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RESEARCH LETTER

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Air travel in patients suffering from pulmonary hypertension—A prospective, multicentre study

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Abstract

The PEGASUS study is the first multicentric and prospective assessment of the safety of air travel flying in pulmonary hypertension (PH) (NCT03051763). Data of air travel from 60 patients with PH was available. No severe adverse events

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occurred. Nine patients self-reported mild adverse events during flight (13%), while after landing, 12 patients reported events (20%). Solely one patient (2%) had an adverse event leading to medical consultation. In patients with PH and World Health Organization functional classes II and III, air travel was safe.

KEYWORDS
flight, patient behavior, pulmonary arterial hypertension

INTRODUCTION

Commercial air traveling is a well-known burden for the cardiovascular system.[1] Hypoxic vasoconstriction is present during flight and has a meaningful impact on the pulmonary circulation, even in healthy individuals.[1] Pulmonary arterial pressure and thereby afterload of the right heart increase during flights even in healthy individuals.[2,3] In the few last decades, treatment options and treatment strategies for pulmonary hypertension (PH) have improved significantly, which has led to increased survival rates, but also to an improvement of quality of life of patients with PH.[4] Accordingly, the ability and desire of patients with PH to travel, including air travel, is increasing. Current guidelines for PH do not give clear recommendations regarding air traveling, apart from the advice of oxygen therapy and dependence of the functional class.[4] Hence, we aimed to identify whether air traveling is safe in patients with PH.

METHODS

All patients diagnosed with PH aged above 18 years were eligible for the multicentric PEGASUS study. In total, nine PH centers in Germany and Switzerland recruited patients between 2017 and 2019. Furthermore, patient recruitment extended to reaching out to the German PH association ("Pulmonale Hypertonie e.V."). Patients were not encouraged to fly, but had planned and discussed their journey with their treating physician independently from the study. Sample size was determined based on feasibility. Patients were contacted at the beginning of participation, after 1 year, after 2 years as well as immediately before and after flight and asked to complete questionnaires. This study was approved by the Central Ethics Committee (Approval No. 206/14).

PEGASUS questionnaire

In brief, flight date and duration, use of additional oxygen supplementation (and if so, oxygen dose), symptoms during or after air traveling, time of onset of symptoms, pulse, and oxygen saturation at different time points of air traveling were assessed. Baseline characteristics including World Health Organization (WHO) functional class, 6-min walking distance (6MWD), and pulmonary hemodynamic were assessed, as available.

Statistical analyses

Data were collected using Microsoft Excel version 2016. Statistical analyses were performed using R version 4.0.4 (The R Foundation) and SPSS version 27 (IBM). Baseline characteristics are shown as mean ± standard deviation, if normally distributed (assessed by Shapiro–Wilk test) and as median [interquartile range] if non-normally distributed. p-Values < 0.05 were considered as statistically significant.

RESULTS

Overall, 239 patients were included in the PEGASUS study of whom 72 patients traveled by air (flight group) during the study period. In 12 patients who traveled by air data about age and sex were not available; thus, these patients were excluded from further analyses. In the flight group 45 patients (75%) were female and median age was 57 [44, 67] (Table 1). Pulmonary hemodynamics were mildly impaired in the study population, with a median mean pulmonary arterial pressure of 33.5 [25.0, 39.2] mmHg and pulmonary vascular resistance of 347 [157, 568] dynscm-5. In patients with at least two available parameters for risk stratification (i.e., 6MWD, WHO functional class, and B-type natriuretic peptide), most of them were classified as intermediate risk, as shown in Table 1. Data about and during flight were available in all patients. Median flight duration was 3 h,[2,5] and median oxygen saturation at the beginning of the flight was 95% [93%, 97%]. Fourteen patients (25%) received additional on-board oxygen supplementation (mean O_2: 2 [2,3] l/min).

TABLE 1 Baseline characteristic of pulmonary hypertension (PH) flight patients.

