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Shareable abstract (@ERSpublications)
Patients with COPD are at an increased risk of altitude-related adverse health effects (ARAHE). This study shows that the hypoxia-altitude simulation test is insufficiently accurate to predict ARAHE. https://bit.ly/3GcmF86

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Abstract

Background/aims Amongst numerous travellers to high altitude (HA) are many with the highly prevalent COPD, who are at particular risk for altitude-related adverse health effects (ARAHE). We then investigated the hypoxia-altitude simulation test (HAST) to predict ARAHE in COPD patients travelling to altitude.

Methods This prospective diagnostic accuracy study included 75 COPD patients: 40 women, age 58±9 years, forced expiratory volume in 1 s (FEV_1) 40–80% pred, oxygen saturation measured by pulse oximetry (S_{pO_2}) ⩾92% and arterial carbon dioxide tension (P_{aCO_2}) <6 kPa. Patients underwent baseline evaluation and HAST, breathing normobaric hypoxic air (inspiratory oxygen fraction (F_{IO_2}) of 15%) for 15 min, at low altitude (760 m). Cut-off values for a positive HAST were set according to British Thoracic Society (BTS) guidelines (arterial oxygen tension (P_{aO_2}) <6.6 kPa and/or S_{pO_2} <85%). The following day, patients travelled to HA (3100 m) for two overnight stays where ARAHE development including acute mountain sickness (AMS), Lake Louise Score ⩾4 and/or AMS score ⩾0.7, severe hypoxaemia (S_{pO_2} <80% for >30 min or 75% for >15 min) or intercurrent illness was observed.

Results ARAHE occurred in 50 (66%) patients and 23 out of 75 (31%) were positive on HAST according to S_{pO_2}, and 11 out of 64 (17%) according to P_{aO_2}. For S_{pO_2}/P_{aO_2} we report a sensitivity of 46/25%, specificity of 84/95%, positive predictive value of 85/92% and negative predictive value of 44/37%.

Conclusion In COPD patients ascending to HA, ARAHE are common. Despite an acceptable positive predictive value of the HAST to predict ARAHE, its clinical use is limited by its insufficient sensitivity and overall accuracy. Counselling COPD patients before altitude travel remains challenging and best focuses on early recognition and treatment of ARAHE with oxygen and descent.

Introduction

>85 million people worldwide live in mountain regions or large settlements above 2500 m where tourism along with air travel has become increasingly popular for professional and recreational reasons [1]. However, the hypobaric hypoxic environment bears the risk of altitude-related adverse health effects (ARAHE) related to the decreased oxygen availability, particularly in patients with pre-existing diseases, such as COPD. COPD is the most common chronic respiratory condition worldwide with a prevalence of 12% [2] and is expected to further increase due to an ageing population, exposure to cigarette smoke, and occupational or environmental toxins including biomass smoke and air pollution. COPD is characterised by chronic productive cough, recurrent respiratory tract infections, progressive hypoxaemia due to

respiratory mechanical constraints, airway obstruction, increasing pulmonary artery pressure and a rarefied pulmonary vascular bed. Whilst travelling to moderate altitude up to around 3000 m does not severely affect most healthy individuals, patients with COPD are at an increased risk for ARAHE, as hypoxia-induced changes are accelerated in the diseased lung. Furthermore, comorbidities, especially cardiac, are highly prevalent in COPD patients with increased risk for cardiac decompensation, accelerated pulmonary artery pressure increase, arrhythmia and sleep disturbances [2–6].

In clinical practice, especially in world regions with nearby mountains, it is a continuing challenge to assess the risks of altitude travel in COPD patients. To address this issue, numerous studies tried to identify factors assessed at low altitude (LA) that would predict ARAHE in COPD patients, including exposing them to normobaric hypoxia, the so-called hypoxia-altitude simulation test (HAST). The HAST was first described in 1984 by Gong *et al.* [7], who studied 22 COPD patients with a mean forced expiratory volume in 1 s (FEV_1) 44±17% predicted breathing different fractional contents of oxygen (F_{IO_2}) (20.9%, 17.1%, 15.1% and 13.9%) or pure oxygen. A linear regression line including baseline arterial oxygen tension (P_{aO_2}) fitted relatively well over the P_{aO_2} assessed whilst breathing the different F_{IO_2}, so that the authors concluded that the HAST can provide objective and useful information for advising COPD patients who wish to fly in aircraft cabins pressurised equal to ∼2500 m or undergo mountain sojourns. Subsequent observational studies, each including a limited number of patients, more or less confirmed that P_{aO_2} and/or oxygen saturation measured by pulse oximetry (S_{pO_2}) measured at LA during the HAST (with 15% F_{IO_2}) was able to predict the P_{aO_2}/S_{pO_2} in an aircraft cabin pressurised to an altitude equivalent of 2500 m, whereas S_{pO_2} on ambient air was less predictive [8–11]. However, a clinically useful prediction test in patients with COPD planning to undergo high altitude (HA) or air travel should not primarily predict the level of hypoxaemia, but rather include symptoms and/or severe oxygen desaturation to a level that is of high concern to be associated with intercurrent illness, cardiac problems or other ARAHE [12, 13]. The main goals of the present investigation were to evaluate the diagnostic accuracy of the HAST to predict ARAHE in COPD patients travelling to HA and to compare the predictive value of HAST parameters with resting S_{pO_2} or other baseline measures [14].

