Pulmonary Artery Pressure Response to Simulated Air Travel in a Hypobaric Chamber

Brandon E. Turner; Peter D. Hodkinson; Andrew C. Timperley; Thomas G. Smith

BACKGROUND: Hypoxia-induced elevation in pulmonary artery pressure during air travel may contribute to the worldwide burden of in-flight medical emergencies. The pulmonary artery pressure response may be greater in older passengers, who are more likely to require flight diversion due to a medical event. Understanding these effects may ultimately improve the safety of air travel.

METHODS: We studied 16 healthy volunteers, consisting of a younger group (aged $<$ 25 yr) and an older group (aged $>$ 60 yr). Using a hypobaric chamber, subjects undertook a 2-h simulated flight at the maximum cabin pressure altitude for commercial airline flights (8000 ft; 2438 m). Higher and lower altitudes within the aeromedical range were also explored. Systolic pulmonary artery pressure (sPAP) was assessed by Doppler echocardiography.

RESULTS: There was a progressive increase in sPAP which appeared to be biphasic, with a small initial increase and a larger subsequent rise. Overall, sPAP increased by 5 $\pm$ 1 mmHg from baseline to 35 $\pm$ 1 mmHg at 8000 ft, an increase of 18%. The sPAP response to 8000 ft was greater in the older group than the younger group.

CONCLUSIONS: This study confirms that pulmonary artery pressure increases during simulated air travel, and provides preliminary evidence that this response is greater in older people. Advancing age may increase in-flight susceptibility to adverse pulmonary vascular responses in passengers, aircrew, and aeromedical patients.

KEYWORDS: aircraft cabin hypoxia, hypoxic pulmonary vasoconstriction, elderly, passenger fitness to fly, aeromedical transportation.

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Using the best available data, it is estimated that, on average, an in-flight medical emergency occurs on a commercial airline flight somewhere in the world every 12 min.[24] Cardiac and respiratory causes are common, and the mildly hypoxic cabin environment may be an important etiological factor in many cases.[7,24] Improving our understanding of the normal cardiopulmonary effects of this environment may help to improve the safety of air travel.

Cabin pressure altitude (PA) is generally maintained between 5000 ft (1524 m) and a maximum of 8000 ft (2438 m) during commercial airline flights, and arterial oxygen saturation (Spo_2) typically falls to approximately 90–95% in healthy passengers.[1,2] Although mild, this cabin hypoxia is sufficient to stimulate classic physiological responses such as a small increase in ventilation and an increase in secretion of erythropoietin.[11,14] Fortunately, these particular responses are generally benign.

However, we have recently established that commercial air travel also stimulates an increase in pulmonary artery pressure, which has the potential to cause adverse clinical effects through the development of pulmonary hypertension and right heart failure.[30] The underlying phenomenon of hypoxic pulmonary vasoconstriction is well known to occur in response to more severe hypoxia but has not been extensively studied in the aviation setting. The effect we observed in healthy passengers was modest and clinically inconsequential, but in a subsequent study we demonstrated that an asymptomatic but genetically susceptible passenger can rapidly develop flight-induced pulmonary hypertension during commercial air travel.[29] Case reports have described the onset of acute cor pulmonale in air passengers,[22,34] and insidious pulmonary vascular responses

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may contribute to the worldwide burden of in-flight medical emergencies, which carry significant morbidity and mortality and lead to many expensive and logistically challenging flight diversions each year.[24]

Older passengers are more likely to require an unscheduled aircraft diversion due to a medical event on a commercial flight.[16,24] Limited indirect data suggest that the pulmonary artery pressure response to hypoxia might increase with age, possibly due to increasing vessel stiffness.[13,17,18] This could in theory translate to a greater risk of adverse responses in older people, who are increasingly traveling by air; over a third of U.S. leisure airline passengers are older than 55 yr,[35] and a recent survey of Europeans found that nearly 20% of those over 55 yr had traveled by air in the previous year.[10] This also applies to aging aircrew and perhaps most particularly to private pilots, who are permitted to fly at more hypoxic cabin altitudes exceeding 10,000 ft (3048 m) and who are increasingly elderly; in the UK there are now hundreds of private pilots aged $\geq$ 75 yr, including many $\geq$ 80 yr and some aged $\geq$ 90.

