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EXECUTIVE SUMMARY

Congress mandated FAA to study the health effects of cabin pressures in accordance with the National Research Council (NRC) recommendation to evaluate safe limits (NRC 2002). The NRC reported that the currently allowed cabin altitude of 2,440 meters (8,000 feet), set decades ago, may not be adequate for cabin crew and passengers of varying age and health status.

This report discusses the Harvard School of Public Health study to investigate the effects of cabin pressures on elderly passengers, some with chronic and stable disease, and all, current users of air transportation. The study investigated three potential risks for hypoxia: age over 50, cardiac disease, and passengers with lowered oxygen saturation at ground level. Health effects of cabin pressures were measured as changes in oxygen saturation during flight, physiological compensation for hypoxia during flight, such as changes in cardiopulmonary indices, and the report of symptoms during flight. These outcomes were first tested in 41 passengers in a hypobaric chamber over two days of 4-5 hours of simulated flight each day; one day at near sea level, and the other day blinded to the condition of 7,000-feet altitude. Subsequent to the chamber studies, 6 of the original 41 passengers had cardiopulmonary responses recorded as they flew three segments aboard commercial flights. Their responses were subsequently compared to earlier chamber results.

Major findings:

Vulnerable senior passengers experience moderate hypoxia during flight.
While previous research showed around a 4% mean drop in oxygen saturation for most individuals at cabin altitude, our study found greater declines. Nearly half of the older passengers in this study desaturated to 90% or below, levels considered as moderate hypoxia. Further, the changes in cardiac and pulmonary function we observed in flight were associated with compensatory mechanisms that aim to regulate hypoxic states. These observations suggest that the observed levels of hypoxia are consequential, in particular for passengers with cardiac disease, and notable, when compared with previous studies that found no evidence of these systemic changes. These results point to the potential for hypoxic stress in seniors with and without chronic disease during ultra long flights, especially if exerting themselves walking the aisles at altitude, or when flying to altitude.

Age is an important risk factor for hypoxia in flight with almost a 1% decrease in oxygen saturation for every decade of life above 50 (the lower age limit of our sample) at cabin pressures of 7,000 feet.

Current medical guidelines that deem sea-level oxygenation greater than 95% as generally protective against the need for in-flight supplemental oxygen underestimate the true risk of hypoxia for many seniors at usual cabin altitudes. In this study, many passengers with “sufficient” baseline oxygenation dropped to hypoxic levels in flight.

Flight altitudes may place additional stress on passengers with underlying cardiac disease. Passengers with pre-existing arrhythmias experienced greater rates of arrhythmia in flight.

At typical cruising altitudes, symptoms may be an insensitive indicator of hypoxia. Symptom reporting was not significantly different on flight days versus control days.

Chamber simulations approximated actual flight experiences according to passenger responses. Passengers monitored aboard the commercial flights responded similarly in the chamber simulation and aboard commercial flights in terms of oxygen saturation, heart rate, and breathing rate.

Strengths of the study:

Blinded trial of human responses to cabin pressures while controlling other environmental conditions in a hypobaric chamber simulation.

Extensive continuous real-time physiological monitoring of passengers.

Repeated measures of the same passengers in both control and flight conditions, thus, limiting noise related to the known inter-individual variability in hypoxic responses and focusing instead on the intra-individual variability in responses related specifically to the hypoxic exposure.

Higher cabin pressures tested (7,000 feet) compared with many prior studies that tested only at the minimum allowable pressure (8,000 feet).

Passenger responses compared between the flight simulations and commercial flights in a subsample of the study population.

Limitations of the findings:

Small in-flight sample and cardiac sub-sample. Results should be repeated in larger samples and over longer flight durations.

Oxygen saturation measures limited by indirect measures, such as, pulse oximetry without co-oximetry to detect carboxyhemoglobin (COHb) in smokers.

The role of prescribed medications in passenger responses to flight was not investigated.

The impact of flight on chronic disease in the post-flight period was not examined.

Recommendations:

In the near term:

- FAA should take a leadership role in protecting the health of passengers by working with airlines to evaluate how senior flyers are identified for in-flight oxygen use and when oxygen supplementation is used. At minimum, senior and vulnerable flyers should be polled to understand the incentives and disincentives for carrying and using personal oxygen equipment in flight.