Methods

Design and setting

This is a prospective diagnostic accuracy study to evaluate the HAST at LA (760 m) to predict ARAHE in COPD patients during a sojourn of 2 days/nights at HA (3100 m). We nested the study within a trial on self-monitoring of COPD patients to detect early signs of ARAHE whilst travelling to HA conducted May–July 2021 at the National Center for Cardiology and Internal Medicine, Bishkek, and the HA clinic Too Ashu, Kyrgyzstan. Participants provided written informed consent, and the protocol was approved by the Ethics Committee in Bishkek (01-7/179), endorsed by the Ethics Committee Zurich and registered at clinicaltrial.gov (NCT04915378).

Participants

Adult men and women living at <800 m diagnosed with COPD Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage II–III revealing a post-bronchodilator FEV_1/forced vital capacity (FVC) <0.7 and a FEV_1 of 40–80% predicted with resting S_{pO_2} ⩾92% and P_{aCO_2} <6 kPa were included. Exclusion criteria were severe COPD (FEV_1 <40% predicted), hypercapnia (P_{aCO_2} >6 kPa), anaemia, body mass index (BMI) >35 $kg \cdot m^{-2}$, COVID-19 positive and unstable cardiovascular disease.

Assessments and interventions

Baseline assessments included demographics, medical history, physical examination, pulmonary function test, pulse oximetry and 6-min walk distance (6MWD) [15, 16]. After baseline evaluations, patients underwent a HAST whilst seated in a comfortable chair and were instructed to breathe normally. Normobaric hypoxic gas (F_{IO_2} 15%) was generated by the Everest Summit II altitude generator (Hypoxico, Bickenbach, Germany) and delivered *via* a mask. After a 5- to 10-min period of quiet rest breathing ambient air, patients were breathing hypoxic gas for 15 min. S_{pO_2} and heart rate were noted at 3-min intervals. At the end of the test before mask removal, a radial arterial blood gas sample was drawn and immediately analysed (epoc® Blood Analysis System; Siemens, Zurich, Switzerland).

A positive HAST was defined according to British Thoracic Society (BTS) guidelines as S_{pO_2} <85% or a P_{aO_2} <6.6 kPa at the end of 15 min whilst breathing normobaric hypoxia [14, 17].

The following day, patients ascended to 3100 m by minivan. They arrived around midday and stayed for 2 days and nights. At HA, patients regularly monitored their S_{pO_2} as well as any ARAHE symptoms and maintained a structured programme, which included three meals and standardised activity including walks.

During nights, patients underwent continuous S_{pO_2} monitoring to timely detect any serious ARAHE defined as follows in accordance with previous trials: [12, 13, 18]

- acute mountain sickness (AMS) defined as Lake Louise questionnaire score [19] >4 including headache, or AMS [20] score ⩾0.7
- severe hypoxaemia: resting S_{pO_2} <80% for >30 min or <75% for >15 min
- any intercurrent illness as judged by an independent physician and requiring medical therapy beyond simple measures such as paracetamol: *e.g.* infection, chest pain/severe dyspnoea and/or ECG signs of cardiac ischaemia, severe hypertension (blood pressure >200/110 mmHg), or any other new diseases or accidents
- any discomfort leading to the wish of a patient to return to LA or withdraw from the study

Patients experiencing ARAHE were treated with oxygen and medication as appropriate and relocated to LA with the next available transport.

Data analysis and statistics

In the primary analysis, positive and negative outcomes of the index test (HAST) and the reference tests (ARAHE) were cross-tabulated to compute sensitivity, specificity, positive and negative predictive values (PPV and NPV) and diagnostic accuracy. Receiver operating characteristic (ROC) curves to plot sensitivity *versus* 1 − specificity including measurements of the area under the curve (AUC) were computed for S_{pO_2} and P_{aO_2} at end of the HAST, and for LA S_{pO_2} at rest and at end the 6MWD. Univariate generalised linear models using logistic regression were computed to predict ARAHE by baseline characteristic and the HAST. Parameters that were significantly predictive for ARAHE in the univariate model were included in multivariable models including age, sex and BMI. Data analysis was performed according to diagnostic accuracy study guidelines (STARD) [21]. A $p<0.05$ was considered statistically significant (R version 4.1.2).

Results

Study population

Of 149 participants screened for the main trial, 75 COPD patients (40 women, mean±SD age 58±9 years and FEV_1 % pred 61±11) who performed the HAST with S_{pO_2} measured at the end were included, of which 64 also had an arterial blood gas analysis (aBGA) (see figure 1, table 1).

