Inspiratory capacity is not altered in operable chronic thromboembolic pulmonary hypertension

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Abstract

Pathological alterations of inspiratory capacity (IC) have been observed in pulmonary hypertension. However, the clinical significance of IC in operable chronic thromboembolic pulmonary hypertension (CTEPH) without other pulmonary diseases remains unknown. CTEPH patients scheduled for pulmonary endarterectomy were prospectively screened. Despite being associated with functional capacity, pathological alterations of IC were not observed.

Patients with pulmonary arterial hypertension (PAH) exhibit an altered respiratory pattern during exercise, with dynamic changes in inspiratory capacity (IC) which partly contribute to the sensation of dyspnea.[1–3] IC abnormalities have been best described in participants with chronic obstructive pulmonary disease (COPD), in whom they significantly contribute to dyspnea sensation, long-term outcome, and functional capacity.[4–6] Preliminary results in a heterogeneous study group including PAH and inoperable chronic thromboembolic pulmonary hypertension (CTEPH) patients showed an association of functional class with IC at rest and during maximum exercise.[1] In idiopathic PAH, the dynamic decrease of IC during maximum exercise reflected overall disease severity, was related to exertional dyspnea, exercise limitation, and altered ventilatory patterns and was attributed to abnormalities in respiratory mechanics.[2,7] Moreover, IC was identified as an independent prognostic factor in idiopathic PAH.[3]

Therefore, evaluation of IC in operable CTEPH is of special interest as it might reflect exercise limitation or disease severity prior to pulmonary endarterectomy (PEA). We conducted a prospective, observational study to assess IC and its relationship with clinical characteristics between December 2012 and December 2013. Exclusion criteria for the study were defined as follows: symptomatic chronic thromboembolic disease with mean pulmonary arterial pressure (mPAP) <25 mmHg prior to PEA;[8] inability to perform treadmill cardio-pulmonary exercise testing (CPET); dependency on high-flow supplemental oxygen (≥ 4 L/min O_2); obstructive and/or restrictive pulmonary disease (FEV_1/vital capacity $\leq 70\%$ and/or total lung capacity [TLC] $\leq 80\%$ predicted); and/or ≥ 10 pack years of smoking history. Eligible patients who met the inclusion criteria entered the study before undergoing PEA and were included in the current analysis if they had complete hemodynamic data before and one year after PEA. All patients gave written, informed consent, and the study was approved by the

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ethics committee of the Faculty of Medicine at the University of Giessen (Approval No. 112/12).

Before undergoing PEA, all patients performed a symptom-limited incremental CPET using a ramp protocol with an incremental rate of 5–15 Watt/min judged by the operator (Masterscreen CPX®, Carefusion®, Germany). Measurement of IC was performed at rest (IC_{rest}), every 2 min during incremental exercise load, and at peak exercise (IC_{peak}). IC maneuvers were performed and analyzed as described previously.[9] ΔIC was defined as the dynamic change of IC from rest to maximum exercise.[1,3] IC% predicted (pred.) was calculated as described previously.[7] Static hyperinflation was assessed by calculating IC_{rest} as a percentage of TLC (IC/TLC_{rest}).[3] Absolute dead space (V_D) was assessed in milliliters and $\dot{V}_D$ was calculated using the Bohr formula.

The two-tailed t test, Wilcoxon signed rank test, or Pearson Chi-square test was used as appropriate to test for differences between groups, with $P < 0.05$ considered statistically significant. Spearman's rank correlation test was used to assess associations of IC, ΔIC, and IC/TLC_{rest} with baseline parameters.

