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.

Keywords
inspiratory capacity, chronic thromboembolic pulmonary hypertension, pulmonary endarterectomy

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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; inability to perform treadmill cardio-pulmonary exercise testing (CPET); dependency on high-flow supplemental oxygen (≥4 L/min O2); obstructive and/or restrictive pulmonary disease (FEV1/vital capacity ≤70% and/or total lung capacity [TLC] ≤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 (ICrest), every 2 min during incremental exercise load, and at peak exercise (ICpeak). IC maneuvers were performed and analyzed as described previously.\(^9\) ΔIC was defined as the dynamic change of IC from rest to maximum exercise.\(^1\) IC% predicted (pred.) was calculated as described previously.\(^7\) Static hyperinflation was assessed by calculating ICrest as a percentage of TLC (IC/TLCrest).\(^3\) Absolute dead space (VD) was assessed in milliliters and VD at rest (%) was used to assess associations of IC, ICrest, and IC/TLCrest with baseline parameters.

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, ICrest, and IC/TLCrest 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. ICrest and ICpeak showed a slight decrease from baseline at one year post-PEA, but this change was only statistically significant for ICrest 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 ICrest (L and % pred.), ICpeak, ΔIC, and IC/TLCrest showed no significant differences between the subgroups with and without residual PH.

Baseline ICrest and ICpeak (L) were significantly associated with baseline six-minute walking distance (6MWD) (\(r = 0.48\) [\(P = 0.02\)]; \(r = 0.41\) [\(P = 0.05\)]). Baseline ICrest 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 ICrest and ICpeak (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 (%)) | None     | 8 (34.8)          | 0.89\(^*\) |
| I                        |          |                   |             |
| II                       | 6 (26.1) | 8 (34.8)          |             |
| III                      | 14 (60.9) | 7 (30.4)         |             |
| IV                       | 3 (13.0) | None              |             |
| 6MWD (m)                 | 391 ± 1 | 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        |
| NT-proBNP (pg/mL)        | 513 [1445] | 236 [606]      | 0.02\(^†\) |
| ICrest (L)               |          |                   |             |
| VD at rest (%)           | 16.0 ± 3.9 | 17.5 ± 3.6       | 0.20        |
| PASP (mm Hg)             | 60.2 ± 24.4 | 50.3 ± 24.8     | 0.06        |
| FEV1 (% 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        |
| VD/FRC (%)               | 101.4 ± 7.9 | 97.7 ± 11.0    | 0.13        |
| TLC (% pred.)            | 985.3 ± 12.3 | 907.5 ± 32.3  | 0.36        |
| FRC (% pred.)            | 107.6 ± 24.7 | 88.0 ± 41.4    | 0.11        |
| Peak VO2 (mL/min/kg)     | 12.9 ± 3.2 | 15.5 ± 4.5       | 0.009       |
| VT at rest (L)           | 0.28 ± 0.16 | 0.28 ± 0.24    | 0.92        |
| VD at peak (L)           | 0.79 ± 0.35 | 0.66 ± 0.23    | 0.23        |
| VT at peak (L)           | 0.76 ± 0.19 | 0.89 ± 0.37    | 0.25        |
| VT at peak (%)           | 1.92 ± 0.58 | 1.95 ± 0.54    | 0.50        |
| VT at peak (L)           | 3.18 ± 0.9 | 30.9 ± 12.8     | 0.97        |
| VD at peak (%)           | 42.1 ± 16.3 | 36.0 ± 9.9     | 0.26        |
| ΔVCO2 from rest (%)      | 7.1 ± 10.5 | 5.4 ± 15.9      | 0.18        |
| IC at rest (%)           | 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 (%)           | 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)
The preserved ICrest and the moderate dynamic decrease of IC during exercise in CTEPH contrast with previous findings in PAH (reduced ICrest 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 artery 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 PH1,2,7 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 muscles, 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 vascular resistance,17 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 PH1,2,7 identify IC as a parameter related to airway and alveolar mechanics but not pulmonary hemodynamics.

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 ICrest 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 ICrest and the moderate dynamic decrease of IC during exercise in CTEPH contrast with previous findings in PAH (reduced ICrest 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 artery 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 PH1,2,7 identify IC as a parameter related to airway and alveolar mechanics but not pulmonary hemodynamics.
therefore contributes to the changes in dynamic IC. The lack of association between IC and $V_D$ could be attributed to the low resting $V_D$ and the relatively small increase in $V_D$ 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.

