^{2–4} Although the expiratory airflow limitation might be minor at rest, it could lead to more pronounced changes during exercise with limiting exercise tolerance.

The causes of impaired airway function in PH are not known. Possible explanations include the mechanical impairment of peripheral airway function by the dilated precapillary pulmonary artery vessels or an effect of pulmonary vascular remodelling involving the adventitia with subsequent impairment of the adjacent airways.^{2,5}

The consequences of airway obstruction on exercise capacity are best described in patients with chronic obstructive pulmonary disease (COPD) with a characteristic shift of lung volumes during exercise due to air trapping and subsequent impaired expansion of tidal volume. The decrease in inspiratory capacity (IC) accompanied by an increase in end-expiratory lung volume (EELV) during exercise is the typical finding of dynamic hyperinflation (DH).⁶ A change in the IC during exercise has also been described in pulmonary fibrosis and in congestive heart failure.^{7,8} If a change of IC during exercise occurs also in PH is not known.

Measurement of IC can be reliably performed by recording flow–volume–loops at rest and maximum exercise during routine cardiopulmonary exercise test (CPET).⁹ The ratio of tidal volume (VT)/IC and IC/total lung capacity TLC, respectively, is regarded as a sensitive measure of utilisation of ventilatory reserves during exercise.⁵

In the present study, we analyse whether patient with PH exhibit a characteristic pattern of IC during exercise in comparison to patients with COPD and pulmonary fibrosis, as well as healthy controls (HC).

Methods

In this single-centre study at the University of Giessen Lung Center, we included patients with established COPD, pulmonary fibrosis, and pulmonary hypertension (either PAH or CTEPH). Patients were referred for further assessment of disease severity and underwent routine CPET when clinically stable. Furthermore, we included healthy individuals who underwent CPET to assess their individual exercise capacity (HC). The study was performed between March 2007 and March 2008.

After taking the patient's history and performing a physical examination, all patients underwent a pulmonary function test including Diffusion capacity for Carbon monoxide (DLCO), blood gas analysis from an arterialised earlobe sample, and a 12-lead electrocardiogram (ECG) at rest. Patients underwent cardiopulmonary exercise test (Vmax 229 SensorMedics, Care Fusion, Yorba Linda, CA, USA). Patients were asked to exercise up to their individual limit on an exercise bicycle in a semi-supine position. The exercise protocol included an increase in exercise load of 30 W every 2 min. The heart rate, ECG and oxygen saturation were recorded continuously, and blood pressure was measured every 2 min. Blood gas analyses from arterialised earlobe samples were retrieved at rest and at maximum exercise to calculate alveolar–arterial oxygen difference (AaDO₂). In patients with PH, right to left shunting had been

excluded prior by standardized contrast enhanced transcranial Doppler sonography.¹⁰

The DH was evaluated by measuring IC at the end of a normal expiration at the level of the end-expiratory lung volume at rest, and during maximum exercise (max).^{9,11} A breathing manoeuvre was started after registration of three regular and uniform breathing cycles. At the end of expiration patients were instructed to take a deep and maximum inspiration followed by a deep expiration. This instruction was repeated prior to and during every IC measurement. The IC was calculated using the recorded flow volume loop. Measurement of IC at rest was performed twice with a maximum variability of 10%. The mean value of both measurements was used in the study. The CPET and measurement of IC was performed 1–2 days before any invasive procedure. In patients with PH, a further workup – according to current guidelines – including right heart catheter, measurement of brain natriuretic peptide (BNP) and 6 min walking distance (6MWD) was performed. Diagnosis of precapillary PH was confirmed by right heart catheter investigation, defined by a mean pulmonary artery pressure (mPAP) > 25 mmHg, a pulmonary arterial occlusion pressure (PAOP) < 15 mm Hg and a normal or reduced cardiac index (CI). Furthermore, patients with manifest PH underwent radiological investigations, including thoracic computed tomography (CT), a CT pulmonary angiogram, and a perfusion scintigraphy scan to detect chronic thromboembolism as an underlying cause of PH.¹

Patients with COPD were diagnosed according to history, symptoms and lung function test in concordance with current guidelines.¹² Patients with interstitial lung disease were diagnosed according to history, pulmonary function tests, high resolution CT scan, and bronchoscopy, if indicated. The final diagnosis was made in a multidisciplinary pathological–radiological–clinical panel.¹³ Patients with COPD and pulmonary fibrosis did not exhibit signs of pulmonary hypertension on transthoracic echocardiography, ECG or imaging studies. HC presented with an uneventful medical history and physical examination and a normal lung function test at rest.

