CHEST

Choosing an Adequate Test to Determine Fitness for Air Travel in Obese Individuals

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BACKGROUND: Air travel is physically demanding and, because obesity is rising, physicians increasingly need to assess whether such patients can fly safely. Our aim was to compare the diagnostic accuracy of two routinely used exercise tests, 50-m walk test and 6-min walk test, and hypoxic challenge testing (HCT) in obese individuals. We further explored the diagnostic potential of perceived dyspnea as measured with the Borg scale because this is often recorded subsequent to walking tests.

METHODS: In this prospective study, we examined 21 obese participants (10 women, age 51 ± 15 [mean ± SD], BMI 36 ± 5 kg/m^2). The most prevalent comorbidity was COPD (n = 11). The reference standard for in-flight hypoxia, defined as oxygen saturation below 90%, was established in an altitude chamber. Diagnostic accuracy of each index test was estimated by area under the receiver operating characteristic curve (AUC).

RESULTS: Of the 21 participants, 13 (9 with COPD) were identified with in-flight hypoxia. HCT was the only test separating the reference groups significantly with AUC 0.87 (95% CI, 0.62-0.96). Neither of the walking tests predicted noticeably above chance level: 50 m walk test had an AUC of 0.63 (0.36-0.84) and 6MWT had an AUC of 0.64 (0.35-0.86). We further observed good prognostic ability of subjective dyspnea assessment when recorded after 6MWT with an AUC of 0.80 (0.55-0.93).

CONCLUSIONS: In-flight hypoxia in obese individuals can be predicted by HCT but not by simple walking tests.

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KEY WORDS: air travel; hypoxic challenge test; obesity; walk test

ABBREVIATIONS: 6MWT = 6-min walk test; 50mWT = 50-m walk test; ALT = altitude chamber; ANOVA = analysis of variance; ATS = ANOVA-type statistic; AUC = area under the ROC curve; HCT = hypoxic challenge test; ROC = receiver operating characteristic; Spo_2 = peripheral oxygen saturation

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Modern society grants individuals with longer lives and a wide range of liberties, including the freedom to travel. At the same time, obesity and cardiopulmonary diseases are on the rise, and a common mode of travel, the airplane, is starting to pose a serious health risk for a growing number of people.[1-3] Obesity affects the respiratory system in multiple ways: fat deposition impairs mechanical lung function and gas exchange, induces ventilation/perfusion mismatch, and narrows the upper airways, predisposing airway occlusion.[4-6] Because of the reduced atmospheric pressure in an airliner cabin, up to an altitude-equivalent of 8,000 ft (2,438 m),[7] obese individuals are at increased risk of in-flight medical complications.[8] Physicians increasingly need to evaluate their patients' ability to fly safely without supplemental oxygen but, unfortunately, practitioners seeking guidance are confronted with inconclusive evidence and even contradictory advice, especially when it comes to examination methods available outside of highly specialized centers.[9,10] An emerging consensus deems common clinical metrics recorded at sea level, such as oxygen saturation (Spo_2) or lung function, unsuitable,[11] whereas the two most frequently proposed methods, either simulation of the corresponding hypobaric atmosphere[12] or, as the next best option, exposure to hypoxic gas,[13] are not routinely available. Several tests have been proposed to fill this gap but although some were quickly rejected, such as a number of predictive equations,[14] the potential of others, such as exercise- or symptom-based assessment, remains uncertain.[15] Numerous past studies did not acknowledge the diagnostic nature of fitness to air travel evaluation and reported results using inadequate metrics, perpetuating uncertainty.[16]

Our primary objective was to evaluate the diagnostic accuracy of three different index tests: 50-m walk test (50mWT), 6-min walk test (6MWT), and normobaric hypoxic challenge testing (HCT) in obese individuals. Fitness to fly was defined as a person's ability to maintain $Spo_2 \geq 90\%$ when exposed to flight conditions because there is no known risk of tissue damage above this level.[17] This reference standard was established in an altitude chamber (ALT). The secondary goal was to explore whether perceived dyspnea recorded with the Borg scale[18] could help to discriminate between reference groups because this is frequently recorded subsequent to walking tests.[19]

