The Prognostic Significance of Inspiratory Capacity in Pulmonary Arterial Hypertension

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Key Words

Cardiopulmonary exercise testing · Dynamic hyperinflation · Inspiratory capacity · Pulmonary arterial hypertension

Abstract

Background: Patients with pulmonary arterial hypertension (PAH) present with an altered inspiratory capacity (IC) reflecting dynamic hyperinflation (DH) that leads to mechanical constraints and excessive ventilatory demand, particularly during exercise, resulting in exertional dyspnea. **Objectives:** Assessment of the long-term consequences of altered IC and DH in PAH. **Methods:** 50 patients with newly diagnosed PAH were prospectively recruited. All patients were assessed by means of right heart catheterization, 6-min walking distance (6MWD) test, lung function and cardiopulmonary exercise testing, including the assessment of IC. **Results:** 37 patients with idiopathic PAH and 13 patients with conditions associated with PAH (29 female; mean age 51.6 ± 15.1 years; World Health Organization, WHO class, 2.7 ± 0.6) presented with a mean pulmonary arterial pressure of 42.8 ± 15.9 mm Hg and pulmonary vascular resistance (PVR) of 737.2 ± 592.8 dyn*s/cm⁵. The mean IC at rest was $87.2 \pm$

17.3% pred. Kaplan-Meier analysis revealed that patients with an IC at rest $>89\%$ pred. had a significantly better 5-year survival than those with lower values (94.1 vs. 75.1% ; log-rank $p = 0.036$). Univariate analysis identified IC at rest ($\%$ pred.) as a predictor of survival with a hazard ratio (HR) of 5.05 (95% confidence interval, CI, 0.97 – 26.24 , $p = 0.054$). In multivariate analysis including PVR, WHO class, 6MWD and peak oxygen uptake as covariates, IC at rest remained an independent predictor of survival (HR: 8.06 , 95% CI 0.92 – 70.34 ; $p = 0.059$). DH expressed as Δ IC or static hyperinflation expressed as IC/total lung capacity at rest revealed no prognostic significance. **Conclusion:** In patients with PAH, IC at rest is of prognostic significance at the time of diagnosis.

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Introduction

Pulmonary arterial hypertension (PAH) is characterized by progressive pulmonary vascular remodeling and right ventricular dysfunction leading to right heart failure

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[1]. In the majority of patients, the first symptom is exertional dyspnea leading to impaired exercise capacity, which, in turn, dramatically impacts quality of life in PAH patients [2, 3]. In the past, the assessment of prognostic factors has identified several parameters related to the exercise capacity of PAH patients, such as the 6-min walking distance (6MWD) test, peak oxygen uptake ($\text{VO}_{2\text{peak}}$) or the ventilatory equivalent for carbon dioxide in PAH patients [4–6].

Recently, abnormalities in respiratory mechanics detected during cardiopulmonary exercise testing (CPET) have been described in patients with PAH, mostly in a subgroup of patients with idiopathic PAH but also in patients with chronic thromboembolic pulmonary hypertension [7, 8]. An altered inspiratory capacity (IC) at rest, with a dynamic decrease during exercise accompanied by an increase in end-expiratory lung volume and restriction of tidal volume (V_T) is known as dynamic hyperinflation (DH), and has been described in approximately 60% of PAH patients differentiating so-called ‘hyperinflators’ from ‘nonhyperinflators’ [7]. The causes for the impaired respiratory mechanics in patients with PAH are not completely understood, but possible explanations include peripheral airway obstruction due to the mechanical forces acting on peripheral airways by the dilated precapillary pulmonary arteries or local inflammatory events [9].

So far, the prognostic impact of an altered IC at rest has been best described in patients with chronic obstructive pulmonary disease (COPD). The predicted IC at rest (% pred.) and the IC in relation to total lung capacity (TLC) at rest have been proven to predict all-cause and respiratory mortality [10, 11]. Furthermore, it was demonstrated that these parameters were rather related to exertional dyspnea and exercise intolerance than parameters derived from static lung function measurements [10, 11]. The measurement of IC can be reliably performed by recording flow-volume loops at rest and at maximum exercise during routine CPET, and thus a specific subgroup of PAH patients with impaired respiratory mechanics may be identified [12].