Statistical analysis: All data were tested for normal distribution by means of Kolmogorov–Smirnov testing. Parameters with normal distributions were displayed as mean ± SD. To test for significant differences between groups, the two-tailed Student's *t*-test was used. Statistical significant changes of IC from rest to exercise have been tested with a paired *t*-test. In cases of multiple testing, correction according to Bonferroni was applied to avoid a type I error. Correlations between two variables were analysed using the Pearson correlation coefficient. A *p*-value < 0.05 was considered as statistically significant.¹⁴

Patients gave written informed consent for entering the study. The study has been approved by the Ethics Committee of the Medical Division of the Justus Liebig University of Giessen (approval number 112/11).

Results

We included 121 patients and 38 healthy controls, among them 75 women with a mean age of 53¹⁵ years. There were 21 patients with COPD, in GOLD stage I (*n* = 3), stage II

($n = 12$), stage III ($n = 5$) and stage IV ($n = 1$). In the fibrosis group, there were 39 patients with a restrictive lung function pattern due to idiopathic pulmonary fibrosis ($n = 30$), cryptogenic organising pneumonia ($n = 2$), chronic hypersensitivity pneumonitis ($n = 6$) and respiratory bronchiolitis- interstitial lung disease ($n = 1$).

Among the 61 patients with PH there were 31 patients with idiopathic PAH ($n = 22$), PAH associated with collagen vascular disease without interstitial lung disease ($n = 5$), PAH due to corrected congenital heart disease ($n = 3$), PAH associated with liver disorder ($n = 1$), and 30 patients with inoperable CTEPH. Patients were in WHO functional class I ($n = 6$), class II ($n = 25$), class III ($n = 30$). None of the PH patients were current smokers, 19 PH patients had stopped smoking >20 years ago with a load less than 10 pack years. Haemodynamic assessment confirmed manifest pulmonary hypertension with a mean pulmonary artery pressure (mPAP) of 47 ± 15 mmHg, cardiac index of 2.5 ± 0.6 l/min/qm, pulmonary capillary occlusion pressure (PAOP) of 8 ± 3 mm Hg, and pulmonary vascular resistance (PVR) of 734 ± 388 dyn*s*cm⁻⁵. The 6MWD was 451 ± 120 m. The serum concentration of BNP was 119 ± 128 pg/ml. Patients received targeted treatment for pulmonary hypertension with endothelin receptor blocker ($n = 14$), inhaled prostanooids ($n = 2$), phosphodiesterase V inhibitors ($n = 40$), and calcium channel blockers ($n = 5$). In the HC group we included 38 healthy volunteers. Anthropometric and lung function data are presented in Table 1.

Peak oxygen uptake (VO₂ peak) was significantly reduced in patient groups compared to HC. Furthermore, there were altered breathing parameters during maximum exercise with a reduced ventilation (VE max) and tidal volume (VT max) in the patient groups compared to HC, according to the underlying respiratory disease, as illustrated in Table 2.

Patients stopped exercise due to dyspnoea (54%), peripheral leg fatigue (34%), or other reasons, e.g.

problems with the mouthpiece (12%), whereas HC stopped exercise due to dyspnoea (18%), peripheral leg fatigue (66%), or other reasons (16%).

In the HC group, no change in IC at rest and during exercise was observed. Patients with COPD exhibited a significant decrease in IC at maximum exercise, while IC at rest was comparable to that of the HC group. In patients with pulmonary fibrosis, the IC at rest was significantly reduced compared to the HC group, but did not change during maximum exercise. In patients with PH, the IC at rest was significantly reduced compared to the HC group. There was a significant reduction in IC during maximum exercise compared to resting IC (Table 2).

The delta IC in the PH group was normally distributed (Kolmogorov Smirnov Z 0,53).

A similar disease characteristic pattern was observed when using the ratio of IC/TLC (Table 2, Fig. 1). The ratio of VT/IC at rest and during exercise was significantly higher in all patients compared to the HC group, but was highest in fibrosis and PH (Table 2).

There was a significant increase in VT and VT/IC ratio in all groups during exercise. In all patient groups, the pCO₂ minimally increased during exercise compared to baseline. The IC and the IC/TLC ratio did significantly decrease in COPD and PH patients during exercise (Table 2).