Materials and Methods

Protocol

This prospective study was approved by the ethical committee of the University of Witten-Herdecke e.V. (approval no. 105/2013). Data recording took place between March 2014 and February 2015 and all participants gave written informed consent before entering the test protocol. Clinical examination, measurement of blood gases at rest, bodyplethysmography, 50mWT, and 6MWT were done at Bethanien Hospital (Solingen). HCT and ALT were performed at the German Aerospace Centre (Cologne). Each session started at 10 o'clock AM and ALT was purposefully done last to keep examiners blind to the reference standard during index tests.

Participants

Participants were recruited at a university-affiliated center for pulmonary diseases (Bethanien Hospital). The primary inclusion criterion was a BMI >30 kg/m^2 and patients were contacted in descending order of last admission. The recruitment process is detailed in Figure 1.

Of the 21 (10 women) obese participants included in the study, mean BMI 36 ± 5 kg/m^2 (median, 35) and average age 51 ± 15 years (median, 50), 11 (4 women) were additionally diagnosed with COPD, defined by a postbronchodilator FEV_1/FVC ratio <0.70.[20] Other comorbidities were hypertension (n = 7), sleep apnea (n = 6), hypothyreosis (n = 4), and osteoarthritis (n = 3).

Test Methods

50mWT: Participants were asked to walk a labeled distance of 50 m as fast as possible.[21] Time required to cover the distance was recorded. Spo_2 was measured using the same device for all participants (Onyx 9500, Nonin Medical).

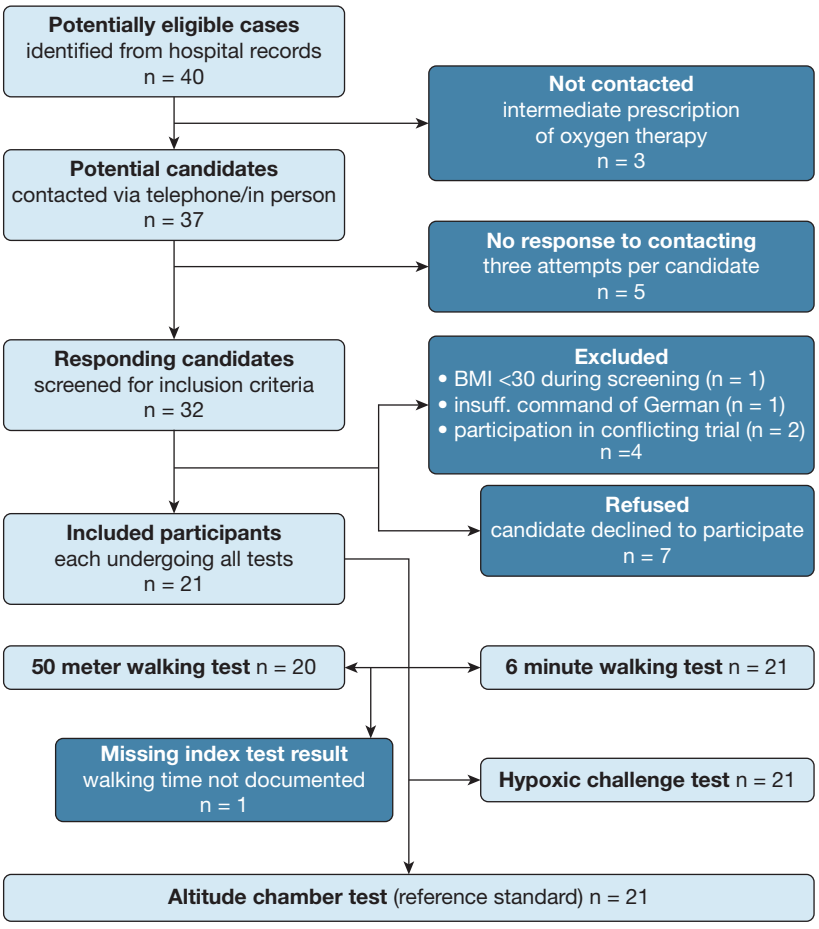
6MWT: 6MWT was performed in standardized manner subsequent to a resting period of at least 5 min after 50mWT.[19] Participants were asked to walk as fast as possible for 6 min on a labeled, flat path. They were allowed to stop, if necessary. The investigator measured the distance covered. Spo_2 was recorded identical to 50mWT.

