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Shareable abstract (@ERSpublications)
Acetazolamide prophylaxis lowers pulmonary artery pressure and improves oxygenation in patients with COPD travelling to altitude. This drug might be a useful treatment for the growing COPD population wanting to participate in mountain and aeroplane travel. https://bit.ly/3eNH9sk

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Abstract

Background COPD may predispose to symptomatic pulmonary hypertension at high altitude. We investigated haemodynamic changes in lowlanders with COPD ascending to 3100 m and evaluated whether preventive acetazolamide treatment would attenuate the altitude-induced increase in pulmonary artery pressure (PAP).

Methods In this randomised, placebo-controlled, double-blind, parallel-group trial, patients with COPD Global Initiative for Chronic Obstructive Lung Disease grades 2–3 who were living <800 m and had peripheral oxygen saturation (S_{pO_2}) >92% and arterial carbon dioxide tension <6 kPa were randomised to receive either acetazolamide (125–250 mg·day^{-1}) or placebo capsules, starting 24 h before ascent from 760 m and during a 2-day stay at 3100 m. Echocardiography, pulse oximetry and clinical assessments were performed at 760 m and after the first night at 3100 m. Primary outcome was PAP assessed by tricuspid regurgitation pressure gradient (TRPG).

Results 112 patients (68% men, mean±SD age 59±8 years, forced expiratory volume in 1 s (FEV_1) 61±12% pred, S_{pO_2} 95±2%) were included. Mean±SD TRPG increased from 22±7 to 30±10 mmHg in 54 patients allocated to placebo and from 20±5 to 24±7 mmHg in 58 patients allocated to acetazolamide (both p<0.05) resulting in a mean (95% CI) treatment effect of −5 (−9 to −1) mmHg (p=0.015). In patients assigned to placebo at 760/3100 m, mean±SD S_{pO_2} was 95±2%/88±3%; in the acetazolamide group, the respective values were 94±2%/90±3% (both p<0.05), resulting in a treatment effect of +2 (1 to 3)% (p=0.001).

Conclusions In lowlanders with COPD travelling to 3100 m, preventive acetazolamide treatment attenuated the altitude-induced rise in PAP and improved oxygenation.

Introduction

An increasing number of people travel to high altitudes for professional and recreational activities, including many tourists with pre-existing cardiopulmonary diseases. Considering the globally high prevalence of COPD, it is to be expected that a high number of travellers to the many cities and areas located at high altitude worldwide are COPD patients [1]. COPD patients are at higher risk of experiencing altitude-related adverse health effects (ARAHE), but few studies in COPD patients exposed to high altitude report potential implications for health and preventive strategies [2–11]. Evidence of an altitude-associated increase in mortality in COPD underscores the need for research in this field [12, 13].

COPD is the most common chronic respiratory disease worldwide [14], with a reported prevalence of ~15% of the general population. It is characterised by chronic airflow obstruction with airway inflammation and remodelling, and parenchymal destruction of the lung in some patients. Cardinal symptoms of COPD are chronic productive cough and dyspnoea on exertion with limited exercise performance related to airflow obstruction, dynamic hyperinflation, exercise-induced hypoxaemia and increase in pulmonary artery pressure (PAP) [15]. Pulmonary hypertension is a common complication in COPD with increasing prevalence with severity of the emphysematous lung destruction and airflow limitation due to increased hypoxic pulmonary vasoconstriction and loss of the pulmonary capillary bed [16]. Exercise-induced pulmonary hypertension usually precedes resting pulmonary hypertension and a sustained PAP elevation may ultimately lead to right ventricular (RV) failure and reduced survival [16–18].

The structural alterations and functional abnormalities of pulmonary vessels resulting from hypoxic pulmonary vasoconstriction in patients with COPD might increase the risk of developing symptomatic pulmonary hypertension when travelling to a hypoxic environment at altitude. In prior studies, we found that generally, patients with COPD tolerated acute exposure to moderate altitude (2590–3100 m) well, although they suffered from a major reduction in exercise performance, pronounced dyspnoea, elevated PAP and other ARAHE, including acute mountain sickness (AMS), and pathological cardiac repolarisation [6, 9, 10, 19]. Therefore, effective means to prevent these limitations would be desirable.

The carbonic anhydrase inhibitor acetazolamide improves oxygenation through stimulation of ventilation by induction of metabolic acidosis *via* renal bicarbonate excretion, an effect that is especially pronounced in hypoxic environments, and proven to prevent AMS in healthy mountaineers [20, 21]. In addition, it has been suggested that acetazolamide may mitigate the excessive rise in PAP observed in individuals susceptible to high-altitude pulmonary oedema when exposed to hypoxia [22–24]. Furthermore, acetazolamide has been used as treatment in patients with mild-to-moderate COPD to increase ventilation and thus improve oxygenation and reduce hypercapnia; no benefit on duration and success of weaning from mechanical ventilation in hospitalised COPD patients has been found [25]. In addition, according to *in vitro*, animal and *in vivo* studies, acetazolamide may reveal a direct pulmonary vasodilator effect, especially in hypoxic conditions [26–30].

The purpose of the current study was to evaluate whether preventive treatment with acetazolamide reduces the hypoxia-induced rise in PAP and ameliorates further echocardiographic indices of cardiac function in lowlanders with COPD travelling to 3100 m.

Methods

Study design and participants

This randomised, placebo-controlled, double-blinded, parallel-group trial took place from May 2017 to August 2018 at the National Center for Cardiology and Internal Medicine (NCCIM) (Bishkek, Kyrgyz Republic; 760 m), and the High-Altitude Clinic Tuja-Ashu (Tuja-Ashu, Kyrgyz Republic; 3100 m). The trial was approved by the ethics committee of the NCCIM (08–2016) and registered at www.clinicaltrials.gov (NCT03173508). Participants gave written, informed consent.