In the PH patient group, there was a significant increase in VT and VT/IC during exercise in all WHO-classes, whereas IC and IC/TLC slightly decreased from rest to maximum exercise (statistically significant in WHO class II and III). (Table 4).

Because of an unequal gender distribution in the PH-group we separately analysed the IC in male and female patients separately. We found a significant higher IC at rest and maximum exercise in male patients, which confirms previous findings.¹⁵ However the reduction of IC at exercise was similar in both gender groups as displayed by a similar delta IC and IC/TLC ratio at rest and max, respectively. Data are shown in Table 3.

Patients with PH exhibited significant differences in haemodynamic parameters, 6MWD and BNP depending on the WHO functional class. Furthermore VO₂ peak, but also IC at rest and at maximum exercise decreased significantly with respect to clinical classification (Table 4 and Fig. 2). There was a weak negative correlation between the change in IC (%) and peak VO₂ ($r = -0.29$; $p = 0.01$) as well as PVR ($r = -0.27$; $p = 0.02$) but not with maximum Watt. There were no significant changes between patients with PAH or CTEPH in exercise parameters (data not shown).

Table 1 Baseline characteristics and pulmonary function tests values represent mean \pm SD; for abbreviations, see text.

	COPD ($n = 21$)	Fibrosis ($n = 39$)	PH ($n = 61$)	HC ($n = 38$)
Male/female	15/6	22/17	26/35	21/17
Age	60 ± 12^b	58 ± 11^b	55 ± 14^a	39 ± 15
Height (cm)	174 ± 10	171 ± 10	170 ± 10	174 ± 12
Weight (kg)	84 ± 19	79 ± 14	74 ± 15	77 ± 16
FEV1 (l) (% pred)	2.0 ± 0.6	2.1 ± 0.8	2.5 ± 0.8	3.6 ± 1.1
	63 ± 15^b	73 ± 20^b	88 ± 20^a	100 ± 13
VC (l) (% pred)	3.3 ± 0.9	2.6 ± 0.9	3.4 ± 1.1	4.4 ± 1.4
	81 ± 17^b	69 ± 18^b	94 ± 16	97 ± 13
FEV1/VC (%)	61 ± 8	82 ± 5	73 ± 7	83 ± 6
TLC (l) (%pred)	6.8 ± 1.2	4.7 ± 1.3	6.2 ± 1.5	6.9 ± 2.0
	105 ± 18	76 ± 15	106 ± 14	108 ± 15
DLCO (%pred)	61 ± 20^b	49 ± 16^b	64 ± 14^b	88 ± 9

^a $p < 0.01$.

^b $p < 0.001$ versus HC.

Discussion

Patients with respiratory diseases exhibited characteristic changes in breathing mechanics during exercise. In the present study we describe the pattern of IC, the IC related to TLC and VT/IC ratio at rest and during exercise in patients with precapillary PH in direct comparison with obstructive and restrictive respiratory diseases, and healthy controls, respectively.

In PH patients, resting IC was reduced similar to COPD and fibrosis, but significantly lower compared to the HC group. This might be a consequence of impaired respiratory

Table 2 Cardiopulmonary exercise test and inspiratory capacity: comparison between rest and exercise and between patient groups and healthy controls values represent mean \pm SD; for abbreviations, see text.

