Manuscript ID: CDT-2020-PPH-10(CDT-20-494)
Title: Altitude exposure in pediatric pulmonary hypertension – are we ready for (flight) recommendations?

Reviewer 1

Comment 1:
Page 5, line 123: I would suggest to add a short introduction at the beginning of the main text explaining the relevance of the topic before going on with pathophysiology.
Reply 1: Thank you for this comment, we added a short introduction:
Nowadays, children and young adults with pulmonary hypertension can be treated with a variety of drugs and interventions thus life expectancy is prolonged and quality of life has improved over the last decade. These individuals wish to take part in a normal life, including traveling by airplane and participating in altitude activities. This article discusses the physiology of altitude exposure, the current state of knowledge in children and adults with pulmonary hypertension, and provides a balanced overview of the latest recommendations for safe travel in pediatric pulmonary hypertension.

Comment 2: Page 5, line 124: Citation of references might be preferably located within the text than in the caption.
Reply 2: we located the references within the text

Comment 3: Page 16, line 408-409: This sentence seems to be incomplete.
Reply 3: we completed the text and changed the text accordingly
Regarding recommendations for neonates and infants we refer to the papers of Samuels, Kohl and Barnett, Bossley and Balfour-Lynn, and Israels et al (21, 58-60).

Comment 4: Page 16, line 414: remove "in".
Reply 4: "in" was removed

Comment 5: Page 24, Table 2: Reference?
Reply 5: This table is an unique table and has not been published before, we added references which support this table as well

Comment 6: Page 24, Table 2: Exaggerated hypoxia at exercise: suggest hypoxemia instead of hypoxia.
Reply 6: Thank you for this comment, we changed the wording to hypoxemia

Comment 7: Page 24, Table 2: Why are shunt lesions regarded as risk factor? They might serve as pop-off.
Reply 7: Thank you for this important comment. We absolutely agree with the reviewer that a shunt lesion may serve as pop-off. Our intention was to draw the attention of the reader to the fact that shunt lesions are risk factors for the development of pulmonary hypertension and later for the development of Eisenmenger´s syndrome. In order to avoid any possibility of misunderstanding, and due to the fact that we mentioned in the text that patients with shunt lesions can develop pulmonary hypertension, we would delete "shunt lesion" in Table 3.

Comment 8: Page 24, Table 2: What is meant with “unilateral absent pulmonary valve syndrome”?
*Reply 8: Thank you for this comment, this is a mistake, we are sorry about this, the wording should be “**unilateral absence of a pulmonary artery’’** (1)*

Comment 9: Page 25, Table 3: I think this table is very important but should ideally be splitted up into separate components that could then be integrated in the corresponding sections of the main text as “info boxes” (i.e. Effects of altitude on the CV system, Assessment, Selection of patients at risk, Guidelines). This would increase clarity and readability of the main text.
Reply 8: Thank you for this suggestion.
As the other reviewers did not see the need to split this table, but found the summary in one table helpful, we kept accordingly to Shrikrishna et al, 2011 table 3 as a complete table. If the editors and reviewers feel that the article would be significantly improved by splitting the table, we are willing to do so.

Reviewer 2

Excellent concise summary on what is known of the influence of altitude exposure on individuals with PH. Very good supporting figures and tables.

Reviewer 3

It is important to note that the authors discuss many aspects of this topic and additionally summarise the key points of current knowledge in table 3 that are very useful for the readers.

Comment 1:
However, I would like to encourage the authors to provide an additional table that summarises the available recommendations from the current guidelines including class of recommendation and level of evidence as given in the text.
Reply 1: we have prepared the additional proposed table and included all previous recommendations with class of recommendation and level of evidence. This table includes both the adult guidelines and the most current European and American pediatric guidelines. Despite many unique characteristics in pediatric PH – the travel recommendations for children with PH are mostly managed on adult guidelines and trials. In addition, the travel guidelines are largely based on expert opinions. There is therefore an urgent need to undertake further scientific studies to achieve a higher level of evidence.
We therefore believe that a tabular presentation of recommendations, which in reality are mainly based on adult data and only to a small extent on studies in children, suggests that the data situation seems to be apparently good. But this is not true. Therefore we summarized and discussed the studies as well as the real life approaches within the text and Table 1. Real life studies show, for example, that not all PH patients FC III have to be excluded from flights. As long as sufficient scientific data are missing, the potential risk of an individual with PH has to be predicted by a balanced evaluation by a PH specialist/physician who is informed about current guidelines as well as clinical data.
In our text, we cited the class of recommendation as well as level of evidence at lines 253-274 of the text previous to the revision [revised document line 261ff – see below] and we referred to the necessity of research, surveys about real life practice and new recommendations in our summary (lines 411-428, revised document lines 418 ff as cited below). Therefore, we should like to keep the format as it is (balanced discussion within the text).