Borg Scale: Participants scored their perceived dyspnea at rest and subsequent to each walking test using a German translation of the Borg scale[18] in its 0- to 10-point form published in 2002.[22]

HCT: HCT reduces the oxygen fraction of inspired gas to simulate the oxygen partial pressure during air travel.[23] HCT was conducted in accordance with published recommendations.[15] Participants were seated in the ALT at ambient pressure of that day (1,000-1,018 mbar). Breathing gas was supplied from a cylinder with 15.1% oxygen in nitrogen (Praxair) and dispensed via face masks with demand regulators (AVOX PressureVak-II, Amron-Int, Vista). Exposure to the hypoxic gas was completed when each participant reached equilibrium Spo_2 for at least 1 min. Steady-state condition was determined by an expert observer on the basis of a waveform of Spo_2 readings. The average time needed to reach equilibrium was 16 ± 5 min. Because of the high probability of artefacts Spo_2 was recorded using four independent devices (OEM-EG00352, Medlab; PalmSat-2500, WristOx-3100, and OEM-III, Nonin Medical).

ALT: The reference standard for fitness to fly was established in the ALT because it reproduces the environmental conditions of an airplane cabin.[24] It captures not only the effect of altered oxygen partial pressure but also the influence of reduced barometric pressure on lung mechanics, which might be relevant for patients with lung hyperinflation or impaired thoracic compliance.[25] The chamber pressure was lowered within 4 min to 753 mbar (8,000 ft) while participants were freely breathing air from the chamber atmosphere.

Figure 1 – *Diagram of recruitment process and study flow.*



Continuous venting with outside air guaranteed normal levels of oxygen and CO_2. Duration of the altitude exposure was determined using the same criterion used during HCT and Spo_2 was recorded with the same devices. The average time needed to reach equilibrium was 5 ± 4 min of breathing air at altitude.

Lung Function and Blood Gas Analysis: Pulmonary function was tested using the Jaeger MasterScreen Body (CareFusion Germany GmbH), applying reference values from the European Coal and Steel Community.[26] Blood gas analyses were done from hyperemic ear lobe blood samples using the ABL800 blood gas analyser (Radiometer GmbH).

Analysis

Calculations were performed using R. version 3.5.1 (R Foundation). Descriptive statistics are presented by mean ± SD. Covariation is reported using Pearson correlation coefficient as a descriptive metric. During HCT and ALT, the equilibrium Spo_2 of each individual was determined by computing the median of all artefact-free pulse oximeter readings during the first minute of equilibrium. The reference standard was dichotomized using a clinical criterion for hypoxia[17]; thus, participants with equilibrium Spo_2 during ALT of ≥90% were considered fit to fly. Overall diagnostic accuracy of the index tests was measured using the area under the receiver operating characteristic curve (AUC). We tested the two-sided hypothesis whether tests performed above chance level (ie, AUC differed from 0.5) to an alpha level of 5% using the nonparametric analysis of variance-type statistic.[27] Covariance matrices were estimated using the same asymptotic approach and a logit-transformation was applied to maintain the meaningful [0, 1] interval for 95% CIs. One observation of the 50mWT was not recorded during testing and treated using an omission approach for missing values in rank-based statistics.[28] Recruitment of participants was guided by the intent to identify promising tests of at least 0.8 AUC while accepting a beta error of 20%. By applying our dichotomization to results reported in a similar study,[24] we estimated a 1:1 ratio between reference groups. Under these assumptions, a minimum of 20 participants appeared sufficient.