	PH flight patients ($N = 60$)
Age (years)	
Mean (SD)	56.3 (15.7)
N	60
Median [*Q*1, *Q*3]	56.5 [43.8, 66.5]
Gender (*N*, %)	
Male	15 (25%)
Female	45 (75%)
PH group (*N*, %)	
1	42 (70%)
2	3 (5%)
3	0 (0%)
4	14 (23%)
5	0 (0%)
NA	1 (2%)
Oxygen therapy	
No	50 (83.3%)
WHO functional class	
I	6 (10%)
II	25 (42%)
III	14 (23%)
IV	1 (2%)
NA	14 (23%)
mPAP (mmHg)	
Mean (SD)	30.8 (17.5)
N	40
Median [*Q*1, *Q*3]	33.5 [25.0, 39.2]
Cardiac index (l/min/m^2)	
Mean (SD)	2.80 (1.02)
N	41
Median [*Q*1, *Q*3]	2.79 [2.47, 3.40]
PVR (dyn)	
Mean (SD)	397 (303)
N	41
Median [*Q*1, *Q*3]	347 [157, 568]
BNP (pg/mL)	
Mean (SD)	94 (221)
N	37
Median [*Q*1, *Q*3]	34 [11, 91]
6MWD, (m/6 min)	
Mean (SD)	306 (267)
N	40
Median [*Q*1, *Q*3]	451 [31, 563]
ESC/ERS score (*N*, %)	
Low risk	17 (28%)
Intermediate risk	22 (37%)
High risk	0 (0%)
NA	21 (35%)

Abbreviations: 6MWD, 6-min walking distance; BNP, B-type natriuretic peptide; ERS, European Respiratory Society; ESC, European Society of Cardiology; mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; SD, standard deviation; WHO, World Health Organization.

Noteworthy, patients without oxygen supplementation showed lower minimal oxygen saturation during flight than patients with oxygen supplementation (89% [84%, 91%] and 92% [89%, 93%], $p = 0.037$). No severe adverse events occurred. Nine patients indicated complaints during flight (13%). Most of the complaints occurred within an hour of the start of the flight (median time until onset of symptoms: 5 [1, 45] min). Four patients (6%) reported pressure in the chest and dizziness. Three patients (4%) reported breathlessness and two patients (3%) reported palpitation. After landing, 12 patients indicated worsening of their symptoms (20%), of whom the complaints of eight patients occurred within 30 min after landing (67%). Five patients (8%) reported dizziness, one patient (2%) exhibited breathlessness and pressure in the chest, respectively. Solely one patient (2%) had an adverse event after flight leading to medical consultation due to tachycardia with treatment neediness.

Interestingly, patients with desaturation (defined as minimal oxygen saturation during flight equal to or lower than 85%[5]) were also more likely to show symptoms during flight (31% vs. 10%, $\chi^2 = 0.076$). In line, patients without oxygen supplementation tended to report more discomfort during the flight than patients with oxygen supplementation (18% vs. 7%, $p = 0.334$).

Reason against air travel

We furthermore investigated the underlying reasons against air traveling. Total of 120 patients (71%) provided information in the questionnaire regarding reasons against air traveling. Mostly, the patients had

no plans to travel during the time of the study (58%). Anxiety and advice from a medical doctor were the further reasons against air traveling in 17% and 13% of the control group, respectively. Interestingly, 44% of patients who did not travel by air stated that they are interested in traveling by air. 98% of patients who did fly during the study period stated that they are willing to fly again.