Therefore, we hypothesized that IC and DH could be prognostic factors in PAH.

Patients and Methods

We prospectively evaluated a cohort of PAH patients at the Pulmonary Hypertension Center (Department of Internal Medicine, University Hospital Giessen) of Giessen, Germany, between March 2007 and July 2009 who were followed up until May 2013. The Ethics Committee of the Faculty of Medicine of the University of Giessen approved the study (approval No. 113/11). Only

patients with newly diagnosed PAH at the first presentation to our center where enrolled in this study. Based on the detection of DH in a heterogeneous group of pretreated pulmonary hypertension (PH) patients in 2007, the current study was planned to prospectively follow up initially therapy-naïve PAH group 1 patients [8].

PH patients classified into World Health Organization (WHO) group 2–5 with a smoking history ≥ 10 pack years and significant evidence of an obstructive and/or restrictive ventilatory pattern, forced expiratory volume in 1 s (FEV_1)/vital capacity $\leq 70\%$ and/or TLC $\leq 80\%$ pred. were excluded from the study. Furthermore, patients who were not able to undergo CPET with measurement of IC at the time of initial presentation and patients lacking follow-up data were excluded.

All PAH patients were diagnosed according to current guidelines and were included when the diagnosis of group 1 PAH was confirmed by right heart catheterization based on a mean pulmonary arterial pressure (mPAP) ≥ 25 mm Hg, a pulmonary arterial wedge pressure (PAWP) < 15 mm Hg and a pulmonary vascular resistance (PVR) ≥ 240 dyn*s/cm, and exclusion of concomitant diseases not compatible with the diagnosis of PAH [5, 13].

All PAH patients enrolled underwent a lung function test, CPET and right heart catheterization, and WHO functional classification, 6MWD and brain natriuretic peptide levels (BNP) were assessed.

Pulmonary function tests were performed according to current recommendations and were presented as percentages of predicted normal values according to the guidelines of the European Respiratory Society (Masterscreen Body®, ViaSys Healthcare®, Jaeger) [14, 15]. Predicted IC was calculated as predicted TLC minus predicted functional residual capacity, as described previously [7, 16].

We performed a symptom-limited incremental CPET ($\text{V}_{\text{max}} 229^\circ$, Carefusion®) according to current recommendations using a cycle ergometer in semisupine position with an initial warm-up of 2 min, followed by increases of 30 W every 2 min until exercise was terminated, either due to exercise-limiting symptoms by the patient or because the end-points were reached [17]. Patients were asked to exercise up to their individual limit. Measurement of IC was performed twice at rest and once during maximum exercise, while the mean value of both measurements at rest was used in the study. IC maneuvers were performed and analyzed as described in detail previously [16, 18, 19].

DH was defined as a decrease in IC (ΔIC) during maximal exercise ≥ 150 ml, which was validated for COPD patients previously [16]. For further analysis, the patient population was separated for ΔIC and dichotomized at a value ≥ -150 ml to characterize hyperinflators and nonhyperinflators. Static hyperinflation was assessed by IC at rest as percentage of TLC (IC/TLC) [16].

After enrollment of the patients into the study, treatment with pulmonary vasoactive therapies was initiated according to the current guidelines [13]. Follow-up data were retrieved from the local PAH database, while patients were routinely followed up every 3–6 months. Clinical worsening was defined as the need for the initiation of additional specific PAH therapies, worsening right heart function, reduction in 6MWD by $> 20\%$ compared with baseline values, worsening functional class, transplantation or death due to all causes.