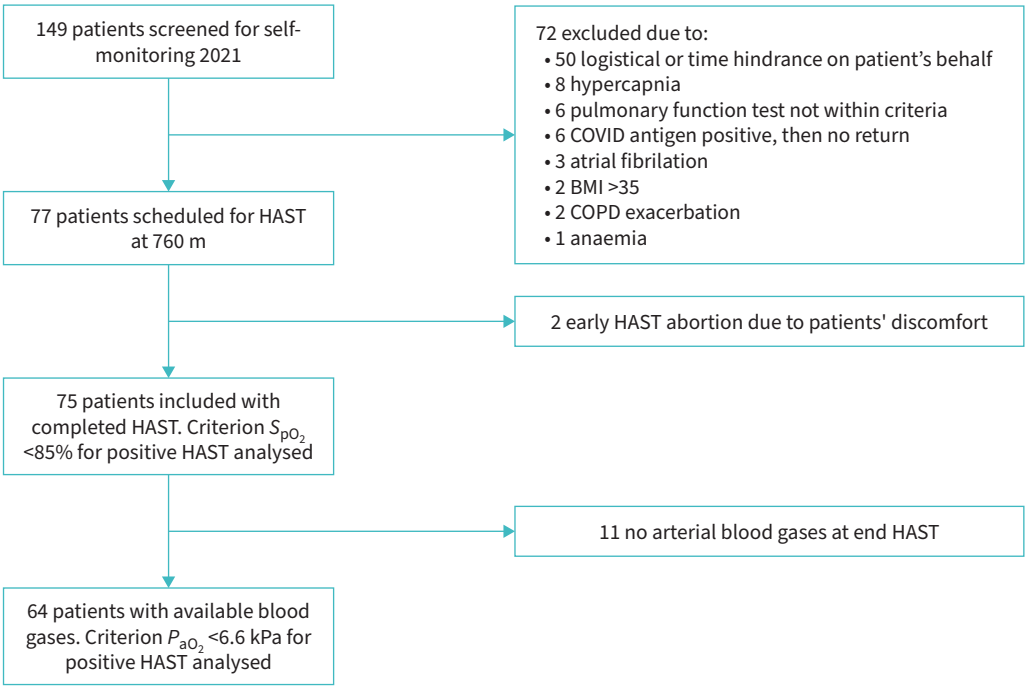

FIGURE 1 The patient study inclusion flow is shown. HAST: hypoxia-altitude simulation test; S_{pO_2}: oxygen saturation measured by pulse oximetry; P_{aO_2}: arterial oxygen tension; BMI: body mass index.

TABLE 1 Baseline characteristics

Demographics	
Patients, n	75
Women, n (%)	40 (53)
Age years, mean±SD	58±9
Body mass index kg·m^{-2}, mean±SD	28.0±4.2
FEV_1 % pred, mean±SD	61.0±11.0
FEV_1/FVC %, mean±SD	58.5±8.7
Dyspnoea mMRC, n (%)	
Grade 0	14 (19)
Grade 1	40 (53)
Grade 2	16 (21)
Grade 3	3 (4)
NA	2 (3)
6MWD m, mean±SD	452±63
Oxygen saturation at rest breathing ambient air %, mean±SD	93±1
Oxygen saturation at end of 6MWD %, mean±SD	86±4
Smoker, n (%)	10 (13)

FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; mMRC: Modified Medical Research Council scale; 6MWD: 6-min walk distance.

HAST and baseline measures to predict ARAHE

The HAST was positive in 27 out of 75 patients (36%) according to the S_{pO_2} criterion and in 11 out of 64 patients (17%) according to P_{aO_2}. Out of the 75 patients investigated with HAST, 50 out of 75 patients (66%) experienced ARAHE at HA, received oxygen and were relocated to LA.

S_{pO_2} cut-off at end-HAST

According to the S_{pO_2} <85% criterion, HAST and ARAHE were positive in 23 patients (31%) (table 2). The PPV was 85%, NPV 44%, the sensitivity 46% and specificity 84% (table 3).

TABLE 2 Diagnostic characteristics for the hypoxia-altitude simulation test (HAST) to predict altitude-related adverse health effects (ARAHE) in patients with COPD travelling to 3100 m

S_{pO_2} criterion	Positive	Negative	Total
ARAHE	50	25	75
HAST	27	48	75
	ARAHE positive	**ARAHE negative**	
HAST by S_{pO_2} positive	23 TP	4 FP	27
HAST by S_{pO_2} negative	27 FN	21 TN	48
Total patients	50	25	75
P_{aO_2} criterion	**Positive**	**Negative**	**Total**
ARAHE	44	20	64
HAST	12	52	64
	ARAHE positive	**ARAHE negative**	**Total patients**
HAST by P_{aO_2} positive	11 TP	1 FP	12
HAST by P_{aO_2} negative	33 FN	19 TN	52
Total patients	44	20	64

Cut-off values for a positive HAST are set as S_{pO_2} <85% and/or P_{aO_2} <6.6 kPa according to the British Thoracic Society (BTS). Positive ARAHE is defined as development of acute mountain sickness, need of oxygen therapy due to severe hypoxaemia (resting S_{pO_2} <80% >30 min or <75% for >15 min) or any other intercurrent illness needing treatment such as chest pain, severe dyspnoea, arrhythmia, hypertensive crisis or others (see text). S_{pO_2}: oxygen saturation measured by pulse oximetry; P_{aO_2}: arterial oxygen tension; TP: true positive; FP: false positive; FN: false negative; TN: true negative.