- The FAA should extend the in-flight studies to test for the effects of prolonged exposure to hypoxia aboard intercontinental commercial flights of longer duration in order to better identify and manage risk. For example, ACER/RITE should conduct epidemiological studies to determine the true burden/cost of in-flight hypoxia to passengers in the post-flight period,

such as in the management of their chronic disease after extended flights. These studies may be helped by the collaboration of health care insurers and providers. The findings would ensure public health protections for all passengers.

- The FAA should evaluate the physiological responses of aging cabin and cockpit crew to cabin pressures. Aging cabin crew who are more active at altitude, such as pushing service carts through the aisles, may be at greater a risk for moderate hypoxia.

In the long term:

- Aircraft manufacturers and airlines should consider higher pressures to provide broader protection for an aging population with and without chronic disease.
- FAA should re-evaluate rules for cabin pressures to tolerate greater than previously expected drops in mean oxygen saturation at altitude based on past research from generally young and healthy populations. Higher cabin pressures may be more protective for vulnerable flyers.

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INTRODUCTION

In the 50 years from 2000 to 2050, the world population of people age 60 and older will more than triple, increasing from 600 million to 2 billion (WHO, 2004). Researchers expect the percentage of the over-65 population who utilize air travel and the frequency with which they do so will be greater than previous over-65 populations because the Boomer generation was the first for which air travel was a common part of life including both low-cost business and recreational travel. This familiarity with air travel is expected to cause more Boomers to fly more often than previous generations (McDougall, 1998; NERASP, 2006).

The increase in older passengers means also an increase in unhealthy persons flying. In the U.S. 11.5% of the population has some type of heart disease, with over 27% of those 65-74 and over 37% of those 75 or older having some type of heart disease (CDC, 2006). Moreover, the National Heart Lung and Blood Institute (NHLBI) estimates that annually 195,000 first heart attacks occur silently, without prior symptoms or their recognition (AHA Statistical Update, 2011). In several observation studies, cardiac events caused 10%-20% of all in-flight incidents (Possick and Barry, 2004) and accounted for 12 of 15 in-flight deaths on the five major US air carriers over a one-year period (DeJohn et al., 2000). The issue of cardiac health aboard aircraft has garnered enough attention to warrant the FAA to mandate the placement of at least one automatic external defibrillator on passenger aircraft (Federal Register, 2004).

Besides the higher prevalence of cardiac disease in aging Americans, these individuals have higher exposures to tobacco smoke from current or past cigarette smoking (either active or passive smoking), the number one risk factor for lung disease. The U.S. Surgeon General's 2004 report on the health effects of smoking indicates that there is sufficient evidence to infer causal relationships between smoking and sub-clinical atherosclerosis, coronary heart disease, stroke, abdominal aortic aneurysm and chronic obstructive pulmonary disease morbidity and mortality (U.S. DHHS. 2004) . Chronic Obstructive Pulmonary Disease (COPD) affected 14.8 million American adults in 2009 (CDC, 2009) and an additional 12 million demonstrate evidence of impaired lung function, indicating a potential under diagnosis of COPD (Mannino et al., 2002). Importantly, individuals with either lung or heart disease face special challenges in even mildly hypoxic environments such as that aboard aircraft.

Even in the absence of overt disease, older passengers may be vulnerable aboard aircraft. Medical scientists acknowledge that advanced age is accompanied by a general decline in organ function, such as the function of the heart or lungs (Priebe, 2000). Although the body generally exhibits compensatory mechanisms to maintain equilibrium, response times and performance may be compromised under stressful conditions (Priebe, 2000). For example, vulnerability due to advanced age may be particularly true in an aircraft environment pressurized in accordance with research findings based on mostly healthy, fit, and younger subjects.

Many industries are studying how to best accommodate the aging population through innovations to make their activities both feasible and comfortable given some of the restrictions of older age. Boeing, for example, has worked with intergenerational designers to understand how to make the cabin design more attuned to the needs of the aging Boomer population and some of their changing capacities with respect to diminished vision, hearing, dexterity, flexibility, strength, and stamina (Ehrenman, 2005).