Data are expressed as means $\pm$ SD for normally distributed parameters, or as medians and interquartile ranges. The 2-tailed t test or Mann-Whitney U test was used to test for differences between groups, as appropriate. Kaplan-Meier analyses with log-rank test

Table 1. Baseline characteristics, pulmonary function tests, CPET, IC and hemodynamics dichotomized at the median for IC

Characteristics	IC		
	total	≤89% pred.	>89% pred.
Patients, n	50	25	25
Male/female ratio	21/29	14/11	7/18
Age, years	51.6±15.1	49.4±13.4	53.8±16.6
BMI, kg/m ²	26±4.6	25±4	27±5.1
WHO functional class	2.7±0.6	2.7±0.6	2.6±0.5
FEV ₁ , liters	2.71±0.7	2.77±0.7	2.63±0.6
FEV ₁ , % pred.	87.1±14.2	82.1±12.3*	92.4±14.3
FEV ₁ /VC, %	76.3±7.2	76.3±8.3	76.3±7.4
FEV ₁ /VC, % pred.	96.3±10.2	95.5±11.7	97.1±8.4
FEF ₇₅ , % pred.	90.7±26.2	90.5±27.1	91±25.9
FEF ₅₀ , % pred.	71.3±28.1	71.4±29.9	71.2±26.2
FEF ₂₅ , % pred.	51.2±25.3	47.4±22.1	55.1±28.1
TLC, % pred.	100.9±15.1	94.6±13.5**	107.3±14.1
FRC, % pred.	102.4±19.9	98.8±19.9	105.6±19.7
IC rest, liters	2.5±0.6	2.4±0.6	2.6±0.5
IC at rest, % pred.	87.2±17.3	72.9±8.3***	101.5±10.8
IC _{peak} , liters	2.4±0.6	2.3±0.7	2.4±0.6
ΔIC from rest, ml	-104±320	-20±305	-190±330
IC/TLC at rest, %	43.6±7.1	38.9±4.9*	43.9±8.1
VT _{peak} , liters	1.8±0.6	1.8±0.6	1.7±0.6
VO _{2 peak} , ml*kg ⁻¹ min ⁻¹	13.7±5.1	13.9±5.4	13.5±4.9
VO _{2 peak} , % pred.	50.8±15.3	48.8±14.8	52.8±15.9
W _{peak} , W	81±34	80±37	82±32
mPAP, mm Hg	42.8±15.9	44.2±17.2	41.3±14.6
PAWP, mm Hg	7.9±3.2	8.4±3.2	7.5±3.2
PVR, dyn*s/cm ⁵	737.2±592.8	839.5±723.4	625.5±393.4
CO, l/min	4.8±1.9	4.4±1.5	5.1±2.3
CI, l/min/m ²	2.6±1.1	2.4±0.8	2.9±1.2
SvO ₂ , %	66.2±8.7	63.9±7.9	68.6±9.1
BNP, pg/ml	125.3±158.6	157.1±171.1	103.9±138.5
6MWD, m	412±112	410±95	414±129
<i>Etiology of disease, n</i>			
Idiopathic	37	18	19
Collagen vascular	9	5	4
Congenital heart defect	2	1	1
Portopulmonary	2	1	1

VC = Vital capacity; FRC = functional residual capacity; CO = cardiac output; CI = cardiac index. Values represent means ± SD; * p < 0.05, ** p < 0.01, *** p < 0.001, vs. >89% pred.

were used to assess differences in survival depending on the initial assessment of IC and DH. Univariate and multivariate Cox regression models were used to assess independent predictors for long-term survival. p < 0.05 was considered statistically significant; for comparisons between groups, Bonferroni correction for multiple testing was considered. For survival analysis, patients where either separated at the median of IC at rest or at a value of -150 ml of ΔIC. Statistical analysis was performed using SPSS, version 21.0 (IBM, Armonk, N.Y., USA).