Patients diagnosed with COPD according the Global Initiative for Chronic Obstructive Lung Disease (GOLD) report (grade 2–3) [14], with post-bronchodilator forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) <0.7 and FEV_1 40–80% predicted, of any gender, aged 18–75 years, living <800 m were recruited among outpatients of the NCCIM and surrounding hospitals. Patients with severe hypoxaemia (peripheral oxygen saturation (S_{pO_2}) <92%), hypercapnia (arterial carbon dioxide tension (P_{aCO_2}) >6 kPa), recent exacerbation, severe or unstable comorbidities and allergy to sulfonamides were excluded.

During the same expedition, comprehensive evaluation of ARAHE and other pathophysiological measures were obtained and are subjects of a separate publication [11]. In this trial, patients were monitored using pulse oximetry during the day and at night and when severe hypoxaemia (defined as S_{pO_2} ⩽75% for ⩾15 min or ⩽80% for ⩾30 min) occurred, oxygen was given and the patient evacuated to the lowlands for safety reasons. Apart from patient characteristics, the data presented herein have not been published previously.

Interventions

After undergoing baseline evaluations at the NCCIM, Bishkek (760 m), patients travelled 3–5 h by minibus to a high-altitude clinic at 3100 m and stayed there for 2 days. Acetazolamide (125–250 mg) or

identical-looking placebo capsules were given, starting 24 h before ascent to and during the stay at 3100 m under supervision of investigators.

Assessments

Medical history was obtained, clinical examination performed, and vital parameters, S_{pO_2} at rest and 6-min walk distance (6MWD) were measured at each altitude. Echocardiography and arterial blood gases (RapidPoint 405; Siemens, Zurich, Switzerland) were assessed at 760 m before treatment initiation and on the day after the first night at 3100 m. Oxygen content of arterial blood (C_{aO_2}) was calculated by haemoglobin × arterial oxygen saturation × 1.34 + (arterial oxygen tension × 0.003). Oxygen delivery was calculated by cardiac output × C_{aO_2}.

Echocardiographic recordings were performed according to current guidelines (CX50; Philips Respironics, Zofingen, Switzerland) [31]. To assess PAP, maximal tricuspid regurgitation pressure gradient (TRPG) was calculated from maximal tricuspid regurgitation velocity (TRV) obtained with continuous-wave Doppler using the modified Bernoulli equation: Δpressure = 4 × TRVmax^2. Right atrial pressure (RAP) was estimated by the diameter of the inferior vena cava and systolic (s)PAP calculated as TRPG + RAP. Mean (m)PAP was calculated from sPAP as 0.61 × sPAP + 2 mmHg [32]. Areas of the right atrium and RV were manually traced and fractional area change calculated. Tricuspid annular plane systolic excursion (TAPSE) was measured by M-mode and the RV free wall velocity using tissue Doppler. Pulmonary artery wedge pressure (PAWP) was calculated as 1.24 × E/e′ (ratio between early mitral inflow velocity and mitral annular early diastolic velocity) + 1.9 [33]. Cardiac output (CO) was calculated using the left ventricular outflow tract velocity time integral. Pulmonary vascular resistance (PVR) ((mPAP − PAWP)/CO), total pulmonary resistance (mPAP/CO) and a pressure flow ratio (TRPG/CO) were calculated. Values of PVR adjusted for haematocrit were determined according to the formula derived by Whittaker and Winton [34, 35]. To this end, PVR was computed for a standard haematocrit of 0.45 as R_0 (45%) = R_0 (haematocrit) × ((1-φ$^{1/3}$)/0.234) [36]. RV–arterial coupling was assessed by TAPSE/sPAP [37]. Stroke volume was calculated as CO/heart rate. Left heart function was assessed according to the current guidelines [31]. B-lines as indices of pulmonary interstitial fluid accumulation were assessed as described previously [38] in a supine position from the second to fourth or fifth intercostal space (left and right hemithorax, respectively) down the parasternal, mid-clavicular, anterior axillary and mid-axillary lines, resulting in 28 total windows of interest (left n=12, right n=16). A B-line was defined as one echogenic, continuous, wedge-shaped signal arising from the uninterrupted pleural interface with a narrow origin in the near field of the image [39]. The number of B-lines was counted for each lung field and totalled.

Randomisation and blinding

Participants were randomised to acetazolamide or placebo treatment with a 1:1 allocation as per computer-generated schedule minimising for age (18–50 and 51–75 years), gender and FEV_1 (40–59% pred and 60–80% pred). An independent pharmacist prepared blister packs containing active and identical-looking placebo capsules labelled with concealed codes. Participants and investigators were blinded to the administered drug until the conclusion of the data analysis.

Primary outcome

Difference in the altitude-induced PAP increase assessed by the TRPG between patients randomised to acetazolamide *versus* placebo.

Secondary outcomes

Vital parameters and S_{pO_2} at rest, 6MWD and blood gas analysis in patients randomised to acetazolamide *versus* placebo and the differences between low and high altitudes were measured.

Data analysis

Data analysis and statistics were performed per protocol according to the data analysis plan and blinding was maintained throughout the process. Data were checked for completeness and multiple imputation with pattern-mixture model by group (low altitude: all participants; high altitude: drug 1 and drug 2) was performed for the main outcome. Data are summarised by numbers and proportions, mean±SD or 95% CI. Treatment effects were assessed by linear mixed-regression models with treatment and altitude as predictors. Analysis of secondary outcomes was performed in the per-protocol population with all available data. The data analyses were conducted with Stata/SE 15. Statistical significance level was set at $p<0.05$ or 95% CI not crossing the zero value.