In addition to the increasing numbers of potentially unhealthy passengers, the consideration of possible physiological effects from mild hypoxic environments on pilots and crew is important because the public relies on their optimal functioning to protect passenger safety in-flight. The Aerospace Medical Association, Aviation Safety Committee, released a position paper (Aerospace Medical Association, 2008) recommending further research about the effects of mild hypoxia for passengers and for these worker groups in particular. A number of research studies have shown performance decrements between 5,000 and 10,000 feet, notably at altitudes below the current requirement for supplemental oxygen. In addition, the aging workforce of crew and pilots may be vulnerable at these altitudes because of the potential for reduced oxygen capacity related to aging and the onset of chronic disease in later life. In addition, the work of crew involves increased metabolic demand for oxygen as they service passengers and push utility carts down the aisles of jumbo planes at 34,000 feet.

In sum, the current FAA regulations for limiting cabin pressures to 8,000-feet equivalent altitudes allow for mildly hypoxic conditions. These environments are expected to have little effect on healthy passengers, pilots or crew, however, older individuals and persons with compromised cardiopulmonary status may be at risk. In addition, even though the FAA sets the minimum pressures for flying at 8,000 feet, the number of excursions from these levels is unknown. More than 30 years have passed since the thresholds for pressure were set. In the meantime, new composite materials in the fuselage that withstand cabin pressures greater than 8,000 feet have been developed and aircraft are able to fly higher and for longer periods, extending the exposure to hypoxia. Also, new portable devices that concentrate and deliver personal oxygen have been approved for medical conditions and for in-flight use. Yet experts argue that current guidelines that determine medical fitness for flying or the need for in-flight oxygen lack sufficient scientific evidence for health protection (Aerospace Medical Association, 2008). At the same time, the rise in older and health-compromised passengers (Figure 1) underscores the need to establish pressure-related health effects more precisely.

