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Effect of acetazolamide on pulmonary vascular hemodynamics in patients with COPD going to altitude: a randomized, placebo-controlled, double-blind trial

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Abstract

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

Methods: In this placebo-controlled, double-blind parallel-group trial, patients with COPD GOLD 2-3 living <800m, SpO_2 >92%, $PaCO_2$ <6kPa, were randomized to receive either acetazolamide (125 0-250 mg/d) or placebo capsules starting 24h before ascent from 760m and during a 2-day-stay at 3100m. Echocardiography, pulse-oximetry and clinical assessments were performed at 760m and after the first night at 3100m. Primary outcome was PAP assessed by tricuspid regurgitation pressure gradient (TRPG).

Results: 112 patients, 68% men, mean±SD age 59±8 y, FEV_1 61±12 %pred, SpO_2 95±2 % were included. TRPG increased from 22±7 to 30±10 mmHg in 54 allocated to placebo and from 20±5 to 24±7 mmHg in 58 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 760/3100m, SpO_2 was 95±2/88±3 %, in the acetazolamide group 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 3100m preventive acetazolamide treatment attenuated the altitude-induced rise in PAP and improved oxygenation.

www.clinicaltrials.gov NCT03173508.

Introduction

An increasing number of people travel to high altitude for professional and recreational activities, amongst which many tourists with preexisting cardiopulmonary diseases. In regard of the globally high prevalence of chronic obstructive pulmonary disease (COPD), a high number of COPD-patients is expected to be within altitude travelers to the many cities and areas located at high altitude worldwide.[1] COPD-patients are at higher risk to experience altitude related adverse health effects (ARAHE), but only few studies in COPD patients exposed to high altitude report about potential implications on health and preventive strategies. [2-11] Evidence for an altitude-associated increase in mortality in COPD underscores the need of research in this field. [12, 13]

COPD is the most common chronic respiratory disease worldwide[14], with a reported prevalence of around15% of the general population. It is characterized by chronic airflow obstruction with airway inflammation and remodeling, and in some patients parenchymal destruction of the lung. Cardinal symptoms of COPD are chronic productive cough and dyspnea on exertion with limited exercise performance related to airflow obstruction, dynamic hyperinflation, exercise induced hypoxemia and increase in pulmonary artery pressure (PAP). [15] Pulmonary hypertension (PH) 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 PH usually precedes resting PH 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 PH when travelling to a hypoxic environment at altitude. In previous studies, we found that patients with COPD tolerated acute exposure to moderate altitude (2590-3100 m) generally well although they suffered from a major reduction in exercise performance, pronounced dyspnea, elevated PAP and other ARAHE, including acute mountain sickness (AMS), pathological cardiac repolarization. [9, 10, 19, 20] Effective means to prevent these limitations would therefore be desirable.

The carbonic anhydrase inhibitor acetazolamide improves oxygenation through stimulation of the ventilation by induction of metabolic acidosis via renal bicarbonate excretion, an effect that is especially pronounced in hypoxic environment and therefore tested successfully in prevention of AMS in healthy mountaineers.[21, 22] It has also been suggested that acetazolamide may mitigate the excessive rise in PAP observed in individuals susceptible to high altitude pulmonary edema when exposed to hypoxia. Acetazolamide has furthermore been used as treatment in patients with mild to moderate COPD to increase ventilation and thus improve oxygenation and reduce hypercapnia whereas no benefit on duration and success of weaning from mechanical ventilation in hospitalized COPD patients has been found. In addition, according to in-vitro, animal and in-vivo studies, acetazolamide may reveal a direct pulmonary vasodilator effect, especially in hypoxic condition. [26-30]

The purpose of the current study was thus 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 randomized, 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, 760 m, and the High-Altitude Clinic Tuja-Ashu, 3100 m, Kyrgyz Republic. 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,[31] with post-bronchodilator forced expiratory volume in 1s (FEV_1)/forced vital capacity (FVC)<0.7 and FEV_1 40-80 % predicted, of all genders, aged 18 to 75 years, living <800m were recruited among outpatients of

the NCCIM and surrounding hospitals. Patients with severe hypoxemia (SpO_2 <92%), hypercapnia ($PaCO_2$ >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 with pulse-oximetry during the day and at night and when severe hypoxemia (defined as SpO_2≤ 75% for ≥15 min or ≤80% for ≥30 min) occurred, oxygen was given and the patient evacuated to lowland for safety reasons. Apart from patients characteristics, the data presented here have not been published.