Using the controlled setting of a hypobaric chamber, this study aimed to verify our previous in-flight echocardiographic findings. The study was focused on a 2-h simulated flight at 8000 ft PA, as this is the maximum cabin altitude that commercial air passengers normally experience. As a preliminary exploration of the possible effect of age, this study also tested the hypothesis that the pulmonary artery pressure response to 2 h at 8000 ft PA is greater in older people (aged over 60 yr) than in younger people (aged less than 25 yr).

METHODS

Subjects

There were 16 healthy volunteers who participated in the study following confirmation of health status by their own general practitioners and by an aviation medicine physician. Subjects were recruited as two separate groups: a younger group, aged $>$ 18 and $<$ 25 yr, and an older group, aged $>$ 60 and $<$ 70 yr. **Table I** shows subject characteristics for the two separate groups and for both groups combined. Subjects had no recent history of exposure to high altitude. All subjects provided written informed consent. The study was approved by the Ministry of Defence Research Ethics Committee and was conducted in accordance with the Declaration of Helsinki.

Table I. Subject characteristics.

CHARACTERISTICS	YOUNGER GROUP	OLDER GROUP	ALL SUBJECTS COMBINED
N	8	8	16
Male:female	5:3	5:3	10:6
Age (yr)	21 ± 1	65 ± 3	43 ± 23
Weight (kg)	74 ± 12	69 ± 11	72 ± 11
Height (m)	1.73 ± 0.07	1.69 ± 0.09	1.71 ± 0.08
Body Mass Index	24.7 ± 3.8	24.3 ± 2.6	24.5 ± 3.1
Hemoglobin ($g \cdot dl^{-1}$)	14.2 ± 1.8	13.2 ± 1.2	13.7 ± 1.6
Baseline Spo_2 (%)	98 ± 2	96 ± 2	97 ± 2
Baseline sPAP (mmHg)	30 ± 3	29 ± 2	30 ± 3

Mean ± SD values are shown. The normal range for hemoglobin is 13.5-18.0 $g \cdot dl^{-1}$ for males and 11.5-16.0 $g \cdot dl^{-1}$ for females. Spo_2, arterial oxygen saturation. sPAP, systolic pulmonary artery pressure.

Protocol

Altitude simulation was undertaken using a hypobaric chamber at the Royal Air Force Centre of Aviation Medicine, RAF Henlow, UK. Subjects breathed ambient air at all times. Barometric pressure in the hypobaric chamber was decreased and increased as required at a rate of 4000 ft (1219 m) per minute to achieve the target pressure altitudes. This is a standard ascent/descent rate used in hypobaric chamber protocols but is more rapid than a commercial aircraft cabin pressure profile. The concentration of oxygen in the chamber remained at 20.9% and the temperature was maintained at 21-24°C. Each subject undertook a single chamber protocol which was centered on a 2-h period at 8000 ft simulating a short-haul commercial airline flight. The range was extended to include an initial period of 30 min at 6000 ft (1829 m) and a final 30 min at 10,000 ft (3048 m), as these altitudes are also relevant to aeromedical physiology. The pressure altitude profile and measurement time-points are shown in **Fig. 1**. The primary outcome measure was the change in systolic pulmonary artery pressure (sPAP) at 8000 ft PA assessed by Doppler echocardiography (Vivid-q portable echocardiography machine, GE Medical Systems, Chalfont St. Giles, Buckinghamshire, UK). Baseline echocardiographic measurements were made prior to commencing the chamber exposure. Subsequent measurements were made at 30 min intervals at each altitude in the chamber, and again 30 min after exiting the chamber. Hemoglobin concentration was determined noninvasively at baseline (Rainbow SET Radical-7 pulse co-oximeter, Masimo Corp, Irvine, CA).