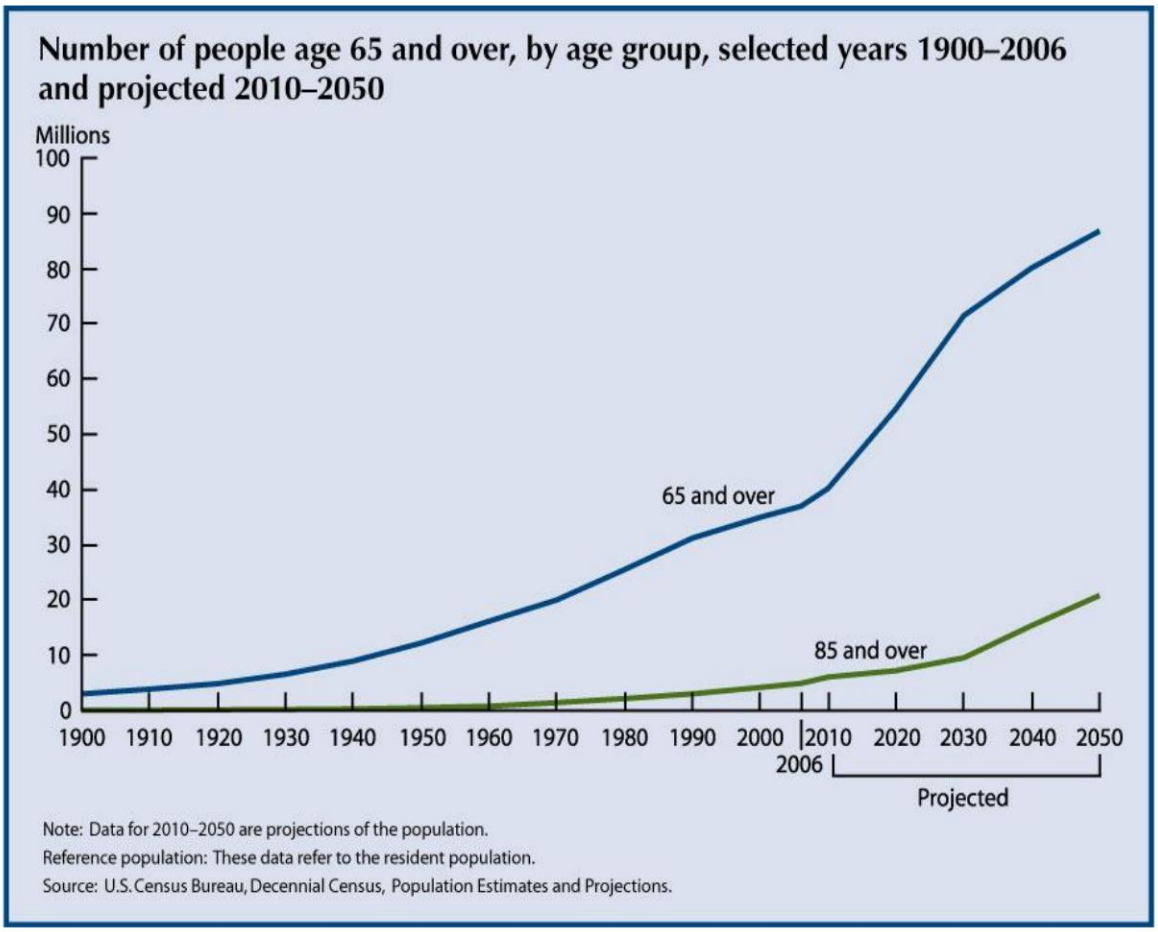


Figure 1. Number of people age 65 and over, by age group, selected years 1900- 2006 and projected 2010-2050

To address the need for more information about the health effects of flying in vulnerable passengers, the current study aimed to answer the following questions:

1. What are the physiological demands on healthy older passengers and older passengers with chronic disease (specifically cardiac disease) related to cabin pressures? For example, what is the impact of age and cardiac disease on oxygen levels and cardiopulmonary loads at typical cabin pressures?

2. Are current medical guidelines that recommend medical evaluation of only those passengers with ground level oxygen saturations below 96% protective of moderate hypoxia in-flight? For example, what is the risk of moderate in-flight hypoxia in seniors when ground level oxygen saturation is above 95%?

3. What is the effect of typical cabin pressures on the passenger's experience of

symptoms?

APPROACH

Overall Design

To understand the effects of mild hypoxia in older passengers, including those with chronic stable disease, we monitored individuals before, during, and immediately after, a 5-hour flight in a hypobaric chamber with pressurization equivalent to a commercial flight at 7,000 feet altitude. (While commercial airplanes usually fly at altitudes around 34,000 feet, pressurization of the cabin results in a pressure equivalent to no less than 8,000 feet.) In addition, we monitored these individuals for the same period of time in the chamber on another day at near sea level altitudes.

Subjects were assigned to one of seven weeks to complete both chamber days (control day and exposure day), with five to six participants in each trial. Each group was blinded to the exposure condition (decreased pressure). The order of the exposure day varied among the groups.

For a subset of the participants (n=6), we repeated the physiological measurements over three days during three commercial flights between Oklahoma City and Baltimore, Baltimore and Las Vegas, and Las Vegas and Oklahoma City.

Study Sample

Participants in the study had a prior history of air travel without reports of health complications. These individuals were over 50 years of age, either male or female, and met criteria for one of three subgroups of particular study interest: “healthy” non-smokers, “healthy” smokers (i.e. smokers without diagnosed cardiac or respiratory disease), and stable cardiac patients without restricted activities of daily living. These subgroups were chosen to represent a “typical” older passenger and to fill gaps in the literature about the effects of flying for these passenger groups. We targeted older passengers because few studies have addressed the health consequences of mildly hypoxic aircraft environments for older passengers specifically. We included high functioning cardiac patients given the prevalence of the disease in this population and the known risks for hypoxia with cardiovascular impairment. Finally, we selected smokers to evaluate the potential for heightened oxygen deprivation at altitude secondary to impaired oxygen uptake in smokers (Nesthus and Wise, 1997).

In 2007, subjects were recruited through medical clinics, newspapers, senior centers and fitness centers in the greater Oklahoma City area because of access to the hypobaric chamber at the Federal Aviation Administration (FAA) Civil Aerospace Medical Institute (CAMI) in Oklahoma City. Volunteers were screened first by a nurse practitioner on the telephone and scheduled for a physical exam with a doctor within two weeks if they met inclusion criteria: age greater than 50, recent flying experiences without health complications, currently well, and no major diagnosed chronic disease, except in the selection for stable heart failure patients. The clinical evaluation further excluded individuals with serious or unstable health conditions and documented the

baseline health status for qualified individuals including oxygen saturation, pulmonary function testing, electrocardiogram, blood pressure, urine and blood tests, and measurement of BMI. Volunteers were accepted into the study on a rolling admission.