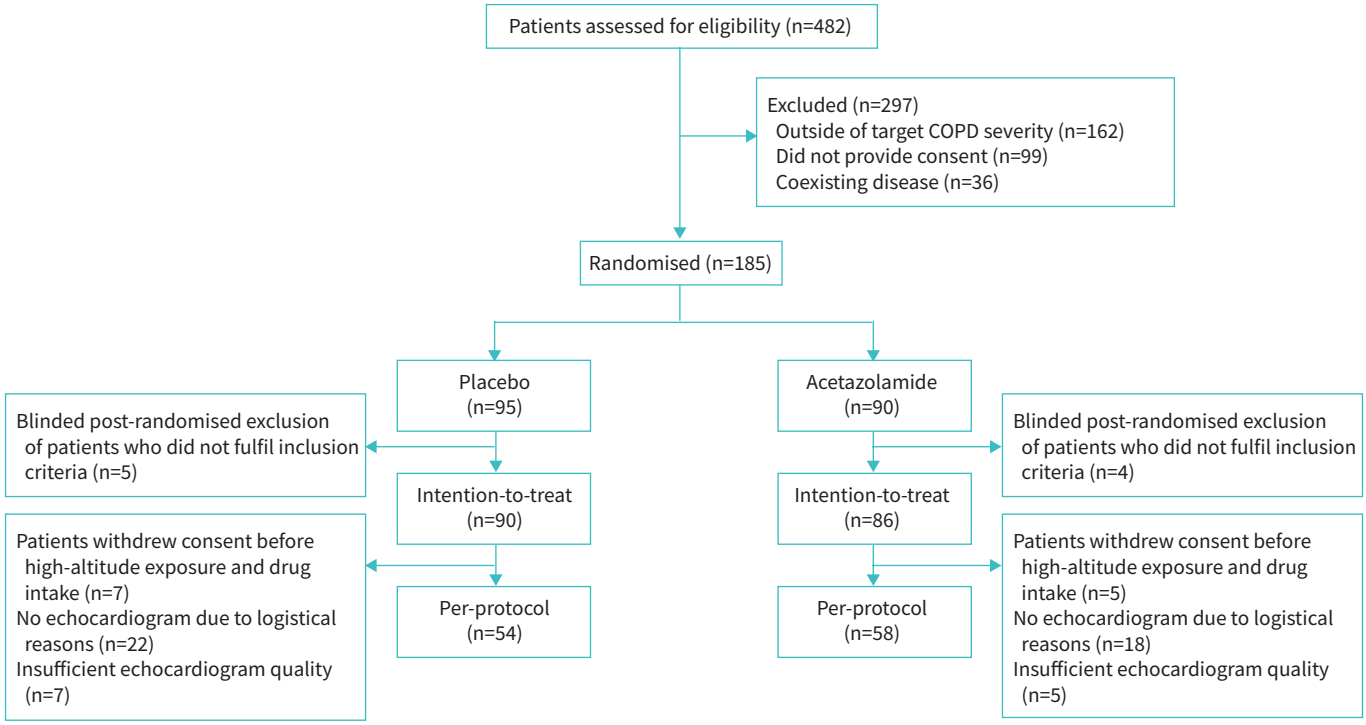

FIGURE 1 Patient flow through the study.

Results

Out of 176 patients representing the intention-to-treat population, 112 patients (68% men; 54 allocated to the placebo and 58 allocated to the acetazolamide group) were included in the per-protocol analysis of echocardiography data. In 40 patients, logistical limitations prevented echocardiography, and in 12 patients, echocardiography of sufficient quality was not available (figure 1). Table 1 shows the subjects' baseline characteristics and medication.

TABLE 1 Participant characteristics

	Placebo	Acetazolamide
Participants	54	58
Men	38 (70)	38 (66)
Age (years)	58.5±9.1	60.0±7.2
Body mass index (kg·m^{-2})	26.5±4.5	27.1±3.7
FEV_1 (% predicted)	61±13	61±11
FEV_1/FVC	59±8	60±9
Cigarette smoking history (pack-years)	15±25	11±16
Medication		
Oral steroids	1 (2)	0 (0)
Inhaled β-adrenergics	10 (19)	10 (17)
Inhaled anticholinergics	12 (22)	11 (19)
Inhaled steroids	8 (15)	8 (14)
Antihypertensive drugs	7 (13)	7 (12)
β-blockers	1 (2)	1 (2)
Aspirin	7 (13)	8 (14)

Data are presented as n, n (%) or mean±SD. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity.

TABLE 2 Echocardiography indices of pulmonary artery pressure and the right heart

