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# Acute hemodynamic changes by breathing hypoxic and hyperoxic gas mixtures in pulmonary arterial and chronic thromboembolic pulmonary hypertension☆

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ABSTRACT

*Background:* There is insufficient evidence to counsel patients with pulmonary hypertension undergoing altitude or air travel. We thus aimed to study hemodynamic response of patients with pulmonary arterial or chronic thromboembolic pulmonary hypertension (PAH/CTEPH) during changes in inspiratory oxygen partial pressure.
*Methods and results:* Consecutive patients undergoing right heart catheterization had hemodynamic assessments whilst breathing ambient air (normoxia, $FiO_2$ 0.21, at altitude 490 m), nitrogen-enriched air (hypoxia, $FiO_2$ 0.16, simulated altitude 2600 m) and oxygen (hyperoxia, $FiO_2$ 1.0), each for 10 min. Data from patients with PAH/CTEPH with mean pulmonary artery pressure (mPAP) ≥25 mmHg, pulmonary artery wedge pressure ≤15 mmHg, were compared to data from controls, mPAP <20 mmHg.
28 PAH/CTEPH-patients, 15 women, median age (quartiles) 62y (49;73), mPAP 35 mmHg (31;44), $PaO_2$ 7.1 kPa (6.8;9.3) and 16 controls, 12 women, 60y (52;69), mPAP 18 mmHg (16;18), $PaO_2$ 9.5 kPa (8.5;10.6) were included. Hypoxia reduced the $PaO_2$ in PAH/CTEPH-patients by median of 2.3 kPa, in controls by 3.3 kPa, difference (95%CI) in change 1.0 (0.02 to 1.9), $p < 0.05$. Corresponding changes in pulmonary vascular resistance, mPAP and cardiac output were nonsignificant in both groups. Hyperoxia decreased mPAP in PAH/CTEPH-patients by 4 mmHg (2 to 6), in controls by 2 mmHg (0 to 3), difference in change 3 mmHg (0 to 5), $p < 0.05$.
*Conclusions:* In patients with PAH/CTEPH, very short-term exposure to moderate hypoxia similar to 2600 m altitude or during commercial air travel did not deteriorate hemodynamics. These results encourage studying the response of PAH/CTEPH during daytrips to the mountain or air travel.


## 1. Introduction

Worldwide, millions of people are travelling to mountain areas or undergo air travel exposing themselves to hypobaric hypoxia. In healthy individuals, moderate hypoxia induces an elevation of pulmonary artery pressure (PAP) that is generally well tolerated. In patients with preexisting pulmonary hypertension (PH) there have been concerns that exposure to even mild hypoxia might induce an excessive further rise in PAP leading to a clinically relevant hemodynamic decompensation with dyspnea, risk of syncope and right heart failure although this has not been conclusively studied. According to current guidelines, patients with PH in NYHA functional classes III/IV and/or $PaO_2$ ≤ 60 mmHg (≤8 kPa) at sea level should avoid altitudes above 2000 m without supplemental oxygen, but this recommendation is based on expert opinion in lack of studies. [1] Some experts recommend to perform a hypoxia simulation test to counsel patients with respiratory conditions with an oxygen saturation <95% at sea level for fitness for flight. [2] However, the contribution of such testing in preventing adverse events during air travel or altitude exposure has not been validated [3, 4].

Pulmonary vascular remodeling is one of the hallmarks of PH that results in increased pulmonary vascular resistance (PVR) and, hence, elevated PAP. PH is associated with arterial hypoxemia, especially during exercise, due to a decreased cardiac output (CO) with low mixed venous oxygen saturation ($SmvO_2$) and inefficiency of pulmonary gas exchange. PH-associated hypoxemia may be a major contributor to a vicious cycle of hypoxic pulmonary vasoconstriction (HPV) [5] that promotes endothelial dysfunction and further worsening of pulmonary hemodynamics. [6] HPV is defined as a homeostatic mechanism triggered via hypoxia, where pulmonary arteries constrict to optimate the ventilation/perfusion matching as well as the systemic oxygen delivery. [7] Unfortunately, data on the acute effects of exposure to

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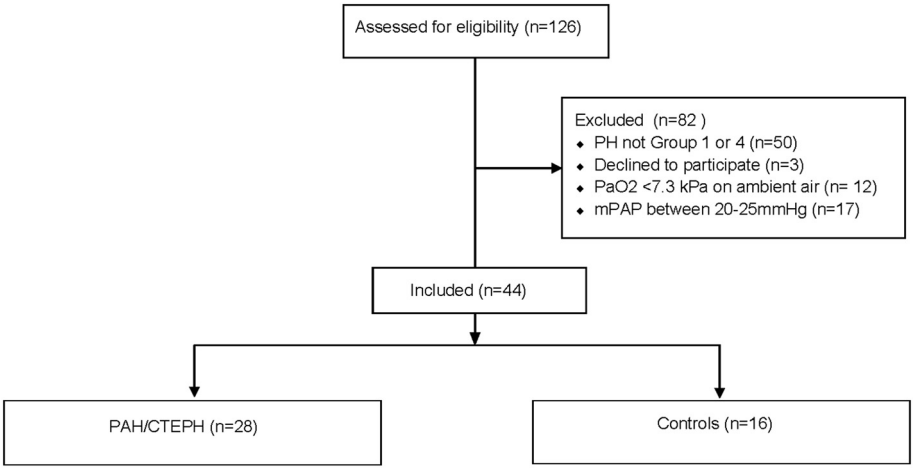


**Fig. 1.** Patient flow.

hypoxia in patients with PH are scant. It is therefore difficult to counsel PH patients wishing to undergo mountain or air travel.