Interventions

After undergoing baseline evaluations at the NCCIM, Bishkek (760 m), patients travelled by minibus within 3-5 hours to a high altitude clinic at 3100 m and stayed there for 2 days. Acetazolamide (125-0-250mg) or identically looking placebo capsules were given starting 24 hours before ascent to and during the stay at 3100 m under supervision of investigators.

Assessments

Medical history was obtained, clinical examination performed, vital parameters and SpO_2 at rest and 6-minute walking distance 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 (CaO_2) was calculated as [CaO_2 = Hb * SaO_2*1.34 + (PaO_2 * 0.003)]. Oxygen delivery was calculated as [DO_2= Cardiac output * CaO_2].

Echocardiographic recordings were performed according to current guidelines (CX 50, Philips, Philips Respironics, Zofingen, Switzerland). [32] To assess PAP, maximal tricuspid regurgitation pressure gradient (TRPG) was calculated from maximal tricuspid regurgitation velocity (TRV) obtained with CW-Doppler using the modified Bernoulli equation: $\Delta Pressure = 4 \times TRVmax^2$. Right atrial pressure (RAP) was estimated by the diameter of the inferior vena cava and systolic PAP (sPAP) calculated as TRPG + RAP. Mean PAP (mPAP) was calculated from sPAP as mPAP = 0.61× sPAP + 2mmHg. [33] Areas of the right atrium and RV were manually traced and fractional area change (FAC) calculated. Tricuspid annular plane systolic excursion (TAPSE) was measured by

M-mode and the RV free wall velocity by tissue Doppler. Pulmonary artery wedge pressure (PAWP) was calculated as 1.24 * (E/e') + 1.9. [34] Cardiac output (CO) was calculated using the left ventricular (LV) 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 hematocrit were determined according to the formula derived by Whittaker and Winton. [35, 36] To this end, PVR was computed for a standard hematocrit of 0.45 as ($R_0(45\%) = R_0(HCT) * ((1-\phi^{1/3}) / 0.234)$)).[37] RV-arterial coupling was assessed by TAPSE/sPAP. [38] Stroke volume (SV) was calculated as SV = CO/HR. Left heart function was assessed according to the current guidelines. [32] B-Lines as indices off pulmonary interstitial fluid accumulation were assessed as described previously [39] in a supine position from the second to fourth or fifth intercostal space (left and right hemi-thorax, respectively) down the parasternal, mid-clavicular, anterior axillary and mid-axillary lines, resulting in 28 total windows of interest (left: 12; right: 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.[40] The number of B-lines was counted for each lung field and totaled.

Randomization and blinding

Participants were randomized to acetazolamide or placebo treatment with a 1:1 allocation as per computer generated schedule minimizing for age (18-50 and 51-75 years), gender and FEV_1 (40-59 and 60-80 %predicted). An independent pharmacist prepared blister packs containing active and identically 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 randomized to acetazolamide vs. placebo.

Secondary outcomes

Vital parameters and SpO_2 at rest and 6-minute walking distance, as well as blood gas analysis in patients randomized to acetazolamide vs. placebo and 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 was checked for completeness and multiple imputation with pattern-mixture model by group (low altitude all participants, high altitude Drug 1 and HA Drug 2) was performed for the main outcome. Data are summarized by numbers and proportions, means ±SD, or 95% confidence intervals (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 StataSE 15. Statistical significance level was set at $p < 0.05$ or 95% confidential interval not crossing the zero value.

Results

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 performance of echocardiography and in 12 patients echocardiography of sufficient quality was not available. (**figure 1**). **Table 1** shows the subjects' baseline characteristics and medication.

Primary Outcome

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

Echocardiographic parameters

Echocardiographic parameters of the right and left heart are displayed in **table 2 and 4**. 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 (-1.0 to -0.2) l/min f(p=0.003). PVR, hematocrit 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 – pulmonary arterial coupling, estimated by TAPSE/sPAP, showed similar deterioration in both treatment arms without treatment effect. TDI tricuspid annular systolic velocity increased at altitude in the placebo 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.