Results

We identified 13 of the 21 participants with a positive reference standard (ie, in-flight hypoxia), of which 9 had COPD. The mean Spo_2 in the ALT was 88 ± 1% in those with this condition present and 92 ± 2% when it was absent. Baseline characteristics, blood gas analysis, and lung function testing of each reference group are provided in Table 1.

Figure 2 shows the primary analysis, receiver operating characteristic curves of HCT with AUC 0.87 (95% CI, 0.62-0.96), 50mWT with AUC

0.63 (0.36-0.84), and 6MWT with AUC 0.64 (0.35-0.86). The mean (± SD) measurements of HCT, 50mWT, and 6MWT for individuals with and without in-flight hypoxia were 89 ± 2 vs 93 ± 3% Spo_2, 34 ± 6 vs 31 ± 5 s, and 484 ± 73 vs 522 ± 81 m. Although both walking tests were in good agreement with each other (r = -0.83), it is apparent that only the prediction of HCT (analysis of variance-type statistic = 7.146, df = 1, $P = .008$) can be distinguished from chance level. Expectedly, ALT is at the verge of strong correlation with HCT (r = 0.70), whereas correlation is weak with 50mWT (r = -0.16) and 6MWT (r = 0.19).

We further explored the prognostic potential of perceived dyspnea as measured with the Borg scale. Evaluation of dyspnea at rest, AUC 0.56 (0.40-0.71), and after 50mWT, AUC 0.62 (0.36-0.82), were insensitive to in-flight hypoxia but AUC increased to 0.80 (0.55-0.93) when done following 6MWT. Figure 3 visualizes the AUC of each strategy explored. Only the 95% CI of HCT and dyspnea after 6MWT do not include 0.5 (ie, chance level).

Discussion

Our results indicate robust diagnostic accuracy of HCT regarding occurrence of in-flight hypoxia in obese individuals, whereas 50mWT and 6MWT did not separate the reference groups. The latter is worrisome. Although evidence supporting actual diagnostic efficacy is sparse, these two walking tests are frequently mentioned in context of fitness to fly evaluation, particularly in gray literature. Any exercise test will arguably provide some crude assessment of cardiorespiratory reserve, but this does not appear to be sufficiently accurate in 50mWT and 6MWT to predict in-flight hypoxia. Walking tests have great appeal because of their ease of implementation, and in combination with circulating superficial knowledge regarding their diagnostic abilities could lull patients or inexperienced physicians into a false sense of safety.

TABLE 1] Participant Characteristics, Blood Gases, and Lung Function by Reference Group