After applying the exclusion criteria, 23 patients were included in the final analysis (66 participants screened for the study, 32 participants fulfilled the exclusion criteria prior to PEA, three participants died during the study, and eight additional participants were excluded because they did not have right heart catheterization data one year after PEA). IC was preserved at rest and showed a moderate decrease from resting values during exercise. Although the included patients showed no restrictive or obstructive ventilatory abnormalities, the maximal expiratory flow at 50% and 25% of expired vital capacity (MEF50; MEF25) was reduced. Functional, hemodynamic, and laboratory parameters were improved from baseline at one year post-PEA. IC_{rest} and IC_{peak} showed a slight decrease from baseline at one year post-PEA, but this change was only statistically significant for IC_{rest} expressed as % pred. There was no dynamic decrease in IC with exercise at one year post PEA; instead, a slightly positive ΔIC was observed (Table 1). Residual PH[10] was found in ten of the 23 participants at one year post PEA; CPET parameters including IC_{rest} (L and % pred.), IC_{peak}, ΔIC, and IC/TLC_{rest} showed no significant differences between the subgroups with and without residual PH. Baseline IC_{rest} and IC_{peak} (L) were significantly associated with baseline six-minute walking distance (6MWD) (r = 0.48 [P = 0.02]; r = 0.41 [P = 0.05]). Baseline IC_{rest} values (L and % pred.) were associated with 6MWD at one year post PEA (r = 0.62 [P = 0.004]; r = 0.64 [P = 0.003]). Baseline IC_{rest} and IC_{peak} (L) were associated with peak oxygen uptake (V_{O2}) at one year post PEA (r = 0.46 [P = 0.05]; r = 0.47 [P = 0.04]).

The present study prospectively evaluated IC in a selected cohort of operable CTEPH patients after exclusion of cofounding pulmonary diseases. Although our findings are based on a limited number of patients and require further

Table 1. Patients characteristics at baseline and at one year post PEA.

	Baseline	One year post PEA	P value
Patients (n)	23		
Male/Female	11/12		
Age (years)	60 ± 11		
BMI (kg/m^2)	26.7 ± 5.1	26.5 ± 8.2	0.87
WHO functional class (n (%))			0.89*
I	None	8 (34.8)	
II	6 (26.1)	8 (34.8)	
III	14 (60.9)	7 (30.4)	
IV	3 (13.0)	None	
6MWD (m)	391 ± 91	462 ± 114	0.005
RHC			
mPAP (mmHg)	43.1 ± 9.3	25.0 ± 10.2	0.001
RAP (mmHg)	7.6 ± 4.7	6.6 ± 3.9	0.45
PVR (dyne*s/cm^5)	672 [408]	196 [399]	0.07†
Cardiac index (L/min/m^2)	2.4 ± 0.9	2.6 ± 0.5	0.60
PAWP (mmHg)	10.6 ± 6.1	10.2 ± 3.7	0.77
Echocardiography			
TAPSE (mm)	16.0 ± 3.9	17.5 ± 3.6	0.20
PASP (mm Hg)	60.2 ± 24.4	50.3 ± 24.8	0.06
NT-proBNP (pg/mL)	513 [1445]	236 [606]	0.02†
Lung function			
FEV$_1$ (% pred.)	87.7 ± 11.5	83.2 ± 30.2	0.48
MEF75 (% pred.)	86.3 ± 19.5	88.0 ± 23.7	0.77
MEF50 (% pred.)	73.3 ± 24.5	77.9 ± 32.6	0.97
MEF25 (% pred.)	60.1 ± 26.1	61.9 ± 31.2	0.77
FEV$_1$/FVC (% pred.)	101.4 ± 7.9	97.7 ± 11.0	0.13
TLC (% pred.)	98.5 ± 12.3	90.7 ± 32.3	0.36
FRC (% pred.)	107.6 ± 24.7	88.0 ± 41.5	0.11
CPET			
Peak V$_{O2}$ (mL/min/kg)	12.9 ± 3.2	15.5 ± 4.5	0.009
V$_D$ at rest (L)	0.28 ± 0.16	0.28 ± 0.24	0.92
V$_D$ at peak (L)	0.79 ± 0.35	0.66 ± 0.23	0.23
V$_T$ at rest (L)	0.76 ± 0.19	0.89 ± 0.37	0.25
V$_T$ at peak (L)	1.92 ± 0.58	1.95 ± 0.54	0.50
$\dot{V}_D$ at rest (%)	31.8 ± 9.1	30.9 ± 12.8	0.97
$\dot{V}_D$ at peak (%)	42.1 ± 16.3	36.0 ± 9.9	0.26
$\Delta\dot{V}_D$ from rest (%)	7.1 ± 10.5	5.4 ± 15.9	0.18
IC at rest (% pred.)	109.0 ± 30.2	97.7 ± 33.0	0.03
IC at rest (L)	2.8 ± 0.8	2.5 ± 0.8	0.10
IC at peak (L)	2.7 ± 0.9	2.6 ± 0.8	0.69
ΔIC from rest (mL)	− 120 ± 33	83 ± 24	0.03
IC/TLC at rest (%)	45.7 ± 10.2	40.6 ± 10.9	0.03
Watts at peak (W)	70.9 ± 31.9	101.0 ± 38.6	0.02
Borg score at rest	1.3 ± 1.7	0.6 ± 1.8	0.003
Borg score at peak	7.6 ± 2.4	6.7 ± 2.3	0.52
ΔBorg score from rest	6.3 ± 1.0	6.6 ± 2.8	0.79