Physiological measurements and arterial blood gas analysis

Clinical parameters and arterial blood gas analysis are presented in **table 3**. From low to high altitude, the heart rate increased significantly in the placebo but not the acetazolamide group, resulting in a treatment-induced reduction of heart rate increase by -5 (-8 to -1) bpm (p = 0.006). Similarly, the altitude-induced increase in blood pressure, was attenuated by acetazolamide, resulting in treatment effects for systolic (-10 (-

15 to -5) mmHg, p< 0.001) and diastolic blood pressure (-5 (-9 to -1) mmHg, p = 0.024). Altitude exposure was associated with a reduced SpO_2 at rest and at peak 6-minute walk test, the acetazolamide group showed a significant smaller drop compared to placebo resulting in treatment effects of resting SpO_2 +2 (1 to 3) %, p = 0.001, and end-exercise SpO_2 +3 (1 to 5) %, p= 0.002). Eighteen (33 %) patients in the placebo and 4 (7 %) in the acetazolamide group received nocturnal oxygen supplementation with 3 l/min according to the predefined safety criteria. Arterial oxygen content was significantly higher in the acetazolamide group). With an increase of HR and CO in the placebo group, oxygen delivery remained the same in both treatment arms. Arterial blood gas analysis revealed a lower $PaCO_2$ in both groups at altitude. In the acetazolamide-group, hematocrit and hemoglobin were increased at altitude. The $PaCO_2$, bicarbonate and pH were significantly lower in the acetazolamide group, indicating the bicarbonate excretion with metabolic acidosis and leading to compensatory hyperventilation.

Oxygenation and pulmonary artery pressure

Correlation between SpO_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 randomized, 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. Furthermore acetazolamide improved SpO_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 traveling to altitude, hypoxic pulmonary vasoconstriction upon exposure to 3100 m induced the well described increase in PAP along with a rise in PVR. [41] This effect has been demonstrated in patients with mild to moderate COPD upon acute exposure to moderate to high altitude before [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, 42, 43] In the present study, preventive treatment with the carbonic anhydrase inhibitor acetazolamide 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 disase. [28-30, 44-46] and which is believed to be mainly related to an increased ventilation due to the acetazolamide-induced metabolic acidosis, therefore improving oxygenation and decreasing hypoxic pulmonary vasoconstriction.[46] 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 PH acutely exposed to hypoxia.[28-30, 44, 47, 48] Therefore, a partial direct vasoactive effect of the study drug is plausible, , especially since regression lines for values of TRPG at certain SpO_2 levels between placebo and acetazolamide did not match, indicating a mechanism independent of the improvement of oxygenation

In contrast to our findings, the group of Berger et al found that acetazolamide did not lower PAP in healthy climbers that are HAPE-susceptible, however with a study size of 13 participants a sufficient sample size according to their calculation could not be reached and therefore results need to be interpreted with caution. Negativeresults were also reported in another study conducted in 15 healthy lowlanders traveling to the Bolivian alitplano in whom acetazolamide neither effected maximum exercise capacity nor pulmonary pressure / cardiac output flow at rest and during exercise.[50]

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, most 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.[51] 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 hypoxic sympathetic nervous system excitation and a reduction in intravascular volume due to the diuretic effect of the study drugBoulet et al investigated the preventive effect of acetazolamide and methazolamide in 11 healthy volunteers exposed to normobaric hypoxia for 60 minutes and found a significant increase in heart rate and blood pressure. 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 refreshment sleep and thus less daily sympathetic stress, remains unclear.

Over the course of the day, the SpO_2 at rest and at end of 6-minute walk distance 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 hypoxemia 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, hematocrit and hemoglobin 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 hematocrit and hemoglobin 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 catheterization at altitude was not feasible due to its

invasive nature and TRPG could be obtained in the vast majority of the present patients. More patients in the placebo group experience ARAHE during the day and night at altitude and were receiving nocturnal oxygen treatment. In a previous study [52] 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 would not have been given oxygen treatment and remained severely hypoxemic up until the performance of the 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 randomized, 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 3,100 m. Apart from the effects of acetazolamideon pulmonary hemodynamics 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]

Acknowledgements and authors contributions

ML, KEB, SU: substantial contributions to the conception and design of the study, interpretation of the data, critical revision for important intellectual content, final approval of the version to be published. SU is the guarantor of the work.

LM, US, MM, MF, AB, PMS, SS, NHM, SS, BO, BE, TS, FC: data acquisition, critical revision for important intellectual content, final approval of the version to be published

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Tables

Table 1 Participant characteristics

Variable	Group assigned to Placebo (n = 54)	Group assigned to Acetazolamide (n = 58)
Men, No. (%)	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
Smoking history, pack-years cigarettes	15 ± 25	11 ± 16
Medication		
Oral steroids, No. (%)	1 (2%)	0 (0%)
Inhaled beta-adrenergics, No. (%)	10 (19%)	10 (17%)
Inhaled anticholinergics, No. (%)	12 (22%)	11 (19%)
Inhaled steroids, No. (%)	8 (15%)	8 (14%)
Anti-hypertensive drug, No. (%)	7 (13%)	7 (12%)
Betablocker, No. (%)	1 (2%)	1 (2%)
Aspirin, No. (%)	7 (13%)	8 (14%)

Values are numbers and proportions or mean ± SD. FEV_1: forced expiratory volume in the first second, FVC: forced vital capacity.