	Fit to Fly			Not Fit to Fly		
	Mean ± SD	Range	% Predicted	Mean ± SD	Range	% Predicted
Participants n	8 (4 women)			13 (6 women)		
Age (y)	47 ± 18	26 - 85		53 ± 13	33 - 76	
BMI (kg/m^2)	37 ± 5	30 - 47		35 ± 6	30 - 42	
No. COPD (GOLD)	2 (1/0/1/0 = stage I/II/III/IV)			9 (2/3/1/3 = stage I/II/III/IV)		
Blood gases (resting at sea level)						
Spo_2 (%)	95 ± 2	91 - 98		95 ± 2	91 - 99	
Pao_2 (mm Hg)	76 ± 12	63 - 99		71 ± 10	58 - 91	
$PaCo_2$ (mm Hg)	38 ± 3	34 - 42		37 ± 3	33 - 41	
HCO_3^- (mmol/L)	27 ± 2	25 - 29		25 ± 2	22 - 27	
pH	7.44 ± 0.02	7.42 - 7.46		7.42 ± 0.02	7.4 - 7.47	
Lung function (resting at sea level)						
FEV_1 (L)	3.3 ± 1.0	1.3 - 4.4	96 ± 16[a]	2.4 ± 1.1	1.1 - 4.6	75 ± 28[a]
FVC (L)	4.0 ± 1.1	2.1 - 5.2	98 ± 16	3.6 ± 1.3	1.8 - 5.9	91 ± 18
FEV_1/FVC (%)	82 ± 10[a]	62 - 93		66 ± 17[a]	42 - 87	
RV (L)	1.9 ± 0.9[a]	1.0 - 3.2	94 ± 32[a]	2.9 ± 1.1[a]	1.7 - 4.9	137 ± 41[a]
TLC (L)	6.0 ± 1.2	4.1 - 8.0	96 ± 17	6.7 ± 1.7	4.6 - 9.6	106 ± 18
ITGV (L)	2.5 ± 0.6[a]	1.6 - 3.5	80 ± 25[a]	3.5 ± 1.3[a]	2.0 - 5.8	109 ± 35[a]
R_{eff} ($kPa \cdot s \cdot L^{-1}$)	0.2 ± 0.1[b]	0.1 - 0.3	61 ± 22[b]	0.4 ± 0.2[b]	0.2 - 1.0	127 ± 75[b]
SR_{eff} ($kPa \cdot s$)	0.6 ± 0.3[b]	0.2 - 1.3	56 ± 33[b]	1.6 ± 0.9[b]	0.5 - 3.0	144 ± 81[b]
ERV (L)	0.7 ± 0.3	0.3 - 1.2	59 ± 18	0.6 ± 0.4	0.2 - 1.5	56 ± 31

ERV = expiratory reserve volume; HCO_3^- = bicarbonate; ITGV = intrathoracic gas volume; $PaCO_2$ = arterial CO_2 pressure; Pao_2 = arterial oxygen pressure; R_{eff} = effective airway resistance; RV = residual volume; Spo_2 = peripheral oxygen saturation; SR_{eff} = specific effective airway resistance; TLC = total lung capacity.

Unadjusted statistical differences between reference groups (Welch) are indicated for descriptive purpose:

[a] $P < .05$

[b] $P \leq .01$

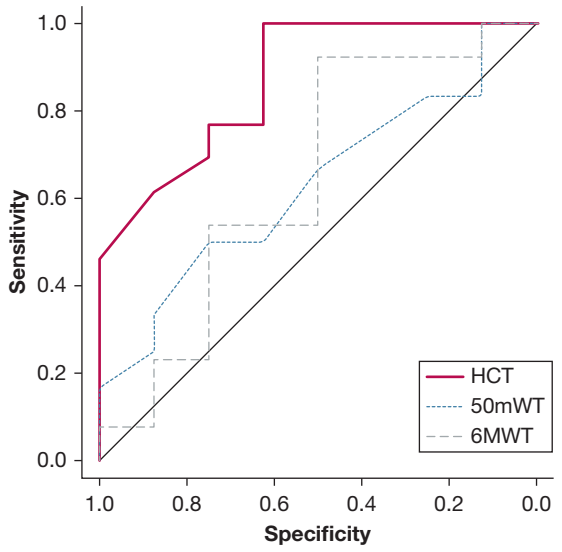


Figure 2 – *Receiver operating characteristic curves of HCT, 50mWT, and 6MWT. 50mWT = 50-m walk test; 6MWT = 6-min walk test; HCT = hypoxic challenge test.*

Alhtough guidelines have started to comment critically on 50mWT, the state of affairs in regarding 6MWT is ill-defined.[15] The test is assumed to correlate with peak oxygen uptake and a moderate correlation of Spo_2 during 6MWT with HCT has been reported.[19,29] We cannot confirm the latter in our cohort (r = 0.22). Moreover, Figure 4 depicts Spo_2 of individuals across all tested conditions and evidently neither Spo_2 at rest nor during 50mWT or 6MWT had any prognostic value.