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Conflict of interest
The author(s) declare the following conflicts of interest: Dr Richter has received support from United Therapeutics and Bayer Pharma AG, and speaker fees from Actelion, Mundipharma, Roche, and United Therapeutics/OMT. Dr Ghofrani has received consultancy fees from Bayer, Actelion, Pfizer, Merck, GSK, and Novartis; fees for participation in advisory boards from Bayer, Pfizer, GSK, Actelion, and Takeda; lecture fees from Bayer HealthCare, GSK, Actelion, and Encysive/Pfizer; industry-sponsored grants from Bayer HealthCare, Aires, Encysive/Pfizer, and Novartis; and sponsored grants from the German Research Foundation, Excellence Cluster Cardiopulmonary Research, and the German Ministry for Education and Research. Dr Guth speaking fees from Actelion, Bayer. Dr Mayer speaking fees from Actelion, Bayer, GSK, Pfizer. Dr Seeger has received speaker/consultancy fees from Pfizer and Bayer Pharma AG. Dr Gall has received fees from Actelion, AstraZeneca, Bayer, GSK, Janssen-Cilag, Lilly, Novartis, OMT, Pfizer, and United Therapeutics. Ms Wittkämper and Dr Reichenberger have nothing to disclose.

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References
1. Richter MJ, Voswinckel R, Tiede H, et al. Dynamic hyperinflation during exercise in patients with precapillary pulmonary hypertension. *Respir Med* 2012; 106(2): 308–313.
2. Laveneziana P, Humbert M, Godinas L, et al. Inspiratory muscle function, dynamic hyperinflation and exertional dyspnoea in pulmonary arterial hypertension. *Eur Respir J* 2015; 45(5): 1495–1498.
3. Richter MJ, Tiede H, Morty RE, et al. The prognostic significance of inspiratory capacity in pulmonary arterial hypertension. *Respiration* 2014; 88(1): 24–30.
4. Guenette JA, Webb KA and O'Donnell DE. Does dynamic hyperinflation contribute to dyspnoea during exercise in patients with COPD? *Eur Respir J* 2012; 40(2): 322–329.
5. O'Donnell DE. Hyperinflation, dyspnea, and exercise intolerance in chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2006; 3(2): 180–184.
6. O’Donnell DE and Laveneziana P. Physiology and consequences of lung hyperinflation in COPD. *Eur Respir Rev* 2006; 15(100): 61–67.
7. Laveneziana P, Garcia G, Joureau B, et al. Dynamic respiratory mechanics and exertional dyspnea in pulmonary arterial hypertension. *Eur Respir J* 2013; 41(3): 578–587.
8. Taboada D, Pepke-Zaba J, Jenkins DP, et al. Outcome of pulmonary endarterectomy in symptomatic chronic thromboembolic disease. *Eur Respir J* 2014; 44(6): 1635–1645.
9. Johnson BD, Weisman IM, Zeballos RJ, et al. Emerging concepts in the evaluation of ventilatory limitation during exercise: the exercise tidal flow-volume loop. *Chest* 1999; 116(2): 488–503.
10. Cannon JE, Su L, Kiely DG, et al. Dynamic risk stratification of patient long-term outcome after pulmonary endarterectomy: results from the UK National Cohort. *Circulation* 2016; 133(18): 1761–1771.
11. van Kan C, van der Plas MN, Reesink HJ, et al. Hemodynamic and ventilatory responses during exercise in chronic thromboembolic disease. *J Thorac Cardiovasc Surg* 2016; 152(3): 763–771.
12. O’Donnell DE, Lam M and Webb KA. Measurement of symptoms, lung hyperinflation, and endurance during exercise in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; 158(5 Pt 1): 1557–1565.
13. O’Donnell DE, Revill SM and Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 164(5): 770–777.
14. Ferguson GT. Why does the lung hyperinflate? *Proc Am Thorac Soc* 2006; 3(2): 176–179.
15. Papazachou O, Anastasiou-Nana M, Sakellariou D, et al. Pulmonary function at peak exercise in patients with chronic heart failure. *Int J Cardiol* 2007; 118(1): 28–35.
16. Manders E, Bonta PI, Kloek JJ, et al. Reduced force of diaphragm muscle fibers in patients with chronic thromboembolic pulmonary hypertension. *Am J Physiol Lung Cell Mol Physiol* 2016; 311(1): L20–28.
17. Kabitz HJ, Bremer HC, Schwoerer A, et al. The combination of exercise and respiratory training improves respiratory muscle function in pulmonary hypertension. *Lung* 2014; 192(2): 321–328.
18. McCabe C, Deboeck G, Harvey I, et al. Inefficient exercise gas exchange identifies pulmonary hypertension in chronic thromboembolic obstruction following pulmonary embolism. *Thromb Res* 2013; 132(6): 659–665.
19. van der Plas MN, Reesink HJ, Roos CM, et al. Pulmonary endarterectomy improves dyspnea by the relief of dead space ventilation. *Ann Thorac Surg* 2010; 89(2): 347–352.