TABLE 3 Diagnostic accuracy test for the hypoxia-altitude simulation test (HAST) by oxygen saturation measured by pulse oximetry (S_{pO_2}) or arterial oxygen tension (P_{aO_2}) cut-offs

	Positive HAST according to:	
	Cut-off S_{pO_2} <85%	Cut-off P_{aO_2} <6.6 kPa
Apparent prevalence (HAST positive/all patients)	0.36 (0.25–0.48)	0.19 (0.10–0.30)
True prevalence (ARAHE present/all patients)	0.67 (0.55–0.77)	0.69 (0.56–0.80)
Sensitivity (TP/(TP+FN))	0.46 (0.32–0.61)	0.25 (0.13–0.40)
Specificity (TN/(TN+FP))	0.84 (0.64–0.95)	0.95 (0.75–1.00)
Positive predictive value (TP/(TP+FP))	0.85 (0.66–0.96)	0.92 (0.62–1.00)
Negative predictive value (TN/(TN+FN))	0.44 (0.29–0.59)	0.37 (0.24–0.51)
Positive likelihood ratio (sensitivity/1 − specificity)	2.87 (1.12–7.41)	5.00 (0.69–36.13)
Negative likelihood ratio (1 − sensitivity/specificity)	0.64 (0.47–0.87)	0.79 (0.65–0.96)
Proportion of correctly classified patients	0.59 (0.47–0.70)	0.47 (0.34–0.60)

Cut-off values for a positive HAST are set as S_{pO_2} <85% and/or P_{aO_2} <6.6 kPa according to the British Thoracic Society (BTS) [14]. Positive ARAHE is defined as development of acute mountain sickness, need of oxygen therapy due to severe hypoxaemia (resting S_{pO_2} <80% >30 min or <75% for >15 min) or any other intercurrent illness needing treatment such as chest pain, severe dyspnoea, arrhythmia, hypertensive crisis or others (see text) [19]. ARAHE: altitude-related adverse health effects; TP: true positive; FP: false positive; FN: false negative; TN: true negative.

P_{aO_2} cut-off at end-HAST

According to the P_{aO_2} <6.6 kPa criterion, HAST and ARAHE were positive in 11 patients (17%). The PPV was 92%, the NPV 37%, the sensitivity 25% and specificity 95%.

The diagnostic accuracy of the HAST with S_{pO_2} or P_{aO_2} cut-offs to predict ARAHE were 59% or 47%.

ROC curves for S_{pO_2} and P_{aO_2} at end-HAST and resting S_{pO_2} and S_{pO_2} at peak 6MWD are shown in figure 2. The AUC for the end-HAST S_{pO_2} and P_{aO_2} were 0.71 (95% CI 0.55–0.83) and 0.76 (95% CI 0.62–0.86), respectively, whereas the AUC for baseline resting S_{pO_2} was 0.57 (95% CI 0.43–0.7) and for S_{pO_2} at peak 6MWD was 0.58 (95% CI 0.45–0.71).

S_{pO_2} and heart rate during the HAST at 3, 6, 9, 12 and 15 min are visualised in figure 3. It shows that the major drop in S_{pO_2} occurs in the first minutes after exposure to hypoxia with a level-off after 9 min (figure 3).

Univariate logistic regression to predict ARAHE from the main baseline variables is given in table 4 and shows that S_{pO_2} and P_{aO_2} at end-HAST significantly predicted ARAHE. Other baseline characteristics such as sex, age, BMI, baseline S_{pO_2}, dyspnoea perception by the Modified Medical Research Council scale grade, FEV_1 and the 6MWD were not significant.

Discussion

In this large prospective study in patients with COPD undergoing an altitude sojourn including 2 days/nights at HA, we showed that recommended cut-offs for S_{pO_2} or P_{aO_2} assessed by the HAST before travel revealed low overall test accuracies with only 59 or 47% of patients correctly classified regarding ARAHE at 3100 m. However, with a PPV of 85 or 92%, a positive HAST at LA quite accurately identified patients with ARAHE, but a negative HAST was insufficient to rule it out. An ROC curve of S_{pO_2} or P_{aO_2} at end-HAST to predict ARAHE reveals that adapting cut-offs would not increase diagnostic accuracy of the HAST, but that end-HAST oxygenation values performs slightly better than baseline or end-exercise S_{pO_2} on ambient air at LA. If a HAST is considered, 6–9 min breathing F_{IO_2} of 15% lowers the S_{pO_2} to a similar extent as 15 min, which indicates time-saving potential.

Facilitated altitude ascent enables an increasing number of people, including highly prevalent COPD patients, to travel from LA to HA, and particularly in patients with respiratory diseases, severe hypoxaemia is feared to cause heart or other vital organs disease [5, 22–25].

Whereas physiological changes with increasing altitude and potential adverse events, such as AMS, have been studied mainly in healthy, younger mountaineers, scientific data on ARAHE in older patients with cardiopulmonary disease remain scarce [12, 26]. Algorithms and managing guidelines like those from BTS [14, 27] and the French Society of Pneumology [28] for patients with respiratory diseases who wish to