Dependent Measures

Echocardiographic measurements were made with subjects reclining in the left lateral position using the standard Doppler technique used in our previous in-flight studies,[29,30] which has been extensively validated.[3,23,36] This technique is widely used in research and clinical practice to calculate sPAP as the sum of the maximum systolic trans-tricuspid pressure gradient (assessed using continuous wave Doppler imaging) and an assumed right atrial pressure of 5 mmHg.[26,27,31] Such measurements correlate closely with invasive measurements of systolic pulmonary artery pressure and with mean pulmonary artery pressure.[3,6,36] As before, cardiac output was determined echocardiographically using a standard technique,[30] and Spo_2, heart rate, and blood pressure were measured at the same time as each echocardiographic measurement.

Statistical Analyses

Differences in means were assessed statistically using Student's two-tailed *t*-tests. Paired *t*-tests were used when analyzing the combined data (Fig. 1) and unpaired *t*-tests were used when comparing the two age groups (**Fig. 2**). The progressive effect of hypoxia over time was further assessed using repeated measures analysis of variance (ANOVA) (Fig. 1). Values of $P < 0.05$

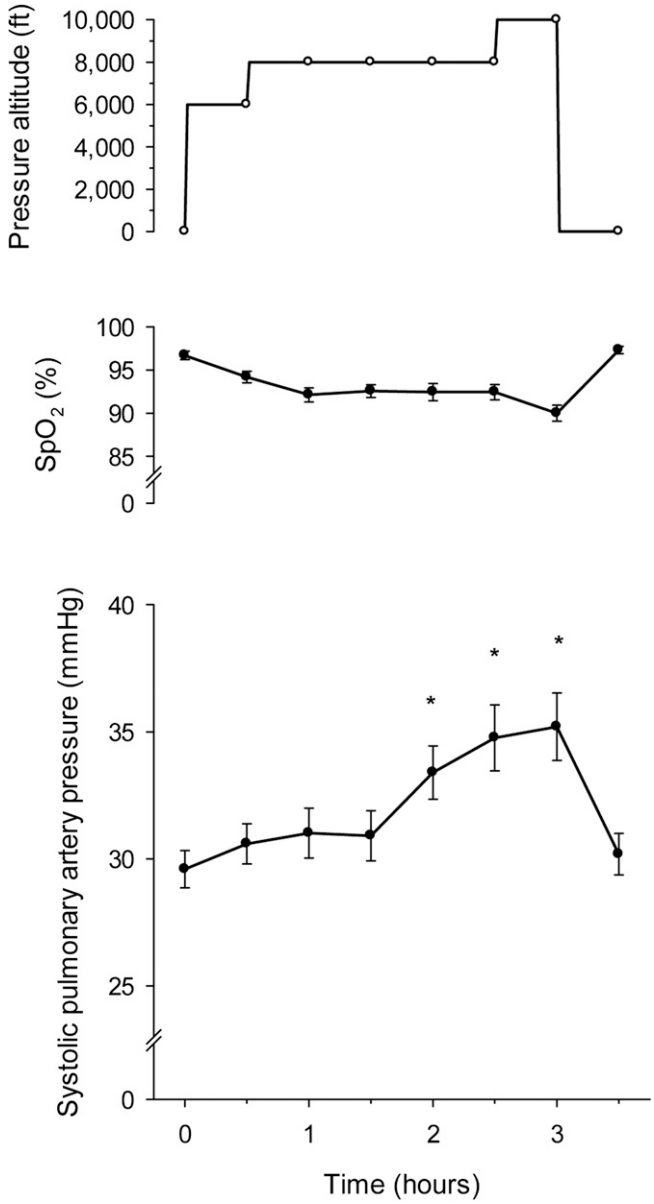

Fig. 1. Pressure altitude (top), arterial oxygen saturation (Spo_2; middle), and systolic pulmonary artery pressure (bottom) during hypobaric hypoxia in all subjects. Measurement time-points are indicated by white symbols in the top panel and black symbols in the lower panels. Data are mean ± SEM and asterisks denote a significant change in systolic pulmonary artery pressure from the baseline value ($P < 0.05$).