(continued)

Table 1. Continued

	Baseline	One year post PEA	P value
Jamieson CTEPH type (n (%))‡			
I	7 (31.8)		
II	6 (27.3)		
III	9 (40.9)		
Time since pulmonary embolism (months)	18.0 [57.0]		
Time since start of symptoms (months)	18.0 [36.0]		

Values represent mean ± SD or median [interquartile range].

*Pearson chi-square test.

†Wilcoxon signed rank test.

‡n = 22.

6MWD, six-minute walking distance; BMI, body mass index; CPET, cardio-pulmonary exercise testing; CTEPH, chronic thromboembolic pulmonary hypertension; ΔIC, dynamic change of inspiratory capacity from rest to maximum exercise; FRC, functional residual capacity; IC, inspiratory capacity; MEF75, maximal expiratory flow at 75% of expired vital capacity; MEF50, maximal expiratory flow at 50% of expired vital capacity; MEF25, maximal expiratory flow at 25% of expired vital capacity; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal fragment of pro-brain natriuretic peptide; PASP, pulmonary artery systolic pressure; PAWP, pulmonary arterial wedge pressure; PEA, pulmonary endarterectomy; pred., predicted; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RHC, right heart catheterization; TAPSE, tricuspid annular plane systolic excursion; TLC, total lung capacity; V_D, absolute dead space; $\dot{V}_D$, dead space ventilation; $\dot{V}_{O2}$, oxygen uptake; V_T, tidal volume; WHO, World Health Organization.

confirmation, our study adds to knowledge of the ventilatory mechanism in CTEPH, which has been less well characterized than the obvious hemodynamic impairment. The key findings of our study are as follows: (1) IC was well preserved and did not show the pathological alterations previously seen in PAH; (2) a moderate dynamic reduction of IC was evident before PEA and was reversed post PEA, though with doubtful clinical relevance; and (3) the well preserved IC before PEA was associated with functional capacity before and one year after PEA.

The exercise limitation, sensation of dyspnea, and impaired functional capacity experienced by CTEPH patients are obviously provoked by circulatory instead of respiratory mechanisms.[11] Nevertheless, in daily clinical practice CTEPH patients are presenting with exertional dyspnea which sometimes cannot be fully explained by pulmonary hemodynamic impairment and therefore might be additionally related to respiratory mechanism. However, alterations of respiratory mechanisms in CTEPH have not been evaluated in detail before. Interestingly, our data indicate for the first time that IC_{rest} is well preserved with only a moderate dynamic decrease during maximum exercise in operable CTEPH before PEA. Based on the assumption that the minimal clinically important difference in IC is about 150 mL,[4] the statistically significant dynamic change in IC is unlikely to be clinically relevant. In addition, the moderate dynamic decrease of IC was reversed one year

after PEA. Of note, IC showed a slight reduction from baseline values one year after PEA, but this is also unlikely to be clinically relevant because IC (% pred.) was still well preserved at almost 100%.