CLINICAL CONDITION	RECOMMENDATIONS	CLASS OF RECOMMENDATION	LEVEL OF EVIDENCE	References
ADULT PULMONARY HYPERTENSION	WHO-FC III and IV class patients and those with PaO_2 consistently <60 mmHg should avoid exposure to altitudes >2,000 m, and they should use oxygen supplementation if exposed to altitudes around 1,500-2,000 m.	I	C	(2)
	PAH patients exposed to air travel should be advised to travel with written information about their PAH and be advised on how to contact local PAH clinics in close proximity to where they are travelling.	I	C	
ADULT CYANOTIC CONGENITAL HEART DISEASE	Living at high altitude is not recommended for patients with cyanotic forms associated with right to left shunt.	I	C	(2)
	In case of heart disease with left to right shunt, it is recommended to stay at low altitude (<1,500 m) to avoid the risk of pulmonary hypertension.	I	C	
	Patients with simple congenital heart disease, surgically treated, may safely ascend to HA.	I	C	
CHILDREN PULMONARY HYPERTENSION	Generally, it is recommended that patients with PH should only fly on commercial airplanes in a stable and compensated condition.	I	C	(3)

	For patients with advanced disease, systemic pulmonary artery pressures and/ or impaired ventricular function, it appears reasonable to use supplemental oxygen during the flight to minimise hypoxic vasoconstriction. The ESC and European Respiratory Society guidelines for PH recommend in-flight supplemental oxygen for patients with PH in FC III or IV and those with arterial partial oxygen pressure consistently <8 kPa (60 mmHg).	*Adapted from adult guidelines (4)*		
	Paediatric patients with PH in the high-risk category should not participate in competitive sports. It is recommended that children with mild to moderate PH/PPHVD should engage in light to moderate aerobic activity, but be allowed to self-limit their activities as required. Children with PH should avoid strenuous and isometric exercise, as well as dehydration.	I	C	
CHILDREN PULMONARY HYPERTENSION	During exercise, it is recommended that pediatric patients with PH engage in light to moderate aerobic activity, avoid strenuous and isometric exertion, remain well hydrated, and be allowed to self-limit as required.	I	C	(5)
	During airplane travel, supplemental oxygen use is reasonable in pediatric patients with PH.	IIa	B	

ADULT PULMONARY HYPERTENSION	There are no studies using flight simulation to determine the need for supplemental O_2 during prolonged flights in patients with PAH. The known physiological effects of hypoxia suggest that in-flight O_2 administration should be considered for patients in WHO-FC III and IV and those with arterial blood O_2 pressure consistently <8 kPa (60 mmHg). A flow rate of 2 l/min will raise inspired O_2 pressure to values seen at sea level. Similarly, such patients should avoid going to altitudes 1,500–2,000 m without supplemental O_2 above. Patients should be advised to travel with written information about their PAH and be advised on how to contact local PH clinics in close proximity to where they are travelling.			(6)

Our text line 261 ff

In the absence of sufficient clinical studies and based on expert opinion, current guidelines recommend that adult patients with advanced PAH (WHO-Functional Class (FC) III and IV) should avoid exposure to altitudes >1,500-2,000 m, and they should use oxygen supplementation if exposed to altitudes around 1,500-2,000 m (Class of recommendation I, Level of evidence C) (ESC Guideline, 2018) (2, 4). During prolonged air travel, in-flight oxygen administration should be considered for patients in WHO-FC III and IV and those with arterial blood oxygen pressure consistently <60 mmHg. A flow rate of 2 l/min is suggested to raise inspired oxygen pressure to values seen at sea level. If patients receive oxygen at sea level, oxygen supply should be doubled. Patients should be advised to travel with written information about their PAH and about how to contact local PAH clinics within close proximity to the final destination (4).