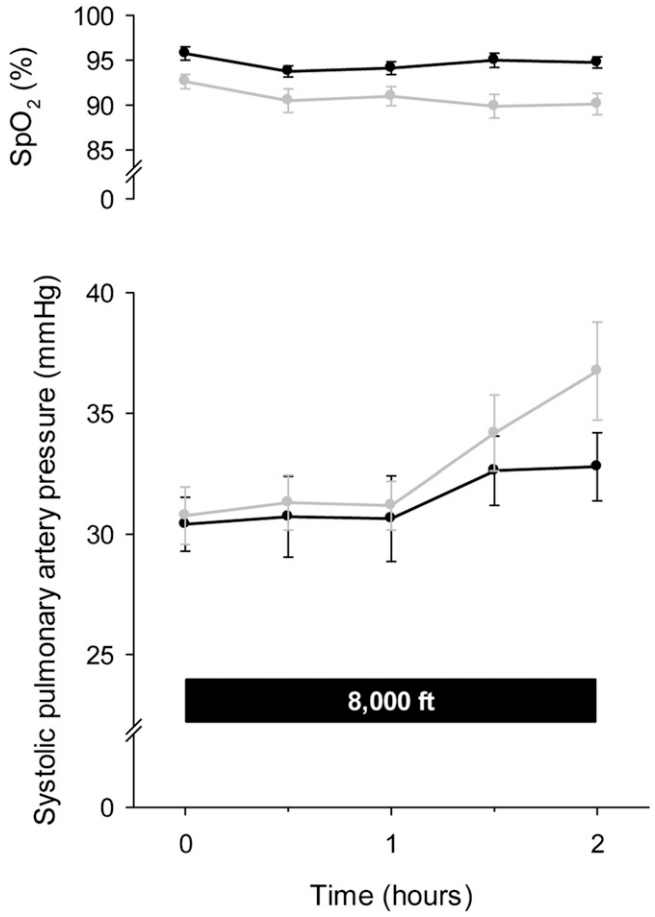

Fig. 2. Arterial oxygen saturation (Spo_2; top) and systolic pulmonary artery pressure (bottom) in younger and older groups during simulated air travel at 8000 ft pressure altitude. Data are from 2 h at 8000 ft, commencing with the transition from 6000 ft. Data from the younger group (age < 25 yr) are shown in black, and data from the older group (age > 60 yr) are shown in gray. Data are mean ± SEM.

were considered statistically significant. Data are reported as mean ± SEM unless otherwise stated.

RESULTS

The protocol was well tolerated by all subjects. Baseline measurements are shown in Table I. In order to investigate the effect of simulated air travel per se, data from all subjects were initially analyzed as a single combined group, and these results are shown in Fig. 1. Spo_2 fell with each step-change in altitude, with a mean of 93 ± 1% at 8000 ft which was significantly lower than baseline [$t(15) = 7.10$, $P < 0.001$]. There was a corresponding progressive increase in sPAP throughout the chamber exposure which reached statistical significance after 2 h [$F(4,60) = 7.90$, $P < 0.001$]. The mean sPAP at 8000 ft was 33 ± 1 mmHg, and by the end of the 8000 ft period sPAP had increased by 5 ± 1 mmHg from baseline to 35 ± 1 mmHg [$t(15) = -3.77$, $P = 0.002$]. This was an average increase of 18%. When measured 30 min after exiting the chamber, sPAP had returned to baseline levels. Heart rate did not increase from baseline (67 ± 3 bpm) to the end of the 8000 ft period (66 ± 3 bpm), and likewise cardiac output did not increase with hypoxia.