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

	Placebo group		Acetazolamide group		Treatment Effect	
	760 m	3100 m	760 m	3100 m	Between-group difference in altitude-induced change (95% CI)	p-value
Pulmonary artery pressure						
Tricuspid regurgitation pressure gradient (TRPG), mmHg	22 ± 7	30 ± 10 #	20 ± 5	24 ± 7 #*	-5 (-9 to -1)	0.015
Tricuspid regurgitation velocity, m/sec	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
Hemodynamics						
Heart rate, bmp	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
Cardiac output (CO), l/min	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/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/ml/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), WU	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
Pulmonary vascular resistance, WU	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
Pulmonary vascular resistance corrected for hematocrit, WU	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
Pulmonary arterial wedge pressure, 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
Tricuspid annular plane systolic excursion (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	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	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

Values are presented as mean ± SD and mean (95% confidence interval). TDI : Tissue Doppler Image, TAPSE/sPAP: Tricuspid annular plane systolic excursion/ systolic pulmonary artery pressure, TRPG/CO: Tricuspid regurgitation pressure gradient/Cardiac Output.

# $p < 0.05$ changes from low (760 m) to high (3100 m) altitude

$ p <0.05 differences between placebo and acetazolamide at 670 m
* p <0.05 differences between placebo and acetazolamide at 3100 m

Table 3 Clinical parameters and arterial blood gas analysis

	Placebo group		Acetazolamide group		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 (Echo), bmp	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
6-minute walk distance, m	506 ± 84	494 ± 84 #	504 ± 78	485 ± 75 #	0 (-25 to 25)	0.999
Oxygen saturation at end of 6 minute walk distance, %	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
$PaCO_2$, mmHg	41.3 ± 3.9	37.2 ± 3.9 #	42 ± 2.9	34 ± 2.8 #*	-4.0 (-5.4 to 2.6)	<0.001
PaO_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/l	24.9 ± 2	23.7 ± 1.5 #	25.1 ± 1.6	18.7 ± 1.6 #*	- 5.3 (-6 to -4.5)	<0.001
Hematocrit, %	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
Hemoglobin, g/dl	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 oxyhemoglobin 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 O_2/dl	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/min	869 ± 238	869 ± 207	851 ± 211	821 ± 198	38 (-11 to 87)	0.130
Severe hypoxemia (pulse oximetry <80% for >30min) during the night						
Number of patients with nocturnal oxygen therapy (%)		18 (33 %)		4 (7%)		<0.001

Values are presented as mean ± SD and mean (95% confidence interval). $PaCO_2$ / O_2: arterial partial pressure of carbon dioxide and oxygen.
# p < 0.05 changes from low (760 m) to high (3100 m) altitude
* p <0.05S differences between placebo and acetazolamide at 3100 m

Table 4 Echocardiographic indices of the left heart function and morphology

	Placebo group (N=54)		Acetazolamide group (N=58)		Treatment Effect	
	760 m	**3100 m**	**760 m**	**3100 m**	Between-group difference in altitude-induced change (95% CI)	p-value
Ejection fraction (biplan), %	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/sec	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/sec	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

Values are presented as mean ± SD and mean (95% confidence interval).