	Placebo		Acetazolamide		Treatment effect	
	760 m	3100 m	760 m	3100 m	Between-group difference in altitude-induced change (95% CI)	p-value
Pulmonary artery pressure						
TRPG (mmHg)	22±7	30±10*	20±5	24±7*,#	−5 (−9 to −1)	0.015
Tricuspid regurgitation velocity (m·s^{-1})	2.3±0.3	2.7±0.4*	2.2±0.3	2.4±0.3*,#	−0.2 (−0.4 to −0.0)	0.033
Systolic pulmonary artery pressure (mmHg)	25±6	34±10*	23±6	28±7*,#	−4 (−8 to −0)	0.039
Mean pulmonary artery pressure (mmHg)	18±4	23±6*	16±4	19±4*,#	−2 (−5 to −0)	0.039
Haemodynamics						
Heart rate (beats·min^{-1})	69±11	76±11*	71±11	74±10	−5 (−8 to −1)	0.006
Stroke volume (mL)	66±12	65±13	66±16	61±13*	−5 (−10 to 1)	0.079
Stroke volume index (mL·m^{-2})	38±6	37±5	37±8	33±6*,#	−2.6 (−5.4 to 0.2)	0.068
CO (L·min^{-1})	4.5±1.1	4.9±1.0*	4.7±1.2	4.4±0.9#	−0.6 (−1.0 to −0.2)	0.003
Cardiac index (L·min^{-1}·m^{-2})	2.6±0.6	2.8±0.5*	2.5±0.7	2.4±0.4#	−0.3 (−0.6 to −0.1)	0.010
TRPG/CO (mmHg·L^{-1}·min)	5.1±1.6	6.4±2.2*	4.4±1.7	5.6±2.0*	−0.0 (−1.0 to 0.9)	0.959
Total pulmonary resistance (mPAP/CO) (Wood Units)	4.3±1.1	4.7±1.5*	3.6±1.2¶	4.6 1.4*	−0.3 (−0.9 to 0.4)	0.430
PVR (Wood Units)	1.6±1.0	2.3±1.4*	1.0±1.0¶	1.9±1.3*	−0.0 (−0.7 to 0.6)	0.881
PVR corrected for haematocrit (Wood Units)	1.7±1.2	2.3±1.4*	1.1±1.1¶	2.1±1.6*	−0.2 (−0.9 to 0.6)	0.660
PAWP (mmHg)	11±4	11±3	11±2	11±3	0 (−1 to 1)	0.549
Right ventricle and right atrium indices						
Right atrial pressure (mmHg)	4±2	4±2	4±2	4±2	−0 (−1 to 1)	0.908
Right atrial area (cm^2)	14±4	14±3	14±3	14±3	0 (−1 to 1)	0.863
Right ventricle end-diastolic area A4C (cm^2)	18±4	18±3	18±5	17±4	−1 (−3 to 1)	0.326
Right ventricle end-systolic area A4C (cm^2)	11±3	11±3	11±3	10±2	0 (−1 to 1)	0.662
Right ventricle fractional area change (%)	42±7	42±8	41±7	38±8#	−3 (−7 to 1)	0.150
Eccentricity index end-diastolic	1.0±0.0	1.0±0.1	1.0±0.1	1.0±0.1	0.0 (−0.0 to 0.0)	0.686
Eccentricity index end-systolic	1.0±0.1	1.0±0.1	1.0±0.2	1.0±0.1	0.0 (−0.0 to 0.0)	0.610
Right ventricle anterior wall diameter (cm)	0.4±0.1	0.4±0.1	0.4±0.1	0.4±0.1	0.0 (−0.0 to 0.0)	0.688
Right ventricle diameter end-diastolic (cm)	3.5±0.6	3.5±0.5	3.4±0.6	3.3±0.5	−0.1 (−0.4 to 0.1)	0.282
Right ventricle/left ventricle ratio	0.8±0.1	0.8±0.4	0.8±0.1	0.8±0.1	−0.1 (−0.2 to 0.0)	0.187
TAPSE (cm)	2.1±0.4	2.1±0.5	2.1±0.3	2.0±0.3*,#	0.1 (−0.2 to 0.1)	0.258
TDI tricuspid annular systolic velocity (cm·s^{-1})	12.4±2.7	13.7±3.2*	12.9±2.6	12.7±2.1#	−1.2 (−2.4 to −0.7)	<0.001
TAPSE/sPAP (mm·mmHg^{-1})	0.9±0.3	0.7±0.3*	1.0±0.3	0.7±0.2*,#	−0.0 (−0.1 to 0.1)	0.421
Extravascular lung water by B-lines						
B-lines	1.0±1.5	2.0±3.1	0.4±1.1	1.3±1.9*	−0.1 (−1.5 to 1.2)	0.859

Data are presented as mean±SD or mean (95% CI), unless otherwise stated. TRPG: tricuspid regurgitation pressure gradient; CO: cardiac output; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; PAWP: pulmonary artery wedge pressure; TAPSE: tricuspid annular plane systolic excursion; TDI: tissue Doppler image; sPAP: systolic pulmonary artery pressure. *: p<0.05 changes from low (760 m) to high (3100 m) altitude; #: p<0.05 differences between placebo and acetazolamide at 3100 m; ¶: p<0.05 differences between placebo and acetazolamide at 760 m.

Primary outcome

In both treatment arms, the TRPG increased significantly between 760 m and 3100 m, with a mitigation of the altitude-induced increase in the acetazolamide compared to the placebo group (mean difference −5 (95% CI −9 to −1) mmHg; treatment effect p=0.015) (table 2, figures 2 and 3).

Echocardiographic parameters

Echocardiographic parameters of the right and left heart are displayed in tables 2 and 3, respectively. While stroke volume was sustained in the placebo group, the acetazolamide group showed a reduced stroke volume at altitude. At altitude, CO was increased in the placebo and unchanged in the acetazolamide group, resulting in a difference of −0.6 (95% CI −1.0 to −0.2) L·min^{-1} (p=0.003). PVR, haematocrit-corrected PVR and total pulmonary resistance increased in both groups at altitude without treatment effect of acetazolamide. Lower pulmonary resistances were found at low altitude in the acetazolamide group compared to the placebo group. Right ventricular to pulmonary arterial coupling, estimated by TAPSE/sPAP, showed similar deterioration in both treatment arms without treatment effect. Tricuspid annular systolic velocity (tissue Doppler image) increased at altitude in the placebo group, but not the acetazolamide group. Extravascular lung water assessed by B-lines increased minimally but significantly in the acetazolamide group; however, no treatment effect at altitude was observed.