Parameter	COPD (n = 21)	Fibrosis (n = 39)	PH (n = 61)	HC (n = 38)
Watt (max)	90 \pm 27 ^a	101 \pm 35 ^a	81 \pm 37 ^a	166 \pm 79
Max Heart rate (/min)	120 \pm 16	127 \pm 19	131 \pm 22	149 \pm 23
% Heart Rate Reserve	75 \pm 9	78 \pm 10	80 \pm 11	83 \pm 11
VO ₂ peak (ml/kg/min)	13.4 \pm 4.7 ^a	15.5 \pm 4.6 ^a	13.7 \pm 3.9 ^a	25.3 \pm 10.1
VE max (l/min)	47 \pm 16 ^f	57 \pm 19	54 \pm 18 ^c	66 \pm 29
% breathing reserve	71 \pm 18	83 \pm 29	65 \pm 19	52 \pm 16
VT rest (l)	0.8 \pm 0.2	0.7 \pm 0.1	0.9 \pm 0.3	0.8 \pm 0.3
VT max (l)	1.6 \pm 0.5 ^{b,d}	1.6 \pm 0.5 ^{a,d}	1.8 \pm 0.6 ^{c,d}	2.1 \pm 0.7 ^d
IC rest (l)	2.6 \pm 0.8	1.8 \pm 0.6 ^a	2.3 \pm 0.6 ^b	3.0 \pm 0.9
IC max (l)	2.0 \pm 0.7 ^{a,d}	1.7 \pm 0.6 ^a	2.1 \pm 0.6 ^{a,d}	3.0 \pm 0.9
delta IC (%)	-20 \pm 13 ^a	-2 \pm 12	-7 \pm 13 ^a	1 \pm 8
VT/IC rest (%)	35 \pm 8 ^b	42 \pm 12 ^a	40 \pm 10 ^a	28 \pm 7
VT/IC max (%)	79 \pm 16 ^{c,d}	90 \pm 13 ^{a,d}	84 \pm 17 ^{a,d}	70 \pm 12 ^d
IC rest/TLC (%)	37 \pm 8 ^b	38 \pm 7 ^b	38 \pm 7 ^b	44 \pm 8
IC max/TLC (%)	30 \pm 7 ^{b,d}	37 \pm 7 ^b	35 \pm 7 ^{b,d}	44 \pm 8
pO ₂ rest (mmHg)	70 \pm 7 ^a	73 \pm 8 ^a	69 \pm 12 ^a	83 \pm 7
pO ₂ max (mmHg)	69 \pm 13 ^a	60 \pm 15 ^{a,d}	64 \pm 15 ^{a,e}	88 \pm 11 ^f
pCO ₂ rest (mmHg)	37 \pm 3	38 \pm 3	32 \pm 4 ^a	38 \pm 3
pCO ₂ max (mmHg)	40 \pm 5 ^{a,e}	40 \pm 4 ^d	33 \pm 4 ^{a,f}	38 \pm 4

^a $p < 0.001$.^b $p < 0.01$.^c $p < 0.05$ versus HC.^d $p < 0.001$.^e $p < 0.01$.^f $p < 0.05$ versus rest.

muscle function, a well know feature of COPD and pulmonary fibrosis but also PH.¹⁶

During exercise PH patients showed a significant reduction of IC without maximum utilisation of breathing reserves or overt respiratory muscular fatigue, as displayed by a stable exercise pCO₂. This effect can be related to exercise induced dynamic hyperinflation in PH patients. The degree of IC reduction was associated with the WHO functional classification of PH, and with the functional parameter VO₂ peak, as well as with 6MWD (albeit weakly). However, there was only a weak association with haemodynamic parameters.

We deliberately included patient with distinct respiratory disease and HC in our study for direct comparison of IC at rest and during exercise. So we were able to describe the typical pattern of IC change according to the underlying disorder in an identical clinical setting (Fig. 1). Patients with PH, COPD, or fibrosis showed a similar reduced IC compared to HC. COPD patients with COPD exhibited the characteristic decrease in IC during exercise as a consequence of dynamic hyperinflation.^{6,17,18} In patients with pulmonary fibrosis the IC did not change during exercise due to restrictive lung disease.^{8,11} In PH, there was a significant decrease in IC during exercise but less pronounced compared to COPD, whereas in HC, IC was identical at rest and during exercise.

The VT/IC ratio as a measure of the utilisation of ventilatory reserves was significantly changed in all patient groups compared to the HC group, but did not exhibit a characteristic pattern with regard to the underlying disorder (Table 2).

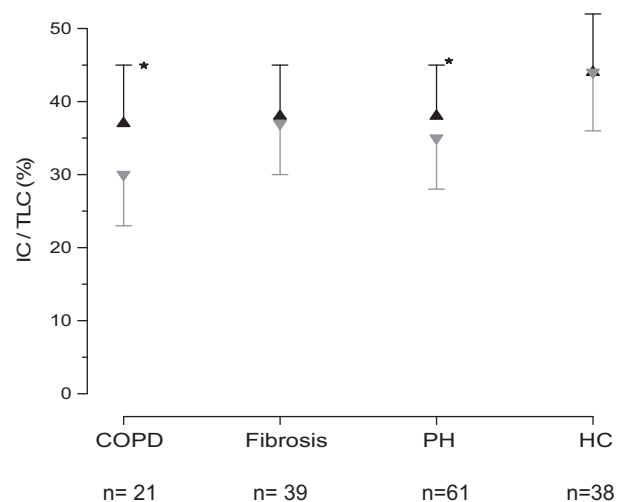
▲ - mean IC/TLC % \pm SD at rest▼ - mean IC/TLC % \pm SD at maximum exercise* $p < 0.0001$ between IC at rest and at maximum exercise. $p < 0.001$ between rest and maximum exercise.**Figure 1** Comparison of inspiratory capacity related to TLC at rest and during maximum exercise in patients with COPD, pulmonary fibrosis, PH, and HC.