# p < 0.05 changes from low (760 m) to high (3100 m) altitude

$ p <0.05 differences between placebo and acetazolamide at 670 m

* p <0.05S differences between placebo and acetazolamide at 3100 m

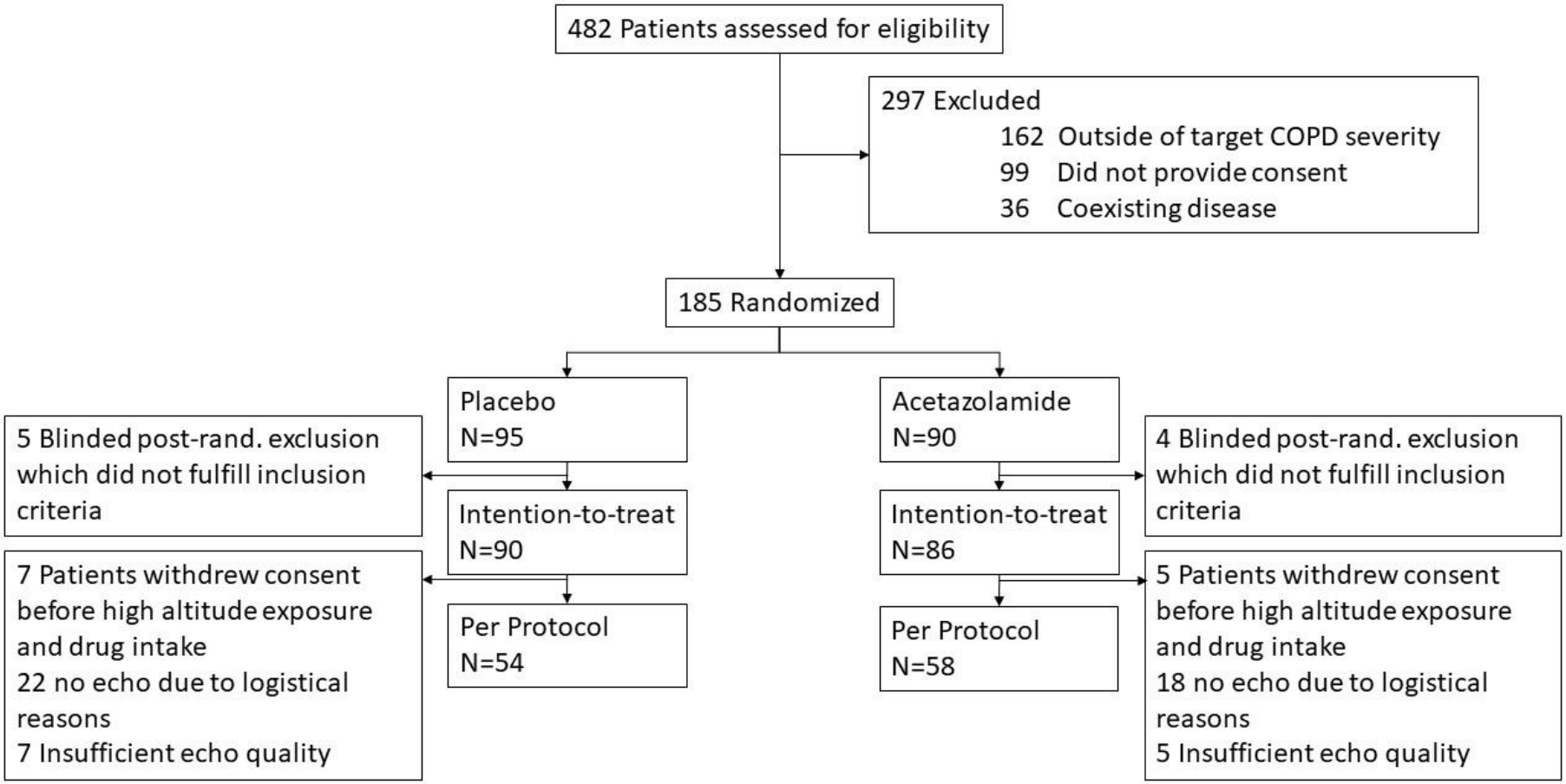
Figure Legend

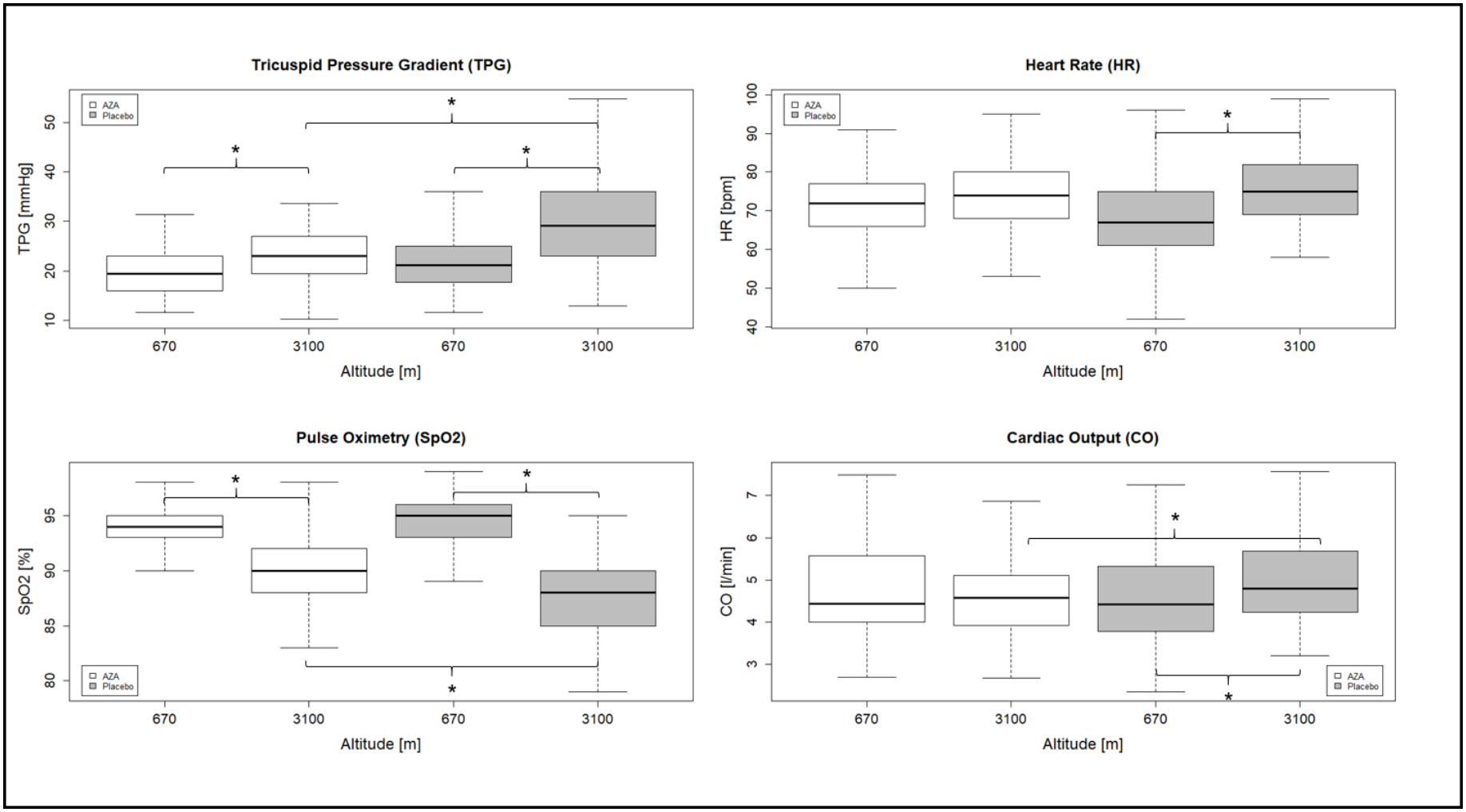
Figure 1 Patient's flow.