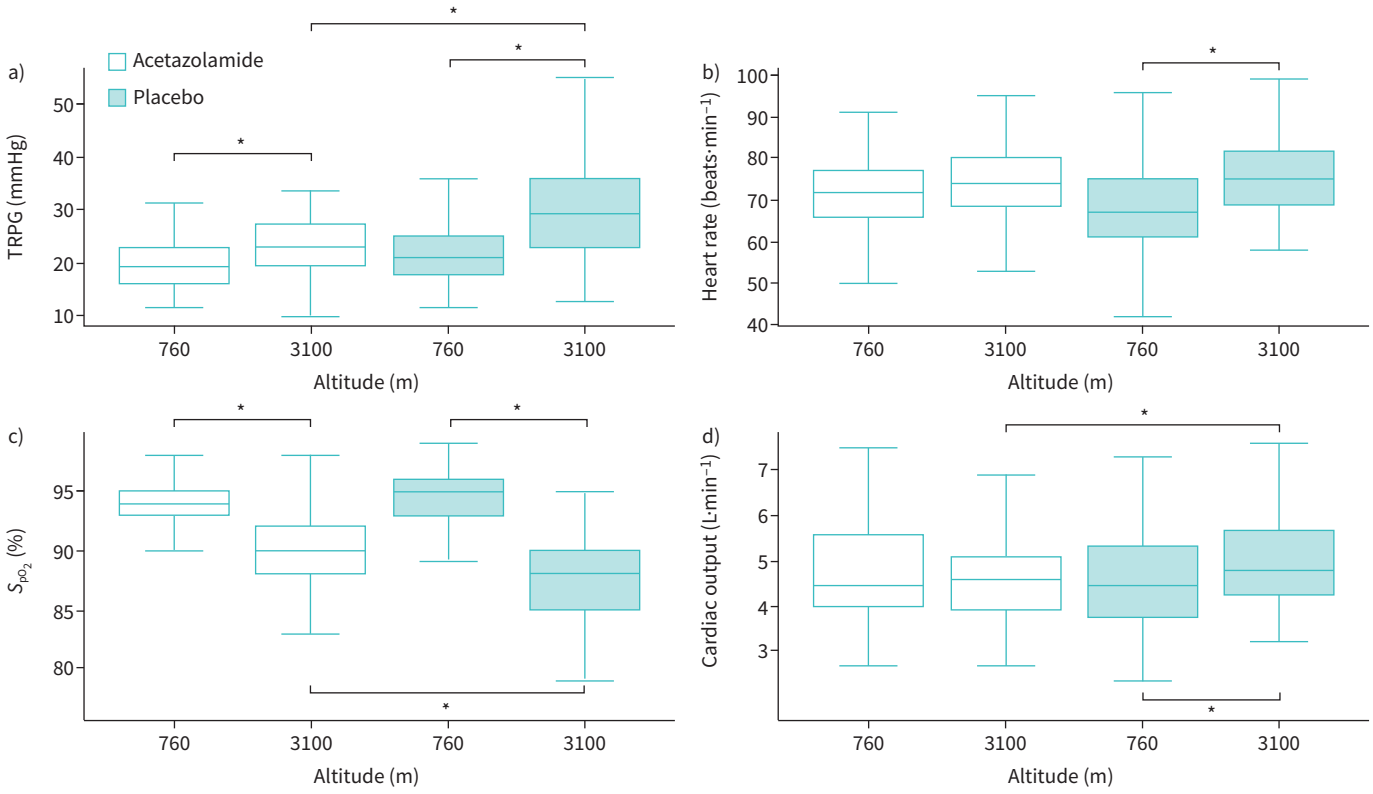

FIGURE 2 a) Tricuspid regurgitation pressure gradient (TRPG), b) heart rate, c) peripheral oxygen saturation (S_{pO_2}) and d) cardiac output in the acetazolamide and placebo groups at low altitude (760 m) and high altitude (3100 m). Boxplots show medians, quartiles and 1.5× the interquartile range. *: p<0.05.

Physiological measurements and arterial blood gas analysis

Clinical parameters and arterial blood gas analysis are presented in table 4. From low to high altitude, the heart rate increased significantly in the placebo group, but not the acetazolamide group, resulting in a mean (95% CI) treatment-induced reduction of heart rate increase by −5 (−8 to −1) beats·min^{-1} (p=0.006). Similarly, the altitude-induced increase in blood pressure was attenuated by acetazolamide, resulting in treatment effects for mean (95% CI) systolic (−10 mmHg, −15 to −5 mmHg; p<0.001) and diastolic blood pressure (−5 mmHg, −9 to −1 mmHg; p=0.024). Altitude exposure was associated with a reduced S_{pO_2} at rest and at peak 6MWD, the acetazolamide group showed a significant smaller drop compared to placebo, resulting in treatment effects of resting S_{pO_2} +2% (1 to 3%; p=0.001) and end-exercise S_{pO_2} +3% (1 to 5%; p=0.002). 18 (33%) patients in the placebo group and four (7%) in the acetazolamide group received nocturnal oxygen supplementation (3 L·min^{-1}) according to the pre-defined safety criteria. Arterial oxygen content was significantly higher in the acetazolamide group. With an increase of heart rate and CO in the placebo group, oxygen delivery remained the same in both treatment arms. Arterial blood gas analysis revealed a lower P_{aCO_2} in both groups at altitude. In the acetazolamide group, haematocrit and haemoglobin were increased at altitude. The P_{aCO_2}, bicarbonate and pH were significantly lower in the acetazolamide group, indicating bicarbonate excretion with metabolic acidosis leading to compensatory hyperventilation.

Oxygenation and pulmonary artery pressure

Correlation between S_{pO_2} and TRPG demonstrated a different regression line for placebo and acetazolamide (figure 4), demonstrating a study drug mechanism independent of the improvement of oxygenation.

Discussion

This randomised, placebo-controlled, double-blind trial shows for the first time that preventive treatment with acetazolamide significantly attenuates the altitude-induced increase in PAP in patients with moderate-to-severe COPD after the first night in hypobaric hypoxia at 3100 m *versus* placebo.