Results

We included 50 PAH patients (29 women and 21 men): 37 patients with idiopathic PAH, 9 patients with PAH associated with connective tissue diseases, 2 patients with portopulmonary hypertension and 2 patients with PAH due to congenital heart disease. Patients presented with a mean age of 51.6 ± 15.1 years, and a body mass index (BMI) of 26 ± 4.6. Patients exhibited a precapillary PH with a mPAP of 42.8 ± 15.9 mm Hg, PAWP of 7.9 ± 3.2 mm Hg and severely increased PVR of 737.2 ± 592.8 dyn*s/cm⁵ while the WHO functional class was 2.7 ± 0.6. BNP levels were elevated at 125.3 ± 158.6 pg/ml. Lung function tests revealed no significant obstructive or restrictive ventilatory abnormalities apart from forced expiratory flow at 50% of FVC (FEF₅₀) and 25% (FEF₂₅; % pred.), which were reduced, indicating small airway disease. Exercise capacity was markedly reduced with VO_{2 peak} of 13.7 ± 5.1 ml*kg⁻¹min⁻¹ (50.8 ± 15.3% pred.) and a 6MWD of 412 ± 112 m (table 1). Measurements of IC revealed a mean IC at rest of 87.2 ± 17.3% pred. with a decrease from rest to maximal exercise of -104 ± 320 ml (ΔIC).

Twenty-one PAH patients exhibited significant hyperinflation with ΔIC ≥150 ml (mean ΔIC of -386 ± 235 ml) while 29 patients presented with a nonhyperinflation pattern (ΔIC of 100 ± 201 ml; p < 0.001). The clinical lung function and hemodynamic parameters did not significantly differ between hyperinflators and nonhyperinflators apart from IC/TLC (table 2).

Patients with a median IC at rest >89% pred. exhibited a significantly higher FEV₁, IC/TLC at rest and TLC while the decrease in IC from rest to maximal exercise of -190 ± 330 ml was not significant in comparison to an IC ≤89% pred. at rest (ΔIC, p = 0.07). BMI and functional and hemodynamic parameters did not differ (table 1).

Survival Analysis

Patients were followed up over a period of up to 74 months during which 8 patients died. The overall 1-, 3- and 5-year survival times were 96.0, 91.3 and 84.7%, respectively. In comparison, patients who died exhibited a significantly reduced exercise capacity with a decreased 6MWD, VO_{2 peak} and peak incremental cycle work rate (W_{peak}), however, no differences in IC, lung function and hemodynamic parameters were evident (table 3).

When dichotomized at the median, Kaplan-Meier survival plots revealed a significantly better 5-year survival for patients having an IC at rest ≥89% pred. compared to those with a lower IC at rest (94.1 vs. 75.1%; log-rank p = 0.036; fig. 1). Furthermore, in patients with an IC at rest

Table 2. Baseline characteristics, pulmonary function tests, CPET, IC and hemodynamics according to hyperinflation and nonhyperinflation

Characteristics	Δ IC from rest	
	hyperinflation	nonhyperinflation
Patients, n	21 (42%)	29 (68%)
Age, years	51.6 $\pm$ 16.6	51.6 $\pm$ 14.2
BMI, kg/m ²	27.2 $\pm$ 5.4	25.2 $\pm$ 3.9
WHO functional class	2.6 $\pm$ 0.5	2.7 $\pm$ 0.6
FEV ₁ , liters	2.6 $\pm$ 0.7	2.8 $\pm$ 0.7
FEV ₁ , % pred.	84.3 $\pm$ 14.8	89.0 $\pm$ 13.6
FEV ₁ /VC, %	75.1 $\pm$ 7.2	77.1 $\pm$ 8.2
FEV ₁ /VC, % pred.	95.4 $\pm$ 8.1	96.9 $\pm$ 11.5
FEF ₇₅ , % pred.	83.4 $\pm$ 22.1	95.9 $\pm$ 28.0
FEF ₅₀ , % pred.	65.2 $\pm$ 24.4	75.4 $\pm$ 30.1
FEF ₂₅ , % pred.	45.4 $\pm$ 24.6	55.1 $\pm$ 25.4
TLC, % pred.	99.5 $\pm$ 16.8	101.9 $\pm$ 13.8
FRC, % pred.	102.6 $\pm$ 23.2	102.2 $\pm$ 17.8
IC rest, liters	2.6 $\pm$ 0.6	2.4 $\pm$ 0.6
IC at rest, % pred.	90.8 $\pm$ 19.7	82.5 $\pm$ 14.6
IC _{peak} , liters	2.2 $\pm$ 0.6*	2.5 $\pm$ 0.6
Δ IC from rest, ml	-386 $\pm$ 235***	100 $\pm$ 201
IC/TLC at rest, %	44.2 $\pm$ 8.2*	39.3 $\pm$ 5.3
VE _{peak} , l*min ⁻¹	51.5 $\pm$ 16.5	54.7 $\pm$ 20.3
VT _{peak} , liters	1.79 $\pm$ 0.6	1.82 $\pm$ 0.6
VO _{2 peak} , % pred.	48.45 $\pm$ 14.9	52.5 $\pm$ 15.6
W _{peak} , W	81 $\pm$ 35	81 $\pm$ 34
mPAP, mm Hg	43 $\pm$ 17	43 $\pm$ 15
PAWP, mm Hg	8 $\pm$ 3.1	8 $\pm$ 3.3
PVR, dyn*s/cm ⁵	612.8 $\pm$ 340.2	841.6 $\pm$ 733.1
CO, l/min	5.2 $\pm$ 2.3	4.5 $\pm$ 1.6
CI, l/min/m ²	2.9 $\pm$ 1.1	2.4 $\pm$ 0.9
SvO ₂ , %	68.5 $\pm$ 8.7	64.6 $\pm$ 8.6
BNP, pg/ml	136.9 $\pm$ 146.2	123.9 $\pm$ 169.4
6MWD, m	429.1 $\pm$ 97.6	400.5 $\pm$ 121.1