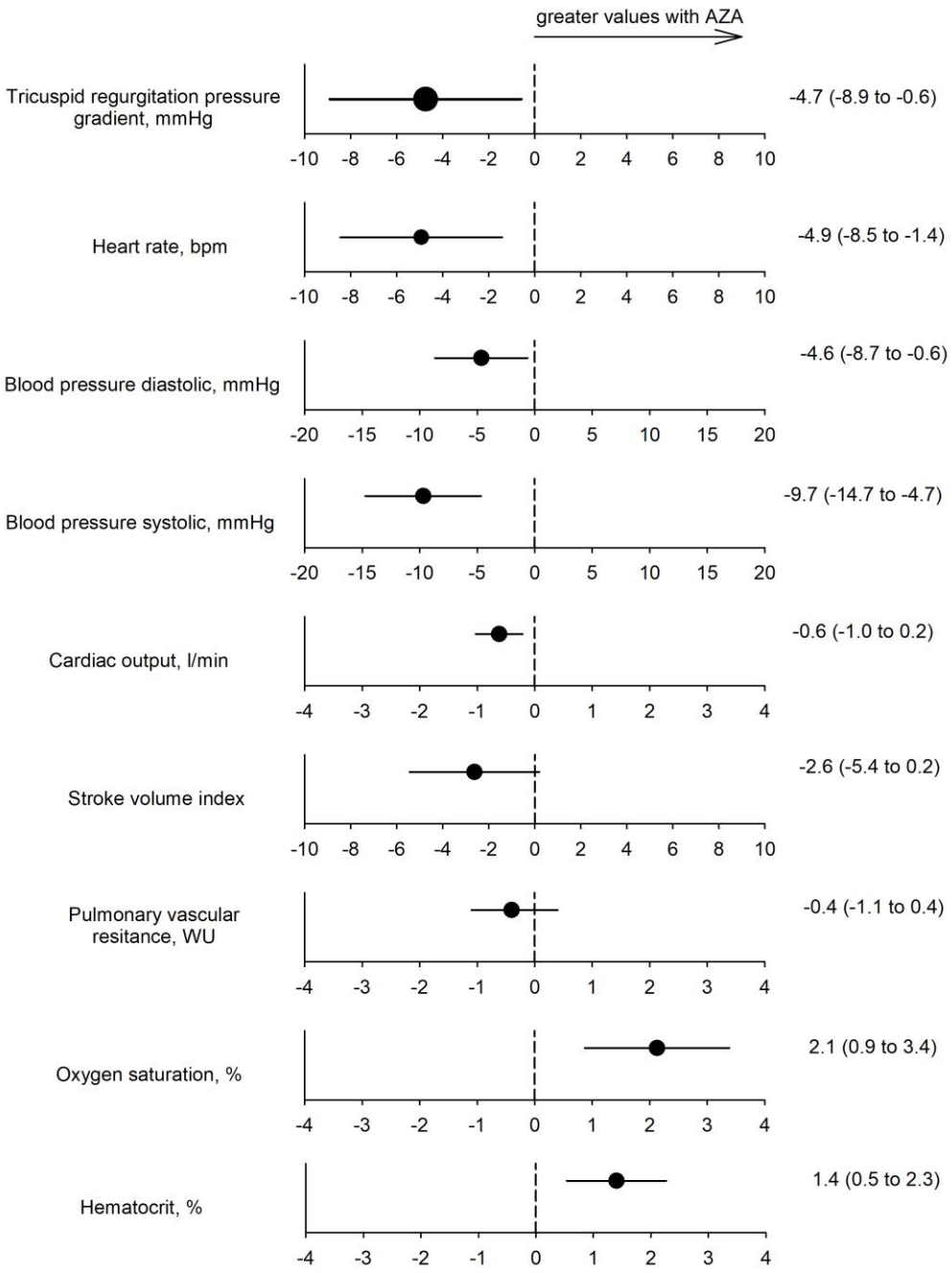
Figure 2 Tricuspid regurgitation pressure gradient, heart rate, blood pressure, cardiac output, stroke volume index, pulmonary vascular resistance, oxygen saturation and hematocrit at low altitude (760 m) and high altitude (3100 m). Boxplots show medians, quartiles, and 1.5× the interquartile range. * indicates significant changes ($p<0.05$)

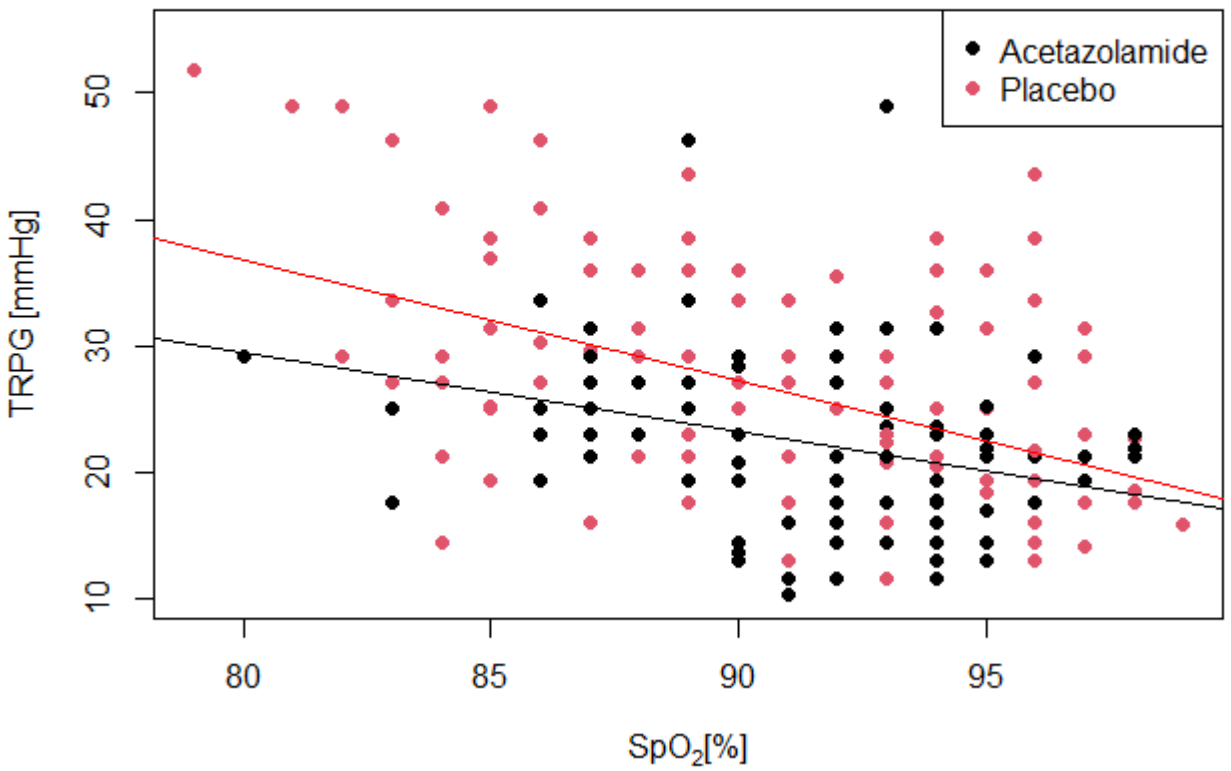
Figure 3 Mean difference between groups in altitude-induced changes and 95% CI in tricuspid regurgitation pressure gradient, heart rate, blood pressure, cardiac output, stroke volume index, pulmonary vascular resistance, oxygen saturation and hematocrit.