Recent Pediatric European Guidelines (3) recommend that pediatric patients with PAH should only fly on commercial airplanes in a stable and compensated condition (Class I, Level of evidence C). Due to the fact, that data on children with PAH exposed to altitude are lacking, the European Guidelines recommend that patients with advanced disease, systemic PAP and/or impaired ventricular function should use supplemental oxygen during the flight to minimise hypoxic vasoconstriction. Patient caregivers should contact the airline in advance regarding the availability of supplemental in-flight oxygen.

The American Guidelines briefly state, that during airplane travel, supplemental oxygen use is reasonable in pediatric patients with PAH (Class IIa, Level of evidence B – moderate strength, moderate evidence) (5).

Data on the acute and prolonged effect of altitude exposure in PAH patients are scant. Therefore, it remains difficult to counsel PAH patients wishing to undergo mountain or air travel. Table 1 summarizes studies on altitude exposure in individuals with different type of pulmonary hypertension. Systematic studies on children with PAH exposed to cabin pressures or high altitude are lacking. However, data from adult trials cannot be easily transferred to the pediatric population, as PAH in childhood is seen in a wide variety of conditions, including not only idiopathic PAH (IPAH), but also PAH associated with CHD and the growing population of pulmonary hypertensive vascular diseases in single ventricle physiology (Fontan) (3). Furthermore, children with PAH may suffer from additional risk factors including restrictive parenchymal or extraparenchymal lung disease after operation, the combination of pre- and postcapillary pulmonary hypertension, and complex syndromal disease (Table 2).

As well as the summary: Line 418 ff

In summary, patients with pulmonary hypertension may be at risk of developing clinically relevant events on altitude exposure. In patients with stable pulmonary hypertension, Eisenmenger's syndrome, heart failure with elevated pulmonary pressure, and Fontan circulation, air travel and mountain excursion at altitudes up to 3,000 m seem to be safe and well tolerated. Identifying those at risk, where compensatory mechanisms are failing, is challenging. Unfortunately, current measures of disease severity, including resting desaturation at sea level or during hypoxic challenge tests and functional class, do not accurately predict the onset of clinically relevant symptoms. At high altitude, exercise leads to further desaturation and a rise in pulmonary pressures, and therefore, it is reasonable to integrate moderate level exercise in fitness-to-fly or fitness-to-climb testing of patients.

Further research is warranted to clarify the risk of altitude travel through implementation of comprehensive cardiac and pulmonary functional testing, including exercise under normo- and hypoxia, longer exposure to hypoxia including overnight stay, and the correlation with real-life data during flights or mountain stays. Based on these scientific data, the clinical relevance of hemodynamic parameters and the relevance of various degrees of desaturation depending on the type of PAH can be determined. This allows for specification of evidence-based guidelines, as well as the development of easy to apply and reliable tests to predict the potential risk of altitude exposure in the individual (7-10).

Comment 2:
One minor revision may be necessary on page 11, line 257 where the text in brackets should be: (Class of recommendation I, Level of evidence C) rather than Class of evidence...)
Reply 2: Thank you for this comment, we changed the text accordingly

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3. Lammers AE, Apitz C, Zartner P, Hager A, Dubowy K-O, Hansmann G. Diagnostics, monitoring and outpatient care in children with suspected pulmonary hypertension/paediatric pulmonary hypertensive vascular disease. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. Heart (British Cardiac Society). 2016;102(Suppl 2):ii1-ii13.
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6. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for

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8. Israels J, Nagelkerke AF, Markhorst DG, van Heerde M. Fitness to fly in the paediatric population, how to assess and advice. European journal of pediatrics. 2018;177(5):633-9.
9. Naqvi N, Doughty VL, Starling L, Franklin RC, Ward S, Daubeney PEF, et al. Hypoxic Challenge Testing (Fitness to Fly) in children with complex congenital heart disease. Heart (British Cardiac Society). 2018;104(16):1333-8.
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