Values represent means $\pm$ SD; * $p < 0.05$, *** $p < 0.001$, vs. non-hyperinflation. CI = Cardiac index; CO = cardiac output; FRC = functional residual capacity; VC = vital capacity. Hyperinflation was defined as a decrease in Δ IC from rest ≥ 150 ml [16].

$\leq 89\%$ pred., mortality was 5-fold increased, while the IC at rest was a predictor of all-cause mortality with a hazard ratio (HR) of 5.05 (95% confidence interval, CI, for HR 0.97–26.24; $p = 0.054$). When age and gender were added to the Cox regression model, IC at rest remained an independent predictor of survival (HR 9.06, 95% CI for HR 1.23–66.65; $p = 0.03$).

Further multivariate Cox regression analysis including PVR, WHO class, 6MWD and VO_{2 peak} as covariates detected IC at rest as significantly related to survival ($p = 0.059$; HR 8.06, 95% CI for HR 0.92–70.34).

Table 3. Comparison of selected baseline characteristics, pulmonary function tests, CPET, IC and hemodynamics according to survival

Characteristics	Alive	Death of all cause
Patients, n	42	8
Age, years	51.5 $\pm$ 15.1	52 $\pm$ 16.5
BMI, kg/m ²	25.9 $\pm$ 4.4	26.2 $\pm$ 5.8
WHO functional class	2.6 $\pm$ 0.5	2.9 $\pm$ 0.6
FEV ₁ , % pred.	88.7 $\pm$ 14.4	79.2 $\pm$ 10.7
FEV ₁ /VC, %	76.6 $\pm$ 7.7	74.8 $\pm$ 8.6
FRC, % pred.	104.3 $\pm$ 20.9	92.3 $\pm$ 10.3
IC at rest, % pred.	89.1 $\pm$ 17.8	77.4 $\pm$ 10.5
Δ IC from rest, ml	-110 $\pm$ 346	-90 $\pm$ 167
IC/TLC at rest, %	41.5 $\pm$ 7.6	40.4 $\pm$ 2.9
VO _{2 peak} , % pred.	53.1 $\pm$ 14.8*	39.4 $\pm$ 13.4
W _{peak} , W	85 $\pm$ 34*	56 $\pm$ 20
mPAP, mm Hg	41 $\pm$ 17	50 $\pm$ 7
PAWP, mm Hg	8 $\pm$ 3.3	7.6 $\pm$ 2.5
PVR, dyn*s/cm ⁵	707.2 $\pm$ 626.1	879.5 $\pm$ 398.9
CI, l/min/m ²	2.7 $\pm$ 1.1	2.1 $\pm$ 0.5
6MWD, m	430 $\pm$ 105**	321 $\pm$ 105
<i>Etiology of disease, n</i>		
Idiopathic	30	7
Collagen vascular	8	1
Congenital heart defect	2	0
Portopulmonary	2	0

Values represent means $\pm$ SD; * $p < 0.05$, ** $p < 0.01$, vs. death of all cause. CI = Cardiac index; FRC = functional residual capacity; VC = vital capacity.