Figure 4 Correlation between oxygenation (SpO_2) and pulmonary artery pressure (TRPG = tricuspid regurgitation pressure gradient). Red displays values for the placebo and black displays values for the acetazolamide group.


482 Patients assessed for eligibility
297 Excluded
162 Outside of target COPD severity
99 Did not provide consent
36 Coexisting disease
185 Randomized
Placebo
N=95
Acetazolamide
N=90
5 Blinded post-rand. exclusion which did not fulfill inclusion criteria
4 Blinded post-rand. exclusion which did not fulfill inclusion criteria
Intention-to-treat
N=90
Intention-to-treat
N=86
7 Patients withdrew consent before high altitude exposure and drug intake
22 no echo due to logistical reasons
7 Insufficient echo quality
5 Patients withdrew consent before high altitude exposure and drug intake
18 no echo due to logistical reasons
5 Insufficient echo quality
Per Protocol
N=54
Per Protocol
N=58


Tricuspid Pressure Gradient (TPG)
TPG [mmHg]
10
20
30
40
50
AZA
Placebo
*
*
*
670
3100
670
3100
Altitude [m]
Heart Rate (HR)
HR [bpm]
40
50
60
70
80
90
100
AZA
Placebo
*
670
3100
670
3100
Altitude [m]
Pulse Oximetry (SpO2)
SpO2 [%]
80
85
90
95
*
*
*
AZA
Placebo
670
3100
670
3100
Altitude [m]
Cardiac Output (CO)
CO [l/min]
3
4
5
6
7
*
*
AZA
Placebo
670
3100
670
3100
Altitude [m]


greater values with AZA
Tricuspid regurgitation pressure gradient, mmHg
-4.7 (-8.9 to -0.6)
-10 -8 -6 -4 -2 0 2 4 6 8 10
Heart rate, bpm
-4.9 (-8.5 to -1.4)
-10 -8 -6 -4 -2 0 2 4 6 8 10
Blood pressure diastolic, mmHg
-4.6 (-8.7 to -0.6)
-20 -15 -10 -5 0 5 10 15 20
Blood pressure systolic, mmHg
-9.7 (-14.7 to -4.7)
-20 -15 -10 -5 0 5 10 15 20
Cardiac output, l/min
-0.6 (-1.0 to 0.2)
-4 -3 -2 -1 0 1 2 3 4
Stroke volume index
-2.6 (-5.4 to 0.2)
-10 -8 -6 -4 -2 0 2 4 6 8 10
Pulmonary vascular resitance, WU
-0.4 (-1.1 to 0.4)
-4 -3 -2 -1 0 1 2 3 4
Oxygen saturation, %
2.1 (0.9 to 3.4)
-4 -3 -2 -1 0 1 2 3 4
Hematocrit, %
1.4 (0.5 to 2.3)
-4 -3 -2 -1 0 1 2 3 4


Acetazolamide
Placebo
TRPG [mmHg]
10
20
30
40
50
80
85
90
95
SpO2[%]