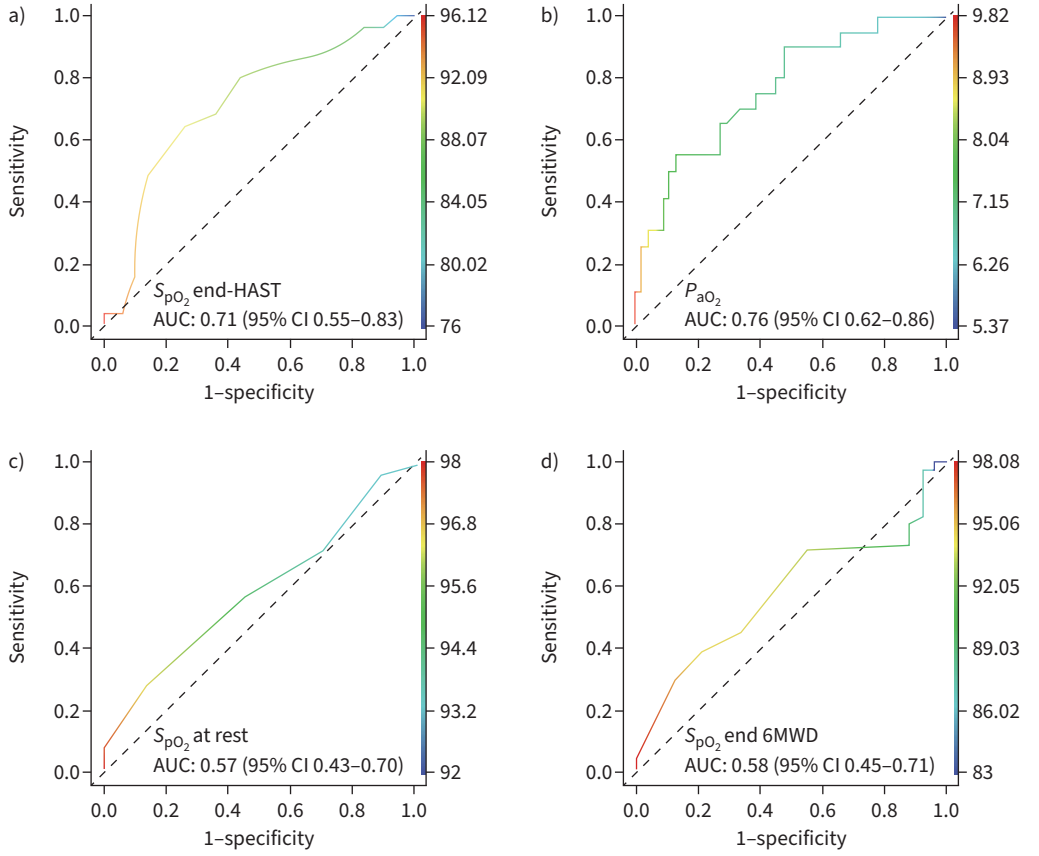

FIGURE 2 Receiver operating characteristic (ROC) curves are shown for a) oxygen saturation measured by pulse oximetry (S_{pO_2}) and b) arterial oxygen tension (P_{aO_2}) at the end of the hypoxia-altitude simulation test (HAST), such as c) baseline resting S_{pO_2} at low altitude before the HAST and d) the S_{pO_2} at the peak 6-min walk distance (6MWD).

ascend to altitude or travel by air are thus mainly based on clinical reasoning and expert consensus in lack of high-quality evidence. According to medical practice, it is recommended to obtain a detailed medical history and symptoms including recent exacerbation, current treatments and adaptation of those if required,

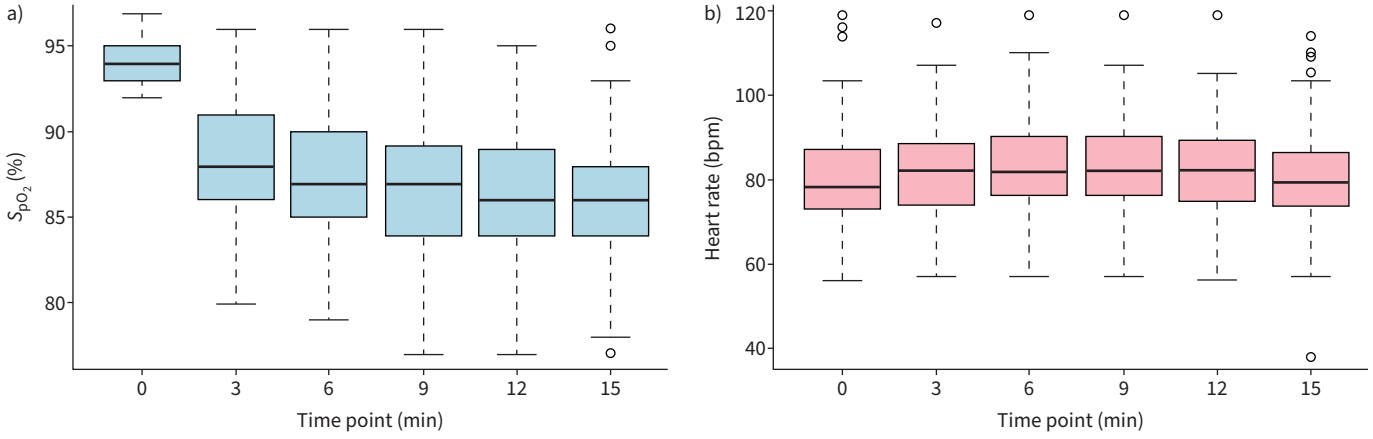

FIGURE 3 Boxplots of a) oxygen saturation measured by pulse oximetry (S_{pO_2}) and b) heart rate during the hypoxia-altitude simulation test (HAST) at the beginning (0 min) and at 3, 6, 9, 12 and 15 min are shown with the line indicating the mean, the box the 25th and 75th quartile and the whiskers revealing the extremes.