Δ IC failed to add any significant prognostic value. Kaplan-Meier plots of survival revealed no statistical difference in Δ IC when dichotomized at -150 ml (fig. 2). Cox regression with Δ IC as continuous variable ($p = 0.665$; HR 1.01, 95% CI for HR 0.964–1.06) and when dichotomized ($p = 0.65$; HR 1.4, 95% CI for HR 0.33–6.07) neither showed any predictive power. In addition, the IC/TLC at rest revealed no significant prognostic value (data not shown). No differences were shown regarding clinical worsening for IC, IC/TLC at rest and Δ IC when analyzed dichotomized or as continuous covariate (data not shown).

Discussion

In PAH patients, an altered respiratory pattern with a slightly reduced IC at rest and DH during maximal exercise can contribute to exercise intolerance and dyspnea, as recently described [7, 8].

Fig. 1. Kaplan-Meier 5-year survival curve in PAH patients. Patients presenting with IC at rest $>89\%$ pred. had a significantly better survival rate compared with patients with an IC at rest $\leq 89\%$ pred. (94.1 vs. 75.1%; log-rank $p = 0.036$; $n = 50$).

Fig. 2. Kaplan-Meier 5-year survival curve in PAH patients. Patients presenting with $\Delta IC < -150$ ml failed to show a significantly better survival rate compared with $\Delta IC \geq -150$ ml (81.5 vs. 86.9%; log-rank $p = 0.892$; $n = 50$).

About 60% of PAH patients exhibit a subclinical peripheral airflow obstruction, which leads to dynamic ‘air trapping’ known as DH during maximal exercise [7]. In the present study, we measured IC during CPET in therapy-naïve PAH patients to assess IC and DH as prognostic factors.

The study group consisted of patients with PAH (WHO 1), who had mostly idiopathic PAH in an advanced stage of disease ($WHO\ 2.7 \pm 0.6$). By definition, these patients exhibit no significant restrictive or obstructive pattern in lung function testing. The mean change in IC during maximal exercise was -104 ± 320 ml in the whole study population. The repeatability of IC measurements during CPET to estimate DH in COPD patients was shown previously [20, 21] and despite the lack of data for PAH patients, we assume no difference in the repeatability and reliability.

In contrast to Laveneziana et al. [7], a significant decrease in IC >150 ml was exhibited by 42% of the PAH patients. This discrepancy is explained by methodological differences: while our study defined DH at a threshold of >150 ml, Laveneziana et al. [7] defined DH as any decrease in IC during exercise. Albeit no validated data for a threshold value of DH exist for PAH patients, Laveneziana et al. [7] use a mean DH of -150 ± 460 ml in the PAH hyperinflation group which is significantly associated with exertional dyspnea [7], and, therefore, we as-

sumed that the clinically important decrease in IC during exercise is ≥ 150 ml, as validated for COPD patients [16]. In our patient population, no significant differences between the hyperinflators and nonhyperinflators with regard to clinical lung function and hemodynamic parameters were evident, which is in line with the findings of Laveneziana et al. [7].

In PAH patients, IC at rest is slightly but significantly reduced compared to healthy controls [7]. In our study, patients with IC at rest $>89\%$ pred. exhibited a stronger but nonsignificant decline in IC during exercise compared with IC at rest $\leq 89\%$ pred. Patients with an IC $\leq 89\%$ pred. may be further limited in their exercise capacity, as reflected by a reduced IC/TLC at rest and the subsequent constraint of VT expansion – not only during exercise but also at rest – indicating severe impairment in respiratory mechanisms in this subgroup of patients. One may speculate that the reduced IC is an indicator of decreased ventilation during exercise and thus influences the maximum $\dot{V}O_2$, as it has been suggested in COPD patients [22].