To address this point, the current study was designed to quantify the hemodynamic response to an exposure to moderate hypoxia similar to that encountered during commercial air travel or at moderate altitude in patients with precapillary PH. We tested the hypothesis that hypoxia would induce a further rise in mPAP or PVR in these patients. In addition, we intended to evaluate potential predictors of an excessive rise in mPAP and PVR during exposure to hypoxia. Since equipment for hypoxic testing is not widely available we investigated whether a pronounced pulmonary vasoreactivity to hyperoxia, i.e., 100% oxygen breathing that can be more conveniently applied than hypoxia, would identify PH patients with a marked response to hypoxia.

## 2. Methods

### 2.1. Study design and participants

This case control study compared acute hemodynamic effects of breathing hypoxic air and oxygen in patients with PAH/CTEPH and dyspneic controls without PH undergoing RHC at the PH-Center, University Hospital Zurich (altitude 490 m, mean barometric pressure 730 mmHg).

Patients were included if they were diagnosed with PAH or CTEPH according to guidelines if mPAP was ≥25 mmHg and pulmonary artery wedge pressure (PAWP) ≤15 mmHg. [8] Patients were excluded if they were severely hypoxemic ($PaO_2 \leq 7.3$ kPa) under ambient air, had PAWP >15 mmHg, relevant lung disease ($FEV_1$ or FVC < 60%), i.e. PH groups other than I and IV. [9] Controls were dyspneic patients undergoing RHC with a mPAP <20 mmHg and PAWP <15 mmHg. [1]

Participants gave written informed consent for RHC and have their data registered. The study was approved by the local ethics committee (KEK: 2016-02136) and registered (clinicaltrials.gov, NCT03195959).

### 2.2. Interventions and assessments

Supine RHC was performed from a jugular venous access using a balloon-tipped, triple-lumen, fluid-filled 7.5F Swan-Ganz catheter and Edwards Vigilance Monitor for CO-measurements by thermodilution. Zero reference was set at the level of the left atrium in mid-axillary line. [10, 11] Baseline measurements were obtained during stable conditions at rest on ambient air ($FiO_2$ 0.21). Subsequently, patients were exposed to hypoxia ($FiO_2$ 0.16, altitude equivalent 2600 m) via a tight-fitting mouthpiece simulated by a SMTEC AltiTrainer for 10 min. [12] Following a 10-minute wash-out period, patients were exposed to hyperoxia (oxygen breathing, $FiO_2$ 1.0) for 10 min, administered via a non-rebreathing valve from a reservoir bag (AmbuSPUR II, Synmedic AG). The following

**Table 1**
Baseline characteristics.

| | PAH/CTEPH patients | Controls |
|---|---|---|
| Subjects, n (females) | 28 (15) | 16 (12) |
| Pulmonary arterial hypertension, n (%) | 13 (46) | – |
| - Idiopathic | 6 (21) | |
| - Associated | 7 (25) | |
| Chronic thromboembolic pulmonary hypertension | 15 (54) | |
| PH-targeted medication, n (%) | 5 (18) | – |
| - Phosphodiesterase 5 inhibitor | 3 (11) | |
| - Endothelin-receptor antagonist | 4 (14) | |
| - Soluble guanylate cyclase stimulator | 1 (4) | |
| Underlying disease in control patients, n (%) | | |
| - Scleroderma | | 5 (31) |
| - No residual PH after pulmonary endarterectomy | | 3 (19) |
| - Asthma | | 3 (19) |
| - Chronic thromboembolic disease without pulmonary hypertension | | 1 (6) |
| - Hyperventilation | | 2 (12.5) |
| - Unknown | | 2 (12.5) |
| NYHA functional class (I/II/III/IV) | 4/16/8/0 | 5/4/6/1 |
| Age, y | 62 (49; 73) | 60 (52; 69) |
| Body mass index, $kg/m^2$ | 25.8 (22.4; 28.9) | 24.5 (22.7; 27.2) |
| 6-minute walk distance, m | 509 (416; 602) | 480 (450; 574) |
| Oxygen saturation ($SpO_2$) at rest, % | 97 (95; 98) | 97 (96; 98) |
| $SpO_2$ at end of 6 min walk, % | 90 (83; 95) | 93 (91; 97)* |
| NT-pro-BNP, ng/l | 232 (107; 1142) | 92 (52; 161)* |
| Hemoglobin, g/dl | 14.8 (13.7; 15.2) | 14.2 (12.7; 14.7) |

* $p < 0.05$ between PH and control group. Data are given as median (quartiles); PEA = pulmonary endarterectomy; NT-pro-BNP = N-terminal-pro brain natriuretic peptide.

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