The pulmonary artery pressure response to 8000 ft varied widely between subjects. The most extreme response occurred in the oldest individual studied (age 69 yr), in whom sPAP increased by 70% from 27 mmHg at baseline to 47 mmHg after 2 h at 8000 ft. Consistent with our understanding of pulmonary vascular physiology,[33] there appeared to be two phases to the change in sPAP during the 2-h period at 8000 ft: an initial small rise followed by a plateau, and then a second larger rise (evident in Fig. 1 and Fig. 2).

In order to investigate the effect of age on the sPAP response to air travel, data from the younger and older groups were compared during the 2-h simulated flight at 8000 ft, when pressure altitude was maintained constant for an extended period. Results from the separate age groups are shown in Fig. 2. Spo_2 did not change significantly in either group over this period, although mean Spo_2 was lower in the older group (90 ± 1%) than in the younger group (94 ± 1%) [$t(14) = 3.14$, $P = 0.007$]. Over the 2 h at 8000 ft, sPAP increased by 2 ± 1 mmHg [$t(7) = -2.67$; $P = 0.03$] in the younger group compared with a larger increase of 6 ± 1 mmHg [$t(7) = -5.34$; $P = 0.001$] in the older group. This was a 19% increase in the older group compared with an 8% increase in the younger group, and this difference between the age groups was statistically significant [$t(14) = -2.52$, $P = 0.024$]. To illustrate this further, at 8000 ft half the members of the older group exceeded the sPAP threshold for pulmonary hypertension (which has been defined as 36 mmHg[20]) compared with only one member of the younger group.

DISCUSSION

This study has confirmed that pulmonary artery pressure increases in healthy people in response to mild hypobaric hypoxia simulating aircraft cabin conditions, and has also provided preliminary evidence that this response becomes greater with increasing age.

The modest pulmonary artery pressure response we observed is similar in magnitude to our previous in-flight measurements, which commenced 3 h after takeoff. The current chamber study allowed earlier and more frequent measurements, from which two temporal components to the emergent sPAP response were apparent. This is consistent with experiments demonstrating a biphasic pattern to early hypoxic pulmonary vasoconstriction in humans.[33] Acute hypoxia stimulates an immediate reflex rise in pulmonary artery pressure that is rapid but limited in magnitude and is complete within several minutes. After a plateau lasting around 30-60 min, a second phase of vasoconstriction begins that is slower but progressive, resulting in an ongoing increase in pulmonary artery pressure that is greater than the initial response.[33] This second phase of vasoconstriction may continue for many hours, and it is therefore possible that pulmonary artery pressure continues to increase throughout long-haul and ultra-long-haul flights.[9,32]

This biphasic response has implications for assessing passengers medically preflight. The hypoxia altitude simulation test (HAST) is a standardized assessment tool in which in-flight responses are predicted by breathing a mildly hypoxic gas mixture for about 20 min.[8] While expanding the HAST to include simultaneous echocardiography (HAST-echo) could help to predict in-flight cardiopulmonary dysfunction, the current data suggest that less than 2 h of hypoxia is unlikely to generate a representative physiological response. This may equally apply to symptoms and signs that a HAST is expected to elicit, and we speculate that insufficient duration of hypoxia may be a factor limiting the usefulness of HAST, which has been questioned.[15,21]

While the responses we observed are unlikely to trouble the vast majority of air passengers, those with pre-existing pulmonary hypertension, whether formally diagnosed or not and whether symptomatic at sea level or not, may suffer clinical decompensation as their pulmonary artery pressure increases with cabin altitude. This includes passengers with hypoxic lung disease, pulmonary arterial hypertension (PAH) or more rarely those with genetic diseases such as Chuvash polycythaemia that predispose to exaggerated pulmonary vascular responses even to mild hypoxia,[12,27,28] which can result in flight-induced pulmonary hypertension in an air traveler who is otherwise generally well.[29] Pulmonary arterial hypertension is particularly challenging as the pathology is inherently vulnerable to direct exacerbation by hypoxia, with potentially catastrophic consequences, yet patients are commonly relatively young and wish to travel by air.[25] Medical decisions regarding the safety of air travel (with or without supplemental in-flight oxygen) are often very difficult in PAH and a stronger evidence base is required.[4,5] Robust data would also be helpful when assessing prospective passengers with other cardiopulmonary diseases such as left ventricular failure.