Selected subjects participated in two days of monitoring in a hypobaric chamber, with a day off in between, during one of seven weeks (seven trials in total) between December 2007 and June 2008. Six of these subjects participated also in three commercial flights in 2009. For the chamber experiment, researchers provided meals and paid participants three hundred dollars. For the commercial flight, participants received their airline tickets and money for meals and travel-related expenses. All study participants were consented in accordance with the protocols approved by the Human Subjects Committees at Harvard School of Public Health, CAMI, and the University of Oklahoma Medical Center.

The final sample for the chamber study consisted of 14 healthy seniors (without acute or chronic illnesses), 13 cardiac patients (12 of the cardiac patients had a diagnosis of mild to moderate heart failure; Grade I or II New York State criteria), and 14 smokers without diagnosed cardiac or respiratory disease. All subjects completed both days of the chamber experiment except one cardiac patient who did not return for the second day because of a work conflict. For the commercial flights, four of the cardiac subjects and two of the healthy non-smoking subjects were included.

Instrumentation: Measures

The CAMI hypobaric chamber was outfitted with 12 commercial airline seats arranged in for rows with three seats across. Participants were seated in rows 2 through 4, one on the aisle and one against the window with the middle seat empty. Chamber gauges recorded humidity, temperature, noise, pressure, carbon dioxide, and pressure. A medical monitor and a research assistant were present in the chamber with the participants during the experiments.

While seated in the chamber and also during the commercial flights, each participant wore a LifeShirt^{TM} (Vivometrics, Inc. Ventura, CA, USA) to monitor cardiac and respiratory function. The LifeShirt is a fitted vest made of light-weight Lycra material that has embedded non-invasive sensors including a single-axis electrocardiograph and two respiratory sensors at the level of the rib cage and abdomen. The respiratory sensors are used for inductive plethsmography to derive respiratory data using the individual's initial calibrations set at the beginning of the test session. Derived respiratory measures include minute ventilation (a proxy for oxygen consumption and directly related to metabolic activity), tidal volume, and respiratory rate. The cardiopulmonary data were recorded into an attached data logger that also collected data about ambulatory blood pressure and pulse oximetry from peripheral devices. The data logger transmitted wirelessly to computer displays outside the chamber for monitoring of each participant's respiratory and cardiac waveforms in real time. During the commercial flights, the data were recorded and later downloaded after the trip. Vivologic software® is used to process and analyze these data according to time, waveform or derived variables.

Subjects completed symptom surveys at baseline and every hour while in the chamber including a post-test immediately following the experiment. The surveys included the Environmental Symptom Questionnaire (ESQ), a survey used to detect symptoms of altitude sickness. The ESQ lists sixty-eight symptoms along with a rating scale that the subject uses to indicate how any symptom is experienced: for example, 0= none at all, 1= slight, 2 = somewhat, 3= moderate, 4= quite a bit and, 5=extreme. In addition to the ESQ, we asked a separate question about how the subject was "feeling now" at each time using a seven-point Likert-type scale anchored by 1= "Poor" and 7= "Excellent" and 4= "Average for me" in the middle of the scale. Lastly, we measured the level of fatigue with a summative score from eight questions that also were rated for severity.

While in the hypobaric chamber, participants were encouraged to behave as they would aboard a commercial flight. They could eat, sleep, rest, read, watch movies, move about or talk freely. The research assistant served meals and snacks during the time in the chamber. A bathroom was located in the back section. For the commercial flights, no restrictions were placed on the passengers and a researcher accompanied the passengers during the commercial flights.

When participants were exposed to altitude in the chamber, research phlebotomists, entering and leaving the chamber through an adjacent pressure-locked room, collected blood specimens for CAMI genomic studies.

Data Analysis

All data were inspected for missing values and for normality. Median values derived from the raw physiological data for each minute were used to trend 5-minute averages of the cardiac and respiratory indices.