Table 3 Inspiratory capacity at rest and maximum exercise in patients with PH according to gender. Values represent mean \pm SD; for abbreviations, see text.

Parameter	male (n = 26)	female (n = 35)
IC rest (l)	2.8 \pm 0.6 ^a	2.0 \pm 0.4
IC max (l)	2.6 \pm 0.5 ^a	1.8 \pm 0.4
delta IC (%)	-5.7 \pm 11	-8.5 \pm 13
IC rest/TLC (%)	38 \pm 7	38 \pm 7
IC max/TLC (%)	35 \pm 6	34 \pm 7

^a $p < 0.001$, male versus female.

Changes in ventilatory parameter during exercise might be influenced by body position during exercise. The potential impact on airway closure might influence comparison with other studies using a different exercise

Table 4 Cardiopulmonary exercise test and inspiratory capacity in patients with PH according to functional classification values represent mean \pm SD; for abbreviations, see text.

Parameter	WHO FC I (n = 6)	WHO FC II (n = 25)	WHO FC III (n = 30)
Watt (max)	133 \pm 46	80 \pm 24	72 \pm 37
Max. heart rate (/min)	149 \pm 20	134 \pm 20	126 \pm 22
% Heart rate reserve	85 \pm 11	81 \pm 10	78 \pm 12
VO ₂ peak (ml/kg/min)	19.0 \pm 3.2	13.5 \pm 2.8	12.8 \pm 4.1
VE max (l/min)	66.6 \pm 24	54.0 \pm 14.4	52.3 \pm 19
% Breathing reserve	57 \pm 19	68 \pm 24	65 \pm 14
VT rest (l)	1.0 \pm 0.5	0.8 \pm 0.2	0.9 \pm 0.2
VT max (l)	2.2 \pm 0.6 ^d	1.7 \pm 0.6 ^d	1.7 \pm 0.6 ^d
IC rest (l)	3.2 \pm 0.5	2.2 \pm 0.4 ^b	2.1 \pm 0.7 ^a
IC max (l)	3.0 \pm 0.4	2.1 \pm 0.5 ^{a,e}	2.0 \pm 0.7 ^{a,e}
delta IC (%)	-4 \pm 10	-8 \pm 14 ^b	-8 \pm 13 ^c
VT/IC rest (%)	36 \pm 6	37 \pm 8 ^b	43 \pm 10 ^a
VT/IC max (%)	78 \pm 17 ^{a,d}	85 \pm 15 ^{b,d}	85 \pm 18 ^{a,d}
IC rest/TLC (%)	44 \pm 6	38 \pm 5 ^b	36 \pm 8 ^b
IC max/TLC (%)	42 \pm 6	34 \pm 5 ^{b,e}	33 \pm 7 ^{b,e}
pO ₂ rest (mmHg)	75 \pm 11	70 \pm 10	67 \pm 13
pO ₂ max (mmHg)	65 \pm 9	64 \pm 14	64 \pm 16
pCO ₂ rest (mmHg)	35 \pm 5	32 \pm 3	32 \pm 4
pCO ₂ max (mmHg)	38 \pm 6	33 \pm 4 ^f	33 \pm 4
mPAP (mmHg)	45 \pm 16	47 \pm 17	46 \pm 14
PVR (dyn*s*cm ⁻⁵)	537 \pm 251	712 \pm 444	797 \pm 352
CI (l/min/qm)	2.7 \pm 0.7	2.6 \pm 0.7	2.2 \pm 0.6
6MWD (m)	565 \pm 94	479 \pm 93	404 \pm 124
BNP (pg/nl)	61 \pm 96	96 \pm 98	148 \pm 149

^a $p < 0.001$.

^b $p < 0.01$.

^c $p < 0.05$ versus HC.

^d $p < 0.001$.

^e $p < 0.01$.