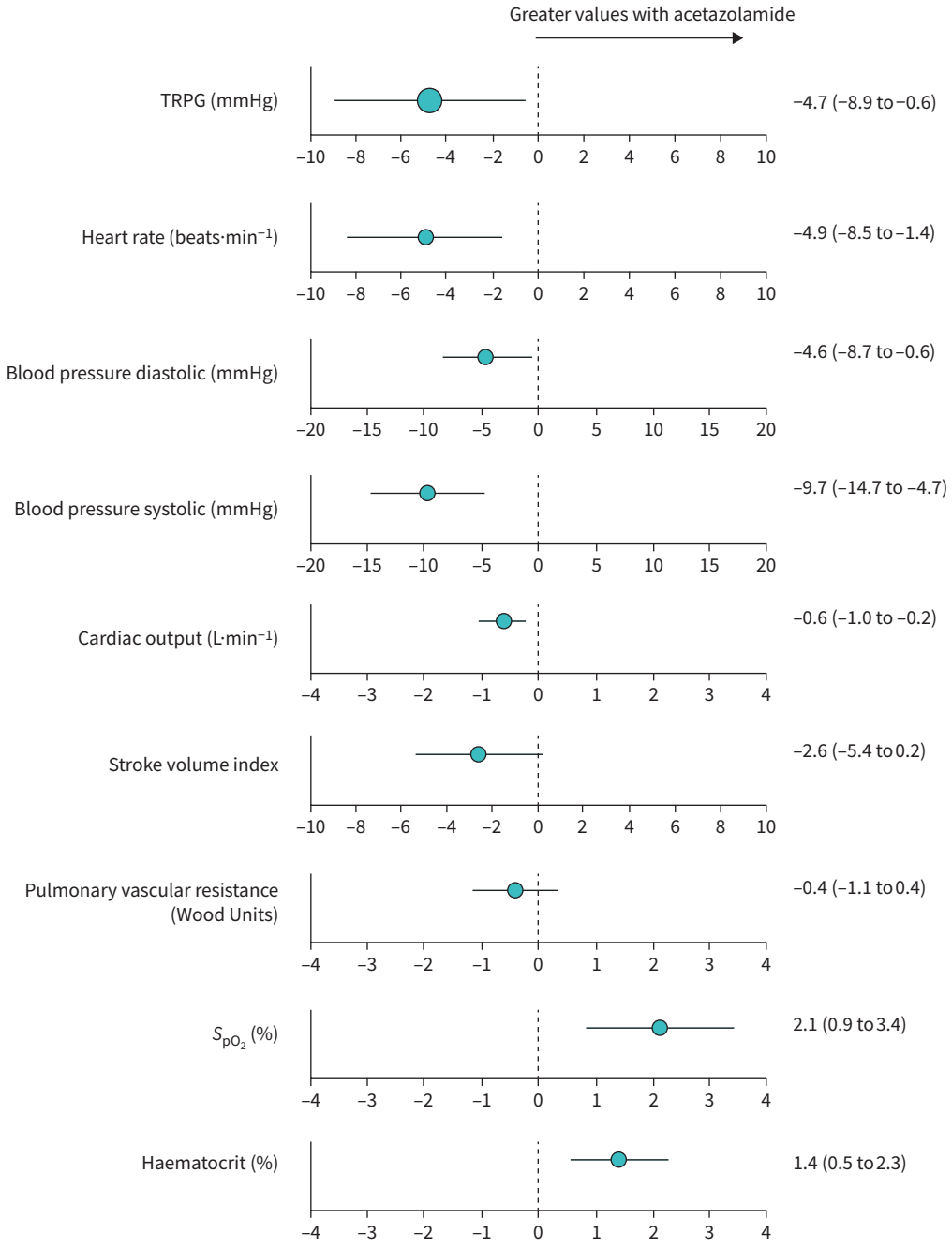

FIGURE 3 Mean difference between groups in altitude-induced changes (95% CI) in tricuspid regurgitation pressure gradient (TRPG), heart rate, blood pressure, cardiac output, stroke volume index, pulmonary vascular resistance, peripheral oxygen saturation (S_{pO_2}) and haematocrit.

Furthermore, acetazolamide improved S_{pO_2} at rest and end-exercise and oxygen content and diminished the increase in heart rate and CO.

In this large cohort of patients with moderate-to-severe COPD travelling to altitude, hypoxic pulmonary vasoconstriction upon exposure to 3100 m induced the well-described increase in PAP along with a rise in PVR [40]. This effect has been demonstrated previously in patients with mild-to-moderate COPD upon acute exposure to moderate-to-high altitude [9], and has been proven to be mitigated by preventive treatment with dexamethasone, a corticosteroid also used in treatment of ARAHE in healthy mountaineers [8, 41, 42]. In the present study, preventive treatment with the carbonic anhydrase inhibitor acetazolamide

TABLE 3 Echocardiographic indices of the left heart function and morphology

	Placebo		Acetazolamide		Treatment effect	
	760 m	3100 m	760 m	3100 m	Between-group difference in altitude-induced change (95% CI)	p-value
Participants	54		58			
Ejection fraction (biplane method) (%)	60±4	60±5	60±6	59±5*	−2 (−4 to −0)	0.045
Interventricular septum diameter (end-diastolic) (cm)	0.9±0.2	0.9±0.2	0.8±0.2	0.8±0.2#	0.0 (−0.2 to 0.2)	0.758
Left ventricle internal dimension end-diastolic (cm)	4.7±0.4	4.7±0.5	4.7±0.5	4.6±0.5	0.0 (−0.1 to 0.1)	0.714
Left ventricle internal dimension end-systolic (cm)	2.9±0.4	2.8±0.4*	2.8±0.5	2.9±0.5	0.0 (−0.2 to 0.3)	0.728
Left ventricle posterior wall end-diastolic (cm)	0.8±0.2	0.9±0.2	0.8±0.2	0.8±0.2	−0.0 (−0.1 to 0.0)	0.398
Aortic diameter (cm)	3.2±0.4	3.2±0.3	3.2±0.4	3.2±0.4	−0.0 (−0.2 to 0.1)	0.791
Left ventricular outflow tract velocity time integral (cm)	19.8±3.7	19.9±3.6	19.8±3.8	18.1±3.0*,#	−1.8 (−3.0 to −0.5)	0.005
Mitral E/A	1.0±0.4	0.9±0.3*	1.0±0.3	0.9±0.3*	0.0 (−0.1 to 0.1)	0.942
Left atrial volume index (cm^2)	23.4±7.2	21.1±5.6*	20.2±5.6¶	18.8±5.7#	1.4 (−1.2 to 4.0)	0.297
Lateral mitral annulus e′ wave ($cm \cdot s^{-1}$)	11.7±10.2	10.7±3.2	10.2±2.4	10.3±2.8	1.1 (−1.8 to 3.9)	0.468
Septal mitral annulus e′ wave ($cm \cdot s^{-1}$)	9.5±8.9	8.2±2.3	8.3±1.9	7.4±2.1*	0.5 (−1.8 to 2.7)	0.698
Average E/e′	7.5±3.5	7.4±2.3	7.4±1.9	7.0±2.0	−0.2 (−1.1 to 0.6)	0.549

Data are presented as n, mean±SD or mean (95% CI), unless otherwise stated. E/e′: ratio between early mitral inflow velocity and mitral annular early diastolic velocity. *: p<0.05 changes from low (760 m) to high (3100 m) altitude; #: p<0.05 differences between placebo and acetazolamide at 3100 m; ¶: p<0.05 differences between placebo and acetazolamide at 760 m.