For SpO2 (peripheral oxygen saturation as measured by pulse oximetry), values of 0% and any measures less than 5 minutes before or after were set to missing. In addition, values less than 70% were set to missing. Then 5-minute averages were calculated and those based on less than three 1-minute measures were set to missing. The main analyses of SpO2 levels compared subjects according to the following baseline characteristics: health/smoking status, physician-assessed SpO2, and age. We were interested in both comparing the magnitude of SpO2 decline from control to flight conditions as well as the absolute level of SpO2 during flight. Using SAS Proc Mixed (Version 9.2), we ran linear mixed effects models including both main effects for each baseline characteristic and interactions between these variables and an indicator for flight versus control day to simultaneous estimate differences in SpO2 during simulated flight as well as the amounts by which they changed from control to simulated flight conditions. A random intercept for subject was included to account for correlation within subject in SpO2 and another random intercept for day nested within subject was included to account for within-day correlation for each subject. Moreover, a first-order autoregressive term was used to account for serial correlation of measures for the same subject on the same day.

Respiratory data were processed to limit motion artifacts at the 1-minute level by restricting breath rates from 5 to 50 breaths per minute and volumes from 50 to 3500 milliliters. Then, 5–minute averages were calculated. Heart rates below 40 were eliminated before generating 5-minute averages. Once again we ran simple and adjusted mixed effect models to include main effects for each baseline characteristic and interactions between these variables. The models included also an indicator variable for flight versus control, a random intercept for subject, a random intercept for day, and a first-order autoregressive term to account for serial correlation of measures for the same subject on the same day.

The passengers' electrocardiograms were also reviewed manually to identify artifact, and supraventricular and ventricular beats. Ectopic beats were compared using logistic and Poisson regression adjusting for time of day, exposure versus control condition and average heart rate (after removing person-hours with no events).

For the symptom surveys, we ran mixed (multilevel) models for each of the outcomes ("feeling now", fatigue score, and total ESQ symptoms) that included random subject effects to account for the correlation among repeated measures taken on a given subject. For each outcome, we fit two models to probe whether symptoms increased during flight compared to control conditions and whether symptoms increased over time. The first model contained the flight variable only, which estimates the effect of flight versus control, averaged over the time since the first survey (using survey number as the proxy). We then fit a second model that included flight, survey number, and the interaction between the two. This model estimates the effect of flight versus control on linear trends in the outcomes over time (survey number).

RESULTS

Characteristics of the Sample

At baseline (collected at the time of the initial clinic evaluation), participants across the subgroups of "healthy", "cardiac", and "smokers", had similar sea level oxygen saturation and body mass index, however, the "healthy" group was slightly older on average and the "cardiac" group had decreased lung function as noted by the percent predicted of forced expiratory volume at one minute (FEV_1) and the percent predicted of forced vital capacity (FVC) (Table 1).

Table 1. Baseline characteristics of the study population.

Measure	Healthy (n=14; females n=6) Mean (SD)	Healthy Range	Cardiac Disease (n=13; females n=3) Mean (SD)	Cardiac Disease Range	Smokers (n=14; females n=5) Mean (SD)	Smokers Range
Age (yr)	67 (6)	60, 77	63 (8)	54, 73	61 (8)	52, 79
BMI (kg/m^2)	28 (5)	20, 41	30 (5)	21, 38	27 (5)	21, 40
SpO_2 (%)	97 (1)	94, 99	97 (2)	94, 99	98 (1)	96, 99
FEV1 (%)	93 (22)	56, 132	71 (14)	47, 91	81 (12)	60, 103
FVC (%)	89 (16)	59, 113	74 (12)	53, 94	88 (12)	64, 109

Measure	Healthy (n=14; females n=6) Mean (SD)	Healthy Range	Cardiac Disease (n=13; females n=3) Mean (SD)	Cardiac Disease Range	Smokers (n=14; females n=5) Mean (SD)	Smokers Range
FEV1/FVC	0.80 (0.11)	0.49, 0.92	0.73 (0.08)	0.58, 0.87	0.71 (0.08)	0.55, 0.81

* FEV1 and FVC are based on percent of predicted capacity based on age, gender and ethnicity

Oxygen Saturation (SpO2) in Control and Flight Conditions

Table 2 below shows the mean oxygen saturation throughout the chamber study stratified by subject characteristics. The mean SpO2, recorded just before or after the experiment (outside the specific time for either the sham exposure or the pressurized exposure), and noted in Table 2 as "ambient conditions", was similar (95%) among subjects, except for a very slight decrease (~.5% to 1%) in the mean value for those subjects with a baseline SpO2 of <96% at the clinic exam or on the day of the chamber testing. Health status ("healthy", "cardiac", or "smoker") and age (dichotomized at <65 years) showed similar mean differences in SpO2 for both ambient conditions and control days of the experiment.