Importantly, the present study indicates for the first time that IC at rest is a predictor of all-cause mortality in PAH patients. We found that PAH patients with IC at rest $>89\%$ pred. had a significantly better prognosis in the long term (1-, 3- and 5-year survival) than patients presenting with an initial IC $\leq 89\%$ pred. We cal-

culated a 5% increase in survival per unit increase in IC at rest. Therefore, an IC at rest $\leq 89\%$ pred. is associated with a 5 times higher all-cause mortality. Interestingly, Δ IC and the IC/TLC ratio at rest, which both express DH and static hyperinflation, failed to reveal any prognostic significance. Confirming previously published data, significantly lower $\text{VO}_{2\text{peak}}$, W_{peak} and 6MWD levels were seen in patients who died during the follow-up (table 3).

In patients with COPD, the IC/TLC ratio and IC at rest are well-reported powerful prognostic parameters of all-cause and disease-specific respiratory mortality as well as the occurrence of exacerbations requiring hospitalization [10, 11].

In COPD, threshold values for IC at rest $\leq 80\%$ pred. and for IC/TLC at rest $\leq 25\%$ have been identified as prognostic indicators. Lower values indicate more severe hyperinflation in COPD patients, which is in contrast to our study on PAH patients, who presented a higher threshold value for IC at rest [10, 11].

Remarkably, to our knowledge, no current study in COPD describes dynamic air trapping measured as Δ IC as a prognostic factor.

What does this observation add to our understanding of respiratory mechanisms in PAH? The cause of the altered respiratory pattern in PAH with a reduced IC at rest and DH is ascribed to subclinical peripheral pulmonary airway obstruction and inspiratory and expiratory muscle weakness in severe disease [9, 23]. Additionally, a significantly reduced IC at rest and decrease throughout exercise associated with impaired functional capacity was also noted in patients with chronic heart failure [24, 25]. In comparison with PAH patients, the expiratory flow limitation in chronic heart failure was even absent at rest, but expiratory flow decreased during exercise. This is supported by our data indicating peripheral small airway disease with reduced FEF_{50} and FEF_{25} in the whole study group, and a more pronounced, albeit not statistically significant, decrease in the subgroup of hyperinflators. However, the major limitation of exercise intolerance in PAH patients is due to impaired pulmonary hemodynamics, while DH or a reduced IC at rest are only further contributing factors.

Our prospective study has failed to demonstrate long-term consequences of DH with regard to the time to clinical worsening and overall survival. Only the altered respiratory pattern, which was displayed by IC at rest, has an impact on overall survival. The usefulness of IC at rest as a prognostic factor is, therefore, probably small and possibly reflects a subgroup of PAH patients with short-

ness of breath due to an overall advanced state of disease. This subgroup of patients can be easily identified by CPET with measurements of IC maneuvers at rest and during maximal exercise. Albeit not significant, PAH patients with an IC at rest $\leq 89\%$ pred. tend to demonstrate further impairment in pulmonary hemodynamics and functional status. Additional measurement of IC at rest during CPET can easily identify PAH patients at risk in addition to already established prognostic factors derived from CPET.

Limitations of this study include the small patient population in a single center study, a selection bias, which was revealed by the better long-term survival in our selected study group, and too few cases in our cohort to perform multivariate analysis. We were not able to differentiate between PH-related and non-PH-related deaths due to the small size of the study group. As only 8 patients of this cohort died, receiver-operating characteristic curve analysis had very low statistical power; therefore, confirmation of our data by future analyses in larger patient cohorts are mandatory.

In conclusion, this is the first study to evaluate IC as a prognostic factor in PAH patients. IC at rest demonstrated prognostic significance in a subgroup of PAH patients with a 5% increase in survival per 1% increase in IC, while DH failed to serve as a prognostic factor. For the evaluation of DH as independent predictor of mortality, future studies in larger patient groups are warranted.

Financial Disclosure and Conflict of Interest

All authors report that no potential conflicts of interest exist with any companies/organizations whose products or services are discussed in this article.

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