^f $p < 0.05$ versus rest.

protocol. However the differences between patients groups within our study should be not affected, as all exercise tests were performed in semi-supine position.

What does this observation add to our understanding of exercise limitation in PH? Certainly, patients with PH are mainly restricted due to cardiovascular impairment and haemodynamic compromise with inappropriate increase in cardiac output during exercise and subsequent changes in muscle function, gas exchange and impaired breathing efficacy.¹⁹ However, the degree of haemodynamic compromise might not always explain the degree of impaired exercise capacity in these patients. Furthermore, exercise capacity measured by VO₂ peak is significantly higher during submaximal exercise compared to maximal exercise tests in these patients.²⁰

Patients with PH exhibit a mild obstructive lung pattern. The expiratory airflow limitation might be minor or even absent at rest, but could result in more pronounced changes during exercise.²⁻⁴

The significant reduction of IC during exercise (similar to DH in COPD) demonstrates the functional consequences of ventilatory impairment in PH patients. These changes might contribute to exercise intolerance in PH, however this is only weakly supported by the negative correlation of change in IC with VO₂ peak and PVR. Based on these findings we consider the role of DHI on exercise limitation in PH as minor and limited to the early stages of the disease.

Patients with COPD benefit from pulmonary rehabilitation with reduction of DH.²¹ It remains speculative whether the beneficial effects of pulmonary rehabilitation in PH might also result in a reduction of DH pattern in these patients.²²

The study has several limitations, particularly the unequal distribution of patients in the disease groups, the

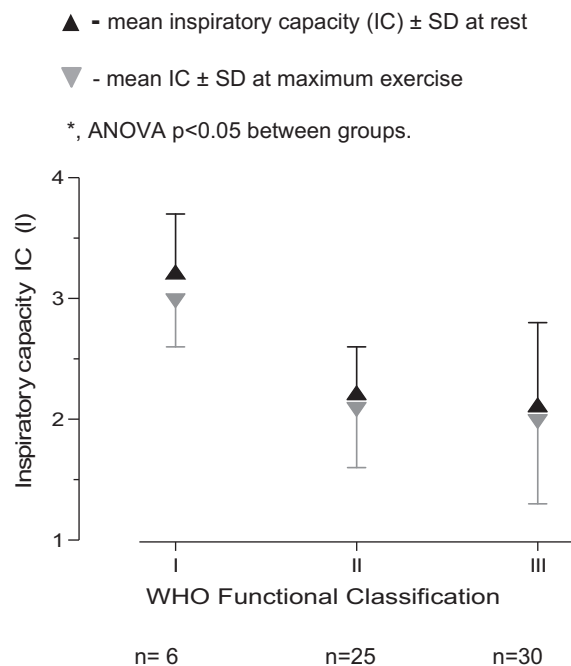


Figure 2 Comparison of inspiratory capacity at rest and during maximum exercise in patients with pulmonary hypertension depending on functional classification.

age difference in the HC group and the lack of assessment of subjective exercise limitation according to Borg scale. Furthermore, we did not relate these observations to therapeutic interventions. This might be subject of further investigations.

In conclusion, patients with PH exhibit a characteristic reduction pattern of IC at rest and at maximum exercise compared to patients with COPD, pulmonary fibrosis and healthy controls. The reduction of IC during exercise might be associated with reduced exercise capacity in PH.

Conflict of interests

Manuel Jonas Richter: no conflict of interests related to this study.

Robert Voswinckel: no conflict of interests related to this study.

Henning Tiede: no conflict of interests related to this study.

Richard Schulz: no conflict of interests related to this study.

Christian Tanislav: no conflict of interests related to this study.

Andreas Feustel: no conflict of interests related to this study.

Rory E. Morty: no conflict of interests related to this study.

Hossein Ardeschir Ghofrani: Conflict of interests: H.A. Ghofrani receives grant and contract support by Pfizer Ltd., Altana Pharma AG, Schering AG; in addition, he serves on advisory board of Pfizer Ltd.

Werner Seeger: Conflict of interests: W. Seeger receives grant and contract support by Schering, Altana Pharma, Myogen Inc. Westminster, LungRX and Aventis Pharma.

Frank Reichenberger: no conflict of interests related to this study.

Ethics statement

The study has been approved by the Ethics Committee of the Medical Division of the, Justus Liebig University of Giessen, Germany (approval number 112/11).

Acknowledgements

The manuscript is part of the doctoral thesis of Manuel J Richter.

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