On flight days, such as during exposure to 7,000 feet, the mean SpO2 of 90% was fairly consistent across the subject characteristics/categories except for a lower mean SpO2 reading in subjects with lower saturation at baseline (<96%).

Table 2. Summary of 5-minute average pulse oxygen saturation readings under ambient and chamber conditions on control and flights.

Period/group	Control Days: Subjects (N)	Control Days: Mean (SD); Range	Flight Days: Subjects (N)	Flight Days: Mean (SD); Range
Ambient conditions				
Overall	40 (452)	95.7 (1.9); 87.2, 99.2	41 (866)	95.6 (2.0); 87.4, 99.3
Healthy	14 (230)	95.6 (1.9); 87.2, 99.2	14 (350)	95.5 (2.2); 87.4, 98.8
Cardiac disease	12 (91)	95.8 (1.6); 91.2, 99.0	13 (288)	95.9 (1.7); 87.5, 99.0
Smoker	14 (131)	95.9 (2.1); 91.3, 99.0	14 (228)	95.6 (2.1); 89.0, 99.3
Pre-post SpO2 ≥96%	23 (294)	96.6 (1.3); 92.2, 99.2	23 (632)	96.5 (1.3); 91.2, 99.3
Pre-post SpO2 <96%	17 (158)	94.0 (1.7); 87.2, 97.6	18 (234)	93.4 (1.8); 87.4, 98.0
Baseline SpO2 ≥96%	34 (379)	95.9 (1.9); 89.8, 99.2	35 (743)	95.8 (2.0); 89.0, 99.3
Baseline SpO2 <96%	6 (73)	95.0 (1.7); 87.2, 97.7	6 (123)	94.5 (1.7); 87.4, 98.0
Age <65y	23 (260)	95.8 (2.1); 87.2, 99.0	24 (497)	95.7 (2.1); 87.4, 99.3
Age ≥65y	17 (192)	95.7 (1.7); 89.8, 99.2	17 (369)	95.6 (1.9); 89.0, 99.0
Chamber period				
Overall	40 (2057)	95.2 (1.7); 86.0, 99.2	41 (2244)	90.6 (2.5); 75.5, 97.0
Healthy	14 (588)	95.4 (1.8); 89.6, 98.6	14 (655)	90.5 (2.4); 81.8, 96.4
Cardiac disease	12 (632)	95.6 (1.6); 87.0, 99.2	13 (765)	90.6 (2.2); 85.6, 96.4
Smoker	14 (837)	94.9 (1.8); 86.0, 99.0	14 (824)	90.7 (2.8); 75.5, 97.0
Pre-post SpO2 ≥96%	23 (1474)	95.8 (1.5); 86.0, 99.2	23 (1568)	91.4 (2.2); 75.5, 97.0
Pre-post SpO2 <96%	17 (583)	93.7 (1.4); 89.6, 97.2	18 (676)	88.7 (1.9); 81.8, 93.6
Baseline SpO2 ≥96%	34 (1845)	95.3 (1.8); 86.0, 99.2	35 (1998)	90.8 (2.5); 75.5, 97.0
Baseline SpO2 <96%	6 (212)	95.0 (1.2); 89.6, 97.2	6 (246)	89.3 (2.1); 83.4, 93.6
Age <65y	23 (1248)	95.3 (1.8); 87.0, 99.2	24 (1336)	91.1 (2.5); 81.8, 97.0

Period/group	Control Days: Subjects (N)	Control Days: Mean (SD); Range	Flight Days: Subjects (N)	Flight Days: Mean (SD); Range
Age ≥65y	17 (809)	95.2 (1.6); 86.0, 98.8	17 (908)	89.9 (2.3); 75.5, 95.8

To further explore the changes in SpO2 from control to flight conditions, we plotted the distribution of mean changes in oxygen saturation for all subjects in Figure 2 below. The points in Figure 2 are each subject's mean change from control to flight condition. The line is based on the mean 5-minute differences for the sample (subtracting the subject's mean SpO2 on control day from each 5-minute measure during flight). We can see crudely from this plot that generally individuals with lower baseline SpO2 declined more in flight. We see also that while this trend was true in general, for a few subjects with higher baselines this was not the case; some subjects with higher SpO2 baselines still experienced large declines in SpO2. For example, five of the subjects with baseline SpO2 above 96% lost ≥ 5 percentage points in oxygen saturation during flight.