DISCUSSION

We investigated the prevalence of adverse events during commercial air traveling in a multicentre prospective PH cohort. Interestingly, no severe adverse events occurred during and after the flight. As expected, we identified oxygen desaturation during flight associated with non-severe self-reported adverse events. Current guidelines recommend oxygen supplementation during air traveling in patients with PH, if arterial oxygen partial pressure is below 60 mmHg or if patients are at WHO functional class III or IV.[4] However, this recommendation is only based on small studies with a limited sample size and it is still unclear whether air travel is safe for patients with PH. Our study gives evidence that air travel is safe in patients with PH, which is in line with previous studies that reported air travel safety in patients with various lung diseases[6] or a retrospective analysis in PH patients.[7]

Interestingly, none of the patients included in the PEGASUS study suffered from severe adverse events during flight. However, nonsevere adverse events were self-reported during flight and after landing, since 13% patients had symptoms such as dizziness or breathlessness during the flight. However, symptoms led to medical consultation only in one patient. This is in line with previously reported data on the occurrence of adverse events during flight by Thamm et al.[7] Roubinian and coworkers recently reported that desaturated patients have a slightly increased likelihood to develop symptoms during flight.[5] Our study gives more evidence for the hypothesis that desaturation during air traveling leads to symptoms in patients with PH[5] and therefore that acute hypobaric hypoxia during air travel may stress the RV to a certain extent,[4] in accordance with findings in healthy individuals. The PEGASUS study also revealed that 13% of the non-flying patients did not fly due to a medical advice. Then again, over 98% of the patients who did already air travel are willing to travel by plane (again). Since oxygen supplementation per se was associated with decreased risk of self-reported adverse events (regardless of WHO functional class or other hemodynamic parameters) our data supports the guideline recommendations that oxygen supplementation should be considered in PH.[4] Our study has, however, several limitations. Only

72 patients were traveling by air during the study period. After adjusting for missing age and sex, solely 60 flight group patients were included into analysis. Our study was obviously not blinded, and patients measured and noted oxygen saturation during air travel themselves, which may had influenced symptoms reported. Despite the inclusion of numerous patients, only a small number of patients actually traveled by air. Therefore, integration of air travel information into the new PVRI Go Deep Meta-registry[8] might generate a larger sample size. Of note, patient self-reported adverse events which may lead to biased and particularly nonsignificant results. Only one patient was classified as WHO functional class IV and none with a high risk, and hemodynamic values showed mild PH, suggesting that mostly patients who were in a good functional and risk status chose to fly. Additionally, missing data as well as the heterogeneity observed among PH groups possibly introduce further bias. Consequently, further and more extensive prospective studies are warranted to enhance the generalizability of our findings. Air travel was short, thus, we cannot draw conclusions on PH patients with high risk profile and longer flights. In conclusion, our prospective data support the hypothesis that air travel may be safe for patients with PH being almost exclusively in WHO functional classes II and III. Moreover, oxygen supplementation during flight was well perceived by patient and helped to reduce reported symptoms.

AUTHOR CONTRIBUTIONS

Athiththan Yogeswaran: Conception; drafting and critical review of the manuscript; study design and data collection; statistical analyses. **Jan Grimminger:** Conception; drafting and critical review of the manuscript; study design and data collection. **Khodr Tello:** Drafting and critical review of the manuscript; study design and data collection. **Lukas Becker:** Drafting and critical review of the manuscript; study design and data collection. **Werner Seeger:** Drafting and critical review of the manuscript; study design and data collection. **Friedrich Grimminger:** Drafting and critical review of the manuscript; study design and data collection. **Natascha Sommer:** Drafting and critical review of the manuscript; study design and data collection. **Hossein A. Ghofrani:** Drafting and critical review of the manuscript; study design and data collection. **Tobias J. Lange:** Drafting and critical review of the manuscript; study design and data collection; **Stefan Stadler:** Drafting and critical review of the manuscript; study