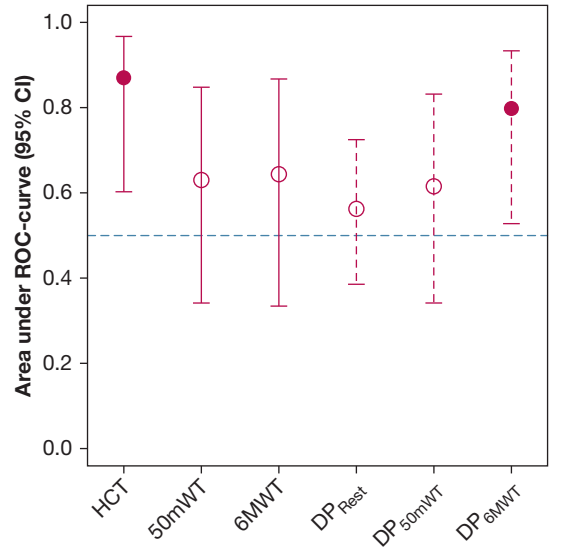


Figure 3 – *Area under the curve estimators and 95% CIs (not symmetrical because of logit transformation) of HCT, 50mWT, 6MWT, and DP_{Rest}, DP_{50mWT}, and DP_{6MWT}. DP_{50mWT} = dyspnea after 50mWT; DP_{6MWT} = dyspnea after 6MWT; DP_{Rest} = dyspnea measured at rest; ROC = receiver operating characteristic. See Figure 2 legend for expansion of other abbreviations.*

Particularly at rest, there is nearly perfect agreement in Spo_2 and blood gases between the reference groups (Table 1), supporting the notion of these parameters being uninformative regarding fitness for air travel.[11]

Remarkably, dyspnea self-assessment after 6MWT appeared to be informative, whereas it did not subsequent to 50mWT. 6MWT might impose a sufficient amount of exercise to elicit the target symptom in those prone to in-flight hypoxia, whereas 50mWT does not. This raises the question as to whether prognostic ability could be further optimized by calibrating the amount of exercise preceding the evaluation. While exercise performance itself might not be as informative as assumed, it might be a valuable means to an end for uncovering relevant diagnostic clues. This implication is coherent with similar observations using a different instrument for dyspnea assessment, the Medical Research Council breathlessness scale.[3] To turn such assessment into a reliable tool, it should be integrated into a stringent diagnostic algorithm.[30]

Preflight assessment is a diagnostic undertaking and it needs to be studied accordingly. Initiatives such as Standards for Reporting of Diagnostic Accuracy Studies[31] and Quality Assessment of Diagnostic Accuracy Studies-2[32] propose reporting standards for diagnostic accuracy trials. Providing complete information for appraisal and replication is pivotal to enable result aggregation and understanding of underlying principles. Revisiting existing data from this perspective could create substantial evidence without fostering new resource-intensive experiments. A critical role in diagnostic studies plays the reference standard (ie, the definition of fitness to fly). Unquestionably, a person not experiencing any negative consequences during and after air travel is fit to fly, but at what point a person is no longer fit to fly is less clear; today, we have no agreed way of quantifying that. Until now, most studies, including this one, used blood oxygenation under some condition as a surrogate marker for fitness to fly; however, it has been reported that oxygenation might not sufficiently predict in-flight medical symptoms and we might need to study domains beyond saturation.[10,33]

The degree of desaturation that will cause cellular injury is not well established and data linking oxygenation during flight to the need for medical attention are missing.[34] Most clinical guidelines define hypoxia as Spo_2 <90%,[17] whereas a threshold of 85% during HCT has been proposed to determine the need for in-flight