The preserved IC_{rest} and the moderate dynamic decrease of IC during exercise in CTEPH contrast with previous findings in PAH (reduced IC_{rest} and substantial dynamic decrease of IC during exercise); one can speculate that this mirrors different pathophysiological findings in the two disease states. In PAH, the altered respiratory pattern was ascribed to subclinical peripheral pulmonary airway obstruction and respiratory muscle weakness, as observed in subjects with severe idiopathic PAH.[1,7] However, Laveneziana et al. pointed out that PAH patients had preserved respiratory muscle function regardless of changes in dynamic IC and related the impairment of IC to abnormalities in respiratory mechanics.[2] In COPD, relevant peripheral airway obstruction and respiratory muscle dysfunction evoke an exercise-elicited, dynamic air-trapping which causes an increase in the functional residual capacity (FRC) (or end-expiratory lung volume [EELV]) with a concomitant decrease in IC.[12,13] It is believed that the TLC (even in COPD patients) remains constant during exercise and the factor aggravating the decrease in IC is the increase in FRC (or EELV).[14] In healthy individuals, IC slightly increases during exercise while the EELV and TLC remain almost unchanged.[14] Taken together, our study and the previous studies in patients with COPD,[12–14] chronic heart failure,[15] or PH[1,2,7] identify IC as a parameter related to airway and alveolar mechanics but not pulmonary hemodynamics.

In that context, one can assume that patients with operable CTEPH experience only moderate dynamic alteration of IC during exercise because of a lack of clinically relevant increase in the FRC (or EELV) due to an absence of relevant dynamic air-trapping. The slight dynamic alteration of IC might be attributable to reduced strength in diaphragm muscle fibers, as previously reported by Manders et al. who showed that CTEPH patients exhibit a relevant respiratory muscle dysfunction.[16] Moreover, baseline MEF50 and MEF25 in our study were reduced, indicating pulmonary involvement primarily affecting the small airways. The observed change of ΔIC post PEA might be attributable to a change of FRC/TLC, as reduced resting values especially of FRC were observed (while the impairment of MEF remained almost unchanged). As all patients undergoing PEA take part in a six- to eight-week rehabilitation program after surgery, longitudinal changes of lung function capacities due to respiratory training might account for this effect.[17] However, we did not directly measure respiratory muscle strength and the changes in lung volumes under exercise pre and post PEA in our study, which would have provided additional information. In addition, our study failed to draw significant associations between IC and $\dot{V}_D$. However, one can speculate that the increased $\dot{V}_D$ during maximal exercise (due to increased ventilation/perfusion mismatch) influences the ventilatory mechanism and

therefore contributes to the changes in dynamic IC. The lack of association between IC and $\dot{V}_D$ could be attributed to the low resting $\dot{V}_D$ and the relatively small increase in $\dot{V}_D$ observed during exercise in our cohort.[18,19] The association of IC with functional capacity one year post PEA might indicate a contributing role of the baseline mechanical status of the respiratory system to the exercise response one year after PEA. However, further studies are warranted to identify underlying factors one year post PEA such as residual pulmonary microvasculopathy, persistent ventilation/perfusion mismatch, or the muscular status.

In conclusion, operable CTEPH patients without other pulmonary diseases did not show pathophysiological IC alterations observed in PAH patients. However, the impact of respiratory mechanism on exertional dyspnea in CTEPH patients merits further investigation.

Acknowledgments

Conflict of interest

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