TABLE 4 Univariate regression analysis of predictors of altitude-related adverse health effects (ARAHE)

Dependent variable = ARAHE	Odds ratio (95% CI)	p-value
Age years	0.971 (0.920–1.024)	0.283
Sex, 1=female	0.725 (0.274–1.903)	0.513
Body mass index kg·m^{-2}	0.934 (0.829–1.048)	0.252
S_{pO_2} on ambient air at 760 m, %	1.315 (0.900–1.971)	0.167
S_{pO_2} at the end of the HAST, %	1.224 (1.066–1.437)	0.007
P_{aO_2} at the end of the HAST, kPA[#]	4.680 (1.920–14.447)	0.002
6-min walk distance m	1.005 (0.997–1.014)	0.182
S_{pO_2} at peak walk distance, %	0.944 (0.798–1.116)	0.494
mMRC grade 1	0.428 (0.138–1.502)	0.183
mMRC grade 2	0.333 (0.077–1.505)	0.163
mMRC grade 3	0.500 (0.023–6.453)	0.604
FEV_1 % predicted	1.014 (0.971–1.060)	0.530

Predictive variables revealing a p<0.05 in univariate analysis were tested with age, sex and BMI in the multivariate model as predefined. S_{pO_2}: oxygen saturation measured by pulse oximetry; HAST: hypoxia-altitude simulation test; P_{aO_2}: arterial oxygen tension; mMRC: Modified Medical Research Council scale; FEV_1: forced expiratory volume in 1 s. [#]: available only in 64 patients who had arterial blood gases at the end of the HAST.

baseline exercise capacity and previous altitude exposure experiences, and the logistics of the intended journey should be reviewed [29]. In addition, screening by the simple and widely accessible pulse oximetry is recommended. Hereby, S_{pO_2} >95% is considered safe for flying or altitude travel [14, 27]. In our study population three out of 14 patients with S_{pO_2} >95% at LA had a positive HAST and seven out of 14 still developed ARAHE at HA, which indicates that neither the HAST nor the baseline resting S_{pO_2} are sufficient to predict event-free altitude travel. In the presence of a S_{pO_2} <92% (P_{aO_2} 67–73 mmHg) and/or additional risk factors (hypercapnia, FEV_1 <50% predicted, cardiac comorbidity) BTS recommends a HAST prior to travel. Concerning the HAST, a subject is advised to use oxygen if P_{aO_2} falls to <6.6 kPa or S_{pO_2} <85% during the HAST, despite no high-quality evidence supporting these cut-off values [30]. The physiological theory behind these cut-off values is that S_{pO_2} stays above the steep part of the oxyhaemoglobin dissociation curve, and 6.6 kPa is considered to represent the lower safety limit for hypoxaemia, before excessive hypoxic pulmonary vasoconstriction can occur, albeit clinical evidence for this is lacking [31]. Patients with COPD frequently reveal cardiac comorbidities, and it is thus feared that hypoxaemia at altitude could provoke or worsen cardiac ischaemia, arrhythmia and other heart disease and accelerate pulmonary hypertension [5, 29, 32]. It is thus of paramount importance when studying patients with cardiopulmonary diseases at altitude to involve all ARAHE, including not only AMS and any other intercurrent illness including cardiac ischaemia, arrhythmia or hypertension, but also severe hypoxaemia requiring oxygen therapy [12, 26]. With the concept of ARAHE including to prescribe supplemental oxygen only if the S_{pO_2} falls below 80% for over 30 min at altitude and following strict safety rules, we observed several hundred patients with COPD at an altitude of up to 3100 m for 3 days without the relevant adverse events seen in previous studies [5, 12, 26, 33]. In the present large prospective study we evaluated the predictive value of the HAST for ARAHE including AMS, severe and potentially live-threating hypoxaemia or any intercurrent illness in COPD patients undergoing a sojourn of 2 days/nights at HA. Herein, the HAST revealed an overall diagnostic accuracy of 59% or 47%, which we consider insufficient for adequate patient counselling. Our study is thus in line with a study by Edvardsen *et al.* [34], who found that the HAST was not able to predict symptoms in 88 COPD patients undergoing air travel, and also in line with the editorial by Howard [35] of the cited paper, our data underscore the claim that hypoxaemia is not the only factor in hypoxia-related symptoms. The fact that the PPV was 85 or 92% with the S_{pO_2} or P_{aO_2} threshold indicates that the HAST has some value for the 27 or 12 patients with a positive HAST at LA in that they are likely to develop ARAHE within 2 days at 3100 m.

Plotting the S_{pO_2} or P_{aO_2} at the end of the HAST as ROC curves (see figure 2) indicates that adjustments of HAST cut-off values would not alter our finding in a clinically relevant way, as higher specificity comes at the expense of lower sensitivity. The AUC for the S_{pO_2} or P_{aO_2} at end-HAST was 0.71 or 0.76 and thus performed slightly better than baseline resting S_{pO_2} on ambient air (AUC 0.57) or S_{pO_2} at the end of the 6MWD (AUC 0.58). Logistic regression analysis showed that the chance of developing ARAHE at HA increases by 22% with every per cent drop in S_{pO_2} at end-HAST (table 4).