TABLE 4 Clinical parameters and arterial blood gas analysis

	Placebo		Acetazolamide		Treatment effect	
	760 m	3100 m	760 m	3100 m	Between-group difference in altitude-induced change (95% CI)	p-value
Clinical parameters						
Heart rate (echocardiography) ($beats \cdot min^{-1}$)	69±11	76±11*	71±11	74±10	−5 (−8 to −1)	0.006
Blood pressure systolic (mmHg)	128±17	135±19*	124±17	123±13#	−10 (−15 to −5)	<0.001
Blood pressure diastolic (mmHg)	82±12	87±12*	81±11	82±9#	−5 (−9 to −1)	0.024
Oxygen saturation (%)	95±2	88±3*	94±2	90±3*,#	2 (1 to 3)	0.001
6MWD (m)	506±84	494±84*	504±78	485±75*	0 (−25 to 25)	0.999
Oxygen saturation at end of 6MWD (%)	94±3	84±6*	94±3	86±5*,#	3 (1 to 5)	0.002
Arterial blood gas analysis obtained in the morning						
pH	7.40±0.02	7.42±0.04*	7.39±0.02	7.36±0.02*	−0.06 (−0.07 to −0.05)	<0.001
P_{aCO_2} (mmHg)	41.3±3.9	37.2±3.9*	42±2.9	34±2.8*,#	−4.0 (−5.4 to −2.6)	<0.001
P_{aO_2} (mmHg)	69.1±5.4	61.4±12.6*	69.4±7.2	60.9±6.2*	−0.8 (−4.4 to 2.8)	0.662
Bicarbonate ($mmol \cdot L^{-1}$)	24.9±2	23.7±1.5*	25.1±1.6	18.7±1.6*,#	−5.3 (−6 to −4.5)	<0.001
Haematocrit (%)	42.8±4.1	42.9±3.7	42.9±4.8	44.5±4.7*,#	1.4 (0.5 to 2.3)	0.001
Haemoglobin ($g \cdot dL^{-1}$)	14.6±1.4	14.6±1.3	14.6±1.6	15.2±1.6*,#	0.5 (0.2 to 0.8)	0.001
Arterial oxyhaemoglobin saturation (%)	93.3±2	88.5±4*	93.1±1.8	88.1±2.8*	−0.2 (−1.5 to 1.0)	0.699
Arterial oxygen content ($mL \cdot dL^{-1}$)	18.4±1.6	17.4±1.5*	18.5±1.9	18.1±1.8*,#	0.4 (0.1 to 0.6)	0.003
Oxygen delivery ($mL \cdot min^{-1}$)	869±238	869±207	851±211	821±198	38 (−11 to 87)	0.130
Severe hypoxaemia (pulse oximetry <80% for >30 min) during the night						
Patients with nocturnal oxygen therapy		18 (33)		4 (7)		<0.001

Data are presented as mean±SD, mean (95% CI) or n (%), unless otherwise stated. 6MWD: 6-min walk distance; P_{aCO_2}: arterial carbon dioxide tension; P_{aO_2}: arterial oxygen tension. *: p<0.05 changes from low (760 m) to high (3100 m) altitude; #: p<0.05 differences between placebo and acetazolamide at 3100 m.

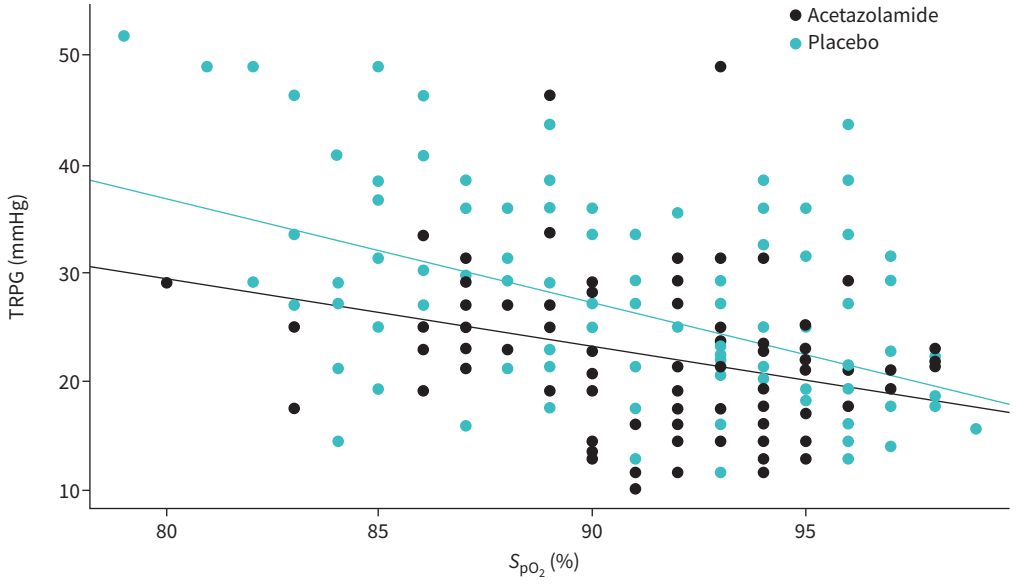

FIGURE 4 Correlation between oxygenation (peripheral oxygen saturation (S_{pO_2})) and pulmonary artery pressure (tricuspid regurgitation pressure gradient (TRPG)).