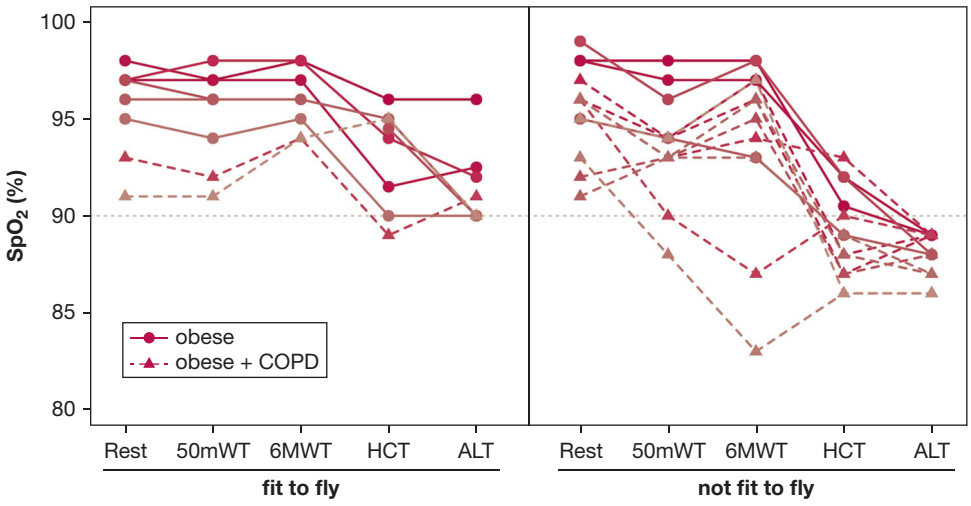


Figure 4 – *Spo_2 profiles of individuals in each reference group at rest, after 50mWT and 6MWT, during HCT and in the ALT. Spo_2 = oxygen saturation. See Figure 2 legend for expansion of other abbreviations.*

oxygen,[23] but HCT is not equivalent to in-flight oxygenation. Observational data from emergency admissions show an increased mortality risk when comparing Spo_2 between 86% and 89% with Spo_2 ≥90%,[35] and episodes of desaturation <90% have been linked to adverse patient outcome in postoperative care.[36] Obese individuals have a greater risk of subclinical myocardial impairment that often remains undiagnosed,[37] taking further into account that medical treatment is often not in close reach during air travel, we considered it the safe choice to use the criterion of in-flight Spo_2 <90% as a reference standard.

Another consideration regarding the validity of our results is whether ALT adequately reflects air travel. In terms of atmospheric conditions and body posture it arguably does, but in terms of exposure duration and behavioral pattern it does not. Extended flight duration, circadian rhythmicity, sleep, food, and alcohol consumption may have effects we did not capture.[2] This is a clear limitation but the alternative, establishing the reference during actual air travel, would have reduced reproducibility and increased risk for participants since exposure could not have been ended in case of emergency.

The effects of obesity are manifold and it is seldom an isolated condition.[1] The most prevalent comorbidity in our sample was COPD, which affected 11 participants to a varying degree. It is unclear whether these two conditions are causally linked, but there is apparent interaction.[38] Although the majority of obese participants without COPD were categorized as fit to fly, only two of those with concurrent COPD showed sufficient oxygenation in the ALT. Obese people commonly suffer from reduced functional residual capacity and peripheral as well as central airway obstruction. In addition to impaired respiratory mechanics, they also tend to accumulate more CO_2, requiring a compensatory increase of ventilation. Patients with COPD additionally suffer from mucus hypersecretion and loss of alveolar tissue, capillaries and supporting interstitial tissue. Although the disadvantages in obesity may be overcome by an increase of ventilation, leading to a homogenization of ventilation-perfusion mismatch, individuals with concomitant COPD might have less compensatory potential in this regard.[39] Because of the small sample size, however, we did not perform an analysis stratified by COPD. Although studies have looked at the isolated effect of COPD in the airplane environment, its interaction with obesity needs further attention.[40]

Conclusion

Given the demographic and public health challenges in modern mobile societies, refinement of the diagnostic instruments for preflight assessment is needed. To leverage research efforts in this direction, we need meaningful ways to quantify fitness for air travel. In this study, HCT showed significant diagnostic accuracy in a cohort of obese individuals, whereas, in contrast to widely held opinion, walking tests did not prove informative regarding in-flight hypoxia. The current study indicates, however, that assessment of perceived dyspnea triggered by exercise could be of substantial diagnostic value.

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