In accordance with our results, other studies concluded that resting LA S_{pO_2} measurements lacked diagnostic accuracy to identify COPD patients requiring oxygen during air travel [11, 36]. The usefulness

of the HAST to titrate inflight oxygen is questionable; some authors did not find an accurate correlation of blood oxygenation found during the HAST with the ones in airplanes, whilst others found technical challenges and some also a correlation [37, 38, 39]. If a HAST is performed, our data indicate that S_{pO_2} drops within the first minutes, then levels off after 6–9 min, which may indicate that a shorter exposure to hypobaric hypoxia is sufficient.

Although the sample size of the present trial is comparably large with 75 COPD patients of both sexes prospectively exposed to a HAST and real altitude in order to assess ARAHE, larger sample sizes may allow subgroups of ARAHE, such as AMS, cardiac events or others, to be specifically addressed, but such field studies would be even more logistically challenging. This study was performed in central Asia, as it has ideal logistics with an altitude clinic located at 3100 m that was easily accessible by buses and guaranteed highest security standards with the possibility to evacuate patients in a timely manner in case of severe unexpected adverse events at any time including at night. Including other populations worldwide of various ethnicities and at different altitudes would have strengthened the results but was logistically not feasible and not financed. A criticism might be that the safety cut-off to give oxygen therapy at S_{pO_2} <80% for >30 min or <75% for >15 min may be arbitrary. We used this cut-off in many newcomers to altitude with COPD up to 3 days, and for other cardiopulmonary diseases such as pulmonary hypertension, and did not observe life-threatening adverse events at altitude. We emphasise that this cut-off might need to be raised if cardiorespiratory patients were exposed to altitude for longer periods, such as weeks or months.

In conclusion, this is the first study to prospectively compare S_{pO_2} or P_{aO_2} at the end of a HAST at LA with ARAHE during a subsequent 3-day stay at HA in a large cohort (75 patients) with COPD travelling to altitude. Our data show that the overall value of the HAST to predict ARAHE at altitude was insufficient to recommend its use in clinical practice. Whereas the relatively high PPV indicates some value of a positive HAST at LA to reliably predict ARAHE development within 48 h at 3100 m, patients with a negative test result are still at considerable risk of developing an ARAHE at altitude. As measures obtained at LA have too low diagnostic accuracy to indicate safe travel at altitude, counselling of COPD patients before ascent should mainly focus on preventive measures, such as acetazolamide, and timely recognition of imminent ARAHE to start oxygen therapy or descent.

Provenance: Submitted article, peer reviewed.

This study is registered at www.clinicaltrials.gov with identifier number NCT04915378. Individual data will be shared upon reasonable research requests to the authors after deidentification of participants.

Author contributions: T. Sooronbaev author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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References

1 Tremblay JC, Ainslie PN. Global and country-level estimates of human population at high altitude. *Proc Natl Acad Sci USA* 2021; 118: e2102463118.
2 Varmaghani M, Dehghani M, Heidari E, *et al.* Global prevalence of chronic obstructive pulmonary disease: systematic review and meta-analysis. *East Mediterr Health J* 2019; 25: 47–57.
3 Griffo R, Spanevello A, Temporelli PL, *et al.* Frequent coexistence of chronic heart failure and chronic obstructive pulmonary disease in respiratory and cardiac outpatients: evidence from SUSPIRIUM, a multicentre Italian survey. *Eur J Prev Cardiol* 2017; 24: 567–576.
4 Latshang TD, Kaufmann B, Nussbaumer-Ochsner Y, *et al.* Patients with obstructive sleep apnea have cardiac repolarization disturbances when travelling to altitude: randomized, placebo-controlled trial of acetazolamide. *Sleep* 2016; 39: 1631–1637.
5 Lichtblau M, Latshang TD, Furian M, *et al.* Right and left heart function in lowlanders with COPD at altitude: data from a randomized study. *Respiration* 2019; 97: 125–134.
6 Furian M, Flueck D, Latshang TD, *et al.* Exercise performance and symptoms in lowlanders with COPD ascending to moderate altitude: randomized trial. *Int J Chron Obstruct Pulmon Dis* 2018; 13: 3529–3538.
7 Gong H, Jr, Tashkin DP, Lee EY, *et al.* Hypoxia-altitude simulation test. Evaluation of patients with chronic airway obstruction. *Am Rev Respir Dis* 1984; 130: 980–986.