mitigated the altitude-induced increase in PAP in patients with COPD, an effect that has previously been observed in animals, healthy volunteers and patients with pulmonary vascular disease [28–30, 43–45] and which is believed to be mainly related to increased ventilation due to acetazolamide-induced metabolic acidosis, improving oxygenation and decreasing hypoxic pulmonary vasoconstriction [45]. However, a direct effect of acetazolamide on the pulmonary vasculature and prevention of hypoxic pulmonary vasoconstriction, independent of carbonic anhydrase inhibition, has been shown in dogs, rodent models, isolated perfused lungs and patients with pulmonary hypertension acutely exposed to hypoxia [28–30, 43, 46, 47]. Therefore, a partial direct vasoactive effect of the study drug is plausible, especially since regression lines for values of TRPG at certain S_{pO_2} levels between placebo and acetazolamide did not match, indicating a mechanism independent of the improvement of oxygenation.

In contrast to our findings, Berger *et al.* [48] found that acetazolamide did not lower PAP in healthy climbers who are susceptible to high-altitude pulmonary oedema; however, with a study size of 13 participants, a sufficient sample size according to their calculation could not be reached and therefore results should be interpreted with caution. Negative results were also reported in another study conducted in 15 healthy lowlanders travelling to the Bolivian Altiplano, in whom acetazolamide affected neither maximum exercise capacity nor pulmonary pressure/CO flow at rest and during exercise [49].

With altitude exposure, a significant increase in PVR and TRPG/CO was observed in both treatment arms, with significantly higher values at altitude in the placebo group. However, a significant treatment effect for PVR or TRPG/CO could not be observed, probably related to the adaptively higher increase in heart rate in the placebo group.

Similar to healthy subjects and as expected, we observed an increase in systemic blood pressure, heart rate and CO in the placebo group of the present COPD cohort at high altitude [50]. In contrast, in the acetazolamide group, the blood pressure and heart rate did not increase, and even a reduction in stroke volume and CO was found consistent with a blunting of the excitation of the hypoxic sympathetic nervous system and a reduction in intravascular volume due to the diuretic effect of the study drug. Boulet *et al.* [45] investigated the preventive effect of acetazolamide and methazolamide in 11 healthy volunteers exposed to normobaric hypoxia for 60 min and found a significant increase in heart rate and blood pressure. It remains unclear whether the observed blunted cardiorespiratory response after 1 night at altitude in the acetazolamide group in the current study is a direct effect of acetazolamide or can be potentially traced back to the improvement of oxygenation especially during the night, leading to more refreshing sleep and thus less daily sympathetic stress.

Over the course of the day, the S_{pO_2} values at rest and at end of 6-min walk test were significantly lower in the placebo group, whereas partial pressure of arterial oxygen measured by blood gas analysis in the morning showed no difference. However, these differences between pulse oximetry and blood gas analysis can be explained by the design of the trial, as patients revealing very severe hypoxaemia at altitude were either transported to low altitude for safety reasons or given oxygen during the night and were therefore not available for morning blood gas analysis. Due to the expected diuretic effect of the study drug, haematocrit and haemoglobin increased significantly in the acetazolamide group. Both groups were able to maintain oxygen delivery, even though the maintenance in the placebo group was only feasible due to the increase in heart rate and CO, whereas the improvement in oxygenation, but also the increase in haematocrit and haemoglobin in the acetazolamide group, might have been sufficient to maintain oxygen delivery.

Limitations

Echocardiography can be challenging, especially in patients with COPD due to acoustic interference in the hyperinflated lung; however, performing right heart catheterisation at altitude was not feasible due to its invasive nature and TRPG could be obtained in the vast majority of the patients present. More patients in the placebo group experienced ARAHE during the day and night at altitude and were receiving nocturnal oxygen treatment. In a previous study [51], we could demonstrate that nocturnal oxygen therapy in COPD patients did not alter TRPG compared to placebo; therefore, the higher percentage of patients receiving oxygen during the night in the placebo group should not have influenced our study results. One might rather speculate that the current results would have been even more pronounced if patients had not been given oxygen treatment and remained severely hypoxaemic until echocardiography. Despite these limitations, the robust design of our study as a placebo-controlled trial applying the same measurement technique to all participants allowed firm conclusions on the effect of acetazolamide. Furthermore, our findings cannot be extrapolated to all patients with COPD, since only patients with moderate-to-severe disease and not mild or very severe COPD were assessed.

Conclusion

The current randomised, placebo-controlled trial showed for the first time that acetazolamide prophylaxis mitigates the altitude-induced PAP increase in lowlanders with COPD (GOLD grade 2–3) travelling to 3100 m. Apart from the effects of acetazolamide on pulmonary haemodynamics reported here, in the same COPD patients the drug also significantly reduced the incidence of ARAHE requiring a medical intervention and descent from high altitude compared to placebo, underlining its potential as clinically useful treatment [11].

Provenance: Submitted article, peer reviewed.

This study is registered at www.clinicaltrials.gov with identifier number NCT03173508. Data will be made available upon request with a methodologically sound research proposal that has been approved by local authorities/ethics committees.

Author contributions: M. Lichtblau, K.E. Bloch and S. Ulrich: substantial contributions to the conception and design of the study, interpretation of the data, critical revision for important intellectual content and final approval of the version to be published. S. Ulrich is the guarantor of the work. L. Mayer, U. Sheraliev, M. Mademilov, M. Furian, A. Buergin, P.M. Schweiwiller, S. Saxer, S.R. Schneider, T. Sooronbaev and F.C. Tanner: data acquisition, critical revision for important intellectual content, final approval of the version to be published. U. Sheraliev, M. Mademilov and T. Sooronbaev take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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