design and data collection; **Karen Olsson:** Drafting and critical review of the manuscript; study design and data collection. **Jan C. Kamp:** Drafting and critical review of the manuscript; study design and data collection. **Stephan Rosenkranz:** Drafting and critical review of the manuscript; study design and data collection. **Felix Gerhardt:** Drafting and critical review of the manuscript; study design and data collection. **Katrin Milger:** Drafting and critical review of the manuscript; study design and data collection. **Michaela Barnikel:** Drafting and critical review of the manuscript; study design and data collection. **Silvia Ulrich:** Drafting and critical review of the manuscript; study design and data collection. **Stéphanie Saxer:** Drafting and critical review of the manuscript; study design and data collection. **Ekkehard Grünig:** Drafting and critical review of the manuscript; study design and data collection. **Satenik Harutynova:** Drafting and critical review of the manuscript; Study design and data collection. **Christian Opitz:** Drafting and critical review of the manuscript; study design and data collection. **Hans Klose:** Drafting and critical review of the manuscript; study design and data collection. **Heinrike Wilkens:** Drafting and critical review of the manuscript; study design and data collection. **Michael Halank:** Drafting and critical review of the manuscript; study design and data collection. **Melanie Heberling:** Drafting and critical review of the manuscript; study design and data collection. **Henning Gall:** Conception; drafting and critical review of the manuscript; study design and data collection; statistical analyses. **Manuel J. Richter:** Conception; drafting and critical review of the manuscript; study design and data collection.

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CONFLICT OF INTEREST STATEMENT

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ETHICS STATEMENT

This study was approved by the Central Ethics Committee (approval number 206/14).

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REFERENCES

1. Oliveira-Silva I, Leicht AS, Moraes MR, Simões HG, Del Rosso S, Córdova C, Boullosa DA. Heart rate and cardiovascular responses to commercial flights: relationships with physical fitness. Front Physiol. 2016;7:648.
2. Smith TG, Talbot NP, Chang RW, Wilkinson E, Nickol AH, Newman DG, Robbins PA, Dorrington KL. Pulmonary artery pressure increases during commercial air travel in healthy passengers. Aviat Space Environ Med. 2012;83(7):673–6.
3. Turner BE, Hodkinson PD, Timperley AC, Smith TG. Pulmonary artery pressure response to simulated air travel in a hypobaric chamber. Aerosp Med Hum Perform. 2015;86(6):529–34.
4. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, Carlsen J, Coats AJS, Escribano-Subias P, Ferrari P, Ferreira DS, Ghofrani HA, Giannakoulas G, Kiely DG, Mayer E, Meszaros G, Nagavci B, Olsson KM, Pepke-Zaba J, Quint JK, Rådegran G, Simonneau G, Sitbon O, Tonia T, Toshner M, Vachiery JL, Vonk Noordegraaf A, Delcroix M, Vachiery JL, Vonk Noordegraaf A, Delcroix M, Rosenkranz S, ESC/ERS Scientific Document Group. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J. 2023;61(1):2200879.
5. Roubinian N, Elliott CG, Barnett CF, Blanc PD, Chen J, De Marco T, Chen H. Effects of commercial air travel on patients with pulmonary hypertension. Chest. 2012;142(4):885–92.
6. Coker RK, Shiner RJ, Partridge MR. Is air travel safe for those with lung disease? Eur Respir J. 2007;30(6):1057–63.
7. Thamm M, Voswinckel R, Tiede H, Lendeckel F, Grimminger F, Seeger W, Ghofrani HA. Air travel can be safe and well tolerated in patients with clinically stable pulmonary hypertension. Pulm Circ. 2011;1(2):239–43.
8. Majeed RW, Wilkins MR, Howard L, Hassoun PM, Anthi A, Cajigas HR, Cannon J, Chan SY, Damonte V, Elwing J, Förster K, Frantz R, Ghio S, Al Ghouleh I, Hilgendorff A, Jose A, Juaneda E, Kiely DG, Lawrie A, Orfanos SE, Pepe A, Pepke-Zaba J, Sirenko Y, Swett AJ, Torbas O, Zamanian RT, Marquardt K, Michel-Backofen A, Antoine T, Wilhelm J, Barwick S, Krieb P, Fuenderich M, Fischer P, Gall H, Ghofrani HA, Grimminger F, Tello K, Richter MJ, Seeger W. Pulmonary Vascular Research Institute GoDeep: A meta-registry merging deep phenotyping data from international PH reference centers. Pulm Circ. 2022;12(3):e12123.

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