8 Dillard TA, Moores LK, Bilello KL, *et al.* The preflight evaluation. A comparison of the hypoxia inhalation test with hypobaric exposure. *Chest* 1995; 107: 352–357.
9 Cogo A, Fischer R, Schoene R. Respiratory diseases and high altitude. *High Alt Med Biol* 2004; 5: 435–444.
10 Kelly PT, Swanney MP, Seccombe LM, *et al.* Air travel hypoxemia vs. the hypoxia inhalation test in passengers with COPD. *Chest* 2008; 133: 920–926.
11 Akero A, Christensen CC, Edvardsen A, *et al.* Pulse oximetry in the preflight evaluation of patients with chronic obstructive pulmonary disease. *Aviat Space Environ Med* 2008; 79: 518–524.
12 Furian M, Lichtblau M, Aeschbacher SS, *et al.* Efficacy of dexamethasone in preventing acute mountain sickness in COPD patients: randomized trial. *Chest* 2018; 154: 788–797.
13 Lichtblau M, Furian M, Aeschbacher SS, *et al.* Dexamethasone improves pulmonary hemodynamics in COPD-patients going to altitude: a randomized trial. *Int J Cardiol* 2019; 283: 159–164.
14 Ahmedzai S, Balfour-Lynn IM, Bewick T, *et al.* Managing passengers with stable respiratory disease planning air travel: British Thoracic Society recommendations. *Thorax* 2011; 66: Suppl. 1, i1–i30.
15 ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002; 166: 111–117.
16 Graham BL, Steenbruggen I, Miller MR, *et al.* Standardization of Spirometry 2019 Update. An official American Thoracic Society and European Respiratory Society technical statement. *Am J Respir Crit Care Med* 2019; 200: e70–e88.
17 Josephs LK, Coker RK, Thomas M. Managing patients with stable respiratory disease planning air travel: a primary care summary of the British Thoracic Society recommendations. *Prim Care Respir J* 2013; 22: 234–238.
18 Schneider SR, Mayer LC, Lichtblau M, *et al.* Effect of a daytrip to altitude (2500 m) on exercise performance in pulmonary hypertension – randomized cross-over trial. *ERJ Open Res* 2021; 7: 00314-2021.
19 Woolcott OO. The Lake Louise acute mountain sickness score: still a headache. *High Alt Med Biol* 2021; 22: 351–352.
20 Prince TS, Thurman J, Huebner K. Acute Mountain Sickness. Treasure Island, StatPearls, 2022.
21 Cohen JF, Korevaar DA, Altman DG, *et al.* STARD 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration. *BMJ Open* 2016; 6: e012799.
22 Latshang TD, Tardent RPM, Furian M, *et al.* Sleep and breathing disturbances in patients with chronic obstructive pulmonary disease traveling to altitude: a randomized trial. *Sleep* 2019: 42: zsy203.
23 Bisang M, Latshang TD, Furian M, *et al.* Risk of cardiac arrhythmias in lowlanders with COPD travelling to high altitude. Randomized trial of nocturnal oxygen therapy. *Respiration* 2017; 94: 76–156.
24 Bisang M, Latshang TD, Aeschbacher SS, *et al.* Nocturnal heart rate and cardiac repolarization in lowlanders with chronic obstructive pulmonary disease at high altitude: data from a randomized, placebo-controlled trial of nocturnal oxygen therapy. *Front Med (Lausanne)* 2021; 8: 557369.
25 Carta AF, Bitos K, Furian M, *et al.* ECG changes at rest and during exercise in lowlanders with COPD travelling to 3100 m. *Int J Cardiol* 2021; 324: 173–179.
26 Furian M, Buergin A, Scheiwiller PM, *et al.* Prevention of altitude-related illness in patients with COPD by acetazolamide. RCT. *Eur Respir J* 2019; 54: Suppl. 63, PA3938.
27 Coker RK, Armstrong A, Church AC, *et al.* BTS Clinical Statement on air travel for passengers with respiratory disease. *Thorax* 2022; 77: 329–350.
28 Perez T, Garcia G, Roche N, *et al.* [Societe de pneumologie de langue francaise. Guidelines for clinical practice. Management of COPD. Update 2012: Pulmonary function tests (Summary)]. *Rev Mal Respir* 2014; 31: 85–90.
29 Georges T, Le Blanc C, Ferreol S, *et al.* Effects of altitude on chronic obstructive pulmonary disease patients: risks and care. *Life (Basel)* 2021; 11: 798.
30 Cramer D, Ward S, Geddes D. Assessment of oxygen supplementation during air travel. *Thorax* 1996; 51: 202–203.
31 Swenson ER. Hypoxic pulmonary vasoconstriction. *High Alt Med Biol* 2013; 14: 101–110.
32 Lichtblau M, Furian M, Aeschbacher SS, *et al.* Right-to-left shunts in lowlanders with COPD traveling to altitude: a randomized controlled trial with dexamethasone. *J Appl Physiol (1985)* 2020; 128: 117–126.
33 Furian M, Mademilov M, Buergin A, *et al.* Acetazolamide to prevent adverse altitude effects in COPD and healthy adults. *NEJM Evidence* 2022; 1: EVIDoa2100006.
34 Edvardsen A, Ryg M, Akero A, *et al.* COPD and air travel: does hypoxia-altitude simulation testing predict in-flight respiratory symptoms? *Eur Respir J* 2013; 42: 1216–1223.
35 Howard LS. Last call for the flight simulation test? *Eur Respir J* 2013; 42: 1175–1177.
36 Christensen CC, Ryg M, Refvem OK, *et al.* Development of severe hypoxaemia in chronic obstructive pulmonary disease patients at 2,438 m (8,000 ft) altitude. *Eur Respir J* 2000; 15: 635–639.
37 Seccombe LM, Kelly PT, Wong CK, *et al.* Effect of simulated commercial flight on oxygenation in patients with interstitial lung disease and chronic obstructive pulmonary disease. *Thorax* 2004; 59: 966–970.
38 Honigman B, Theis MK, Koziol-McLain J, *et al.* Acute mountain sickness in a general tourist population at moderate altitudes. *Ann Intern Med* 1993; 118: 587–592.
39 Akero A, Christensen CC, Edvardsen A, *et al.* Hypoxaemia in chronic obstructive pulmonary disease patients during a commercial flight. *Eur Respir J* 2005; 25: 725–730.