The wide range in pulmonary artery pressure response observed in this study reflects the high variation in pulmonary vascular sensitivity to hypoxia between individuals.[13] In addition to this normal variation, approximately 10% of the population are thought to have a disproportionate or "hypertensive" pulmonary artery pressure response to hypoxia, which may predispose to hypoxia-induced illnesses such as high-altitude pulmonary edema.[13] Our current findings raise the possibility that an unusually extreme innate response, combined with advancing age, could have adverse sequelae during a long-haul flight. It is not clear whether the greater sPAP response we observed in the older group derived from a true difference in pulmonary vascular sensitivity, or whether it simply derived from the lower Spo_2 in the older group, which in turn reflects the gradual fall in oxygenation that accompanies normal aging. This is an interesting scientific question that warrants further study.

In addition to passengers, these findings are also relevant to aircrew. Overall, the risk of sudden incapacitation arising from harmful pulmonary vascular responses is anecdotally low. However, the risk may be higher in elderly pilots, especially in the presence of diagnosed or undiagnosed cardiopulmonary disease, and particularly when operating in the general aviation sector, where regulations permit considerably higher cabin pressure altitudes with scope for more severe hypoxia. For example, in Europe, general aviation pilots are only required to use supplemental oxygen for flights above 10,000 ft lasting longer than 30 min, while in the United States, supplemental oxygen is encouraged for flights above 10,000 ft and required for flights above 12,500 ft lasting more than 30 min. Military flight operations likewise carry a potential for more severe hypoxic exposures, and the possible consequences for older military aircrew also require consideration.

This study's results also have implications for elderly patients undergoing aeromedical transportation, where even subtle changes in cardiopulmonary function are undesirable. Currently, supplemental oxygen is commonly used in air ambulance patients with moderate-severe illness or known cardiopulmonary disease. Should our preliminary results be confirmed, it may be appropriate to consider providing supplemental oxygen routinely in elderly patients undergoing specialist air ambulance transportation regardless of their medical status, at least for longer flights.

This study has several limitations, including the limited sample size and the relatively short duration of hypoxia. Also, while pulmonary artery catheterization was considered to be too invasive for this study, in principle it would be preferable to use direct measurements of pulmonary artery pressure, particularly when the changes being studied are small. We are only aware of one study which has done this during a comparable hypobaric chamber exposure (2-3 h at 2500 m).[19] Conducted over 40 yr ago, the pulmonary vascular response in 10 respiratory patients appeared to be similar to our current noninvasive observations, though no statistical analyses were presented.[19] Other similar data are very limited, although one study of veterans with actual or suspected cardiac disease included a single echocardiographic measurement of mean pulmonary artery pressure in a hypobaric chamber, and reported a 43% increase at 2500 m that was subsequently replicated at a terrestrial altitude of 2500 m.[17]

In summary, this study demonstrates that pulmonary artery pressure increases during simulated air travel in healthy people, consistent with previous in-flight observations. This study also provides preliminary evidence that the pulmonary artery pressure response to simulated air travel is greater in older people than in younger people. Further studies are warranted to explore whether avoiding even mild cabin hypoxia may be beneficial in elderly aeromedical patients. Further research is also required to determine whether accurate prediction of excessive pulmonary hypertensive responses in air passengers can improve preflight medical screening and reduce flight-induced morbidity and mortality while maximizing access to air travel.

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