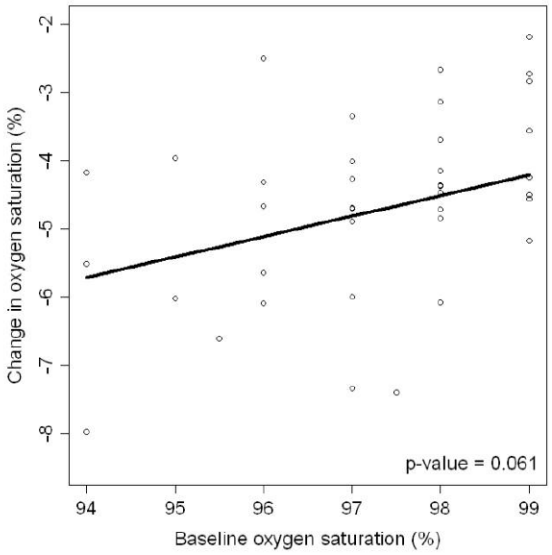


Figure 2. Subject-level mean changes in SpO2 during flight according to baseline oxygen saturation

We can see, further, the overall effect of baseline oxygen saturation on the level of oxygen saturation in flight in Figure 3. Here we plot the proportion of time any 5-minute average oxygen saturation value fell within a specific SpO2 measure during flight according to the individual's baseline SpO2 category (<96% vs ≥96%). In other words, the total person-time across all data points in flight was distributed according to whether the subject started below 96% SpO2 at baseline. For subjects starting with a lower baseline (the top box in Figure 3), the distribution of in-flight 5-minute values shifts to the left, and more points fall below 90% SpO2, compared with subjects that began with higher oxygen saturation. Importantly, even when subjects started with

higher oxygen saturation at baseline (≥ 96%), there was still a considerable amount of person-time spent below 90% saturation during flight in this sample of older passengers.

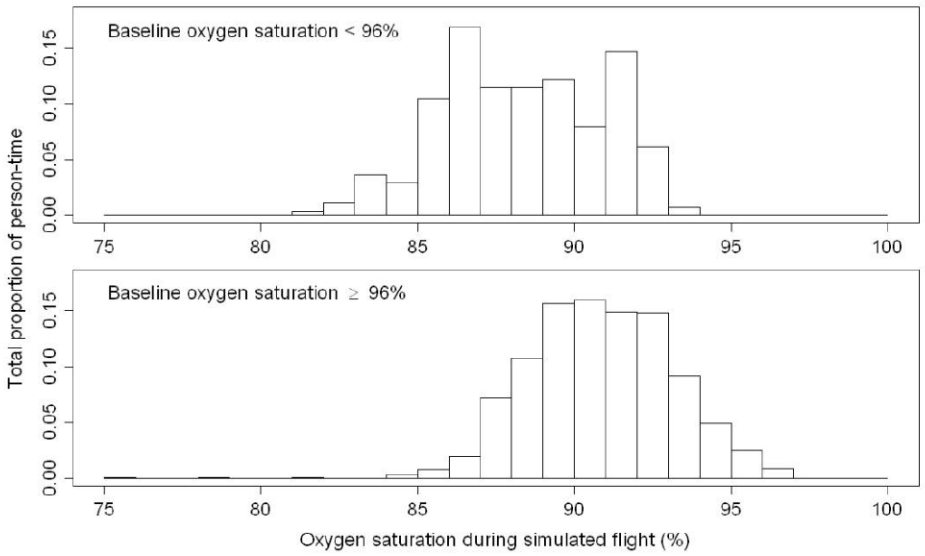


Figure 3. The distribution of 5-minute average SpO2 values according to baseline SpO2<96%

We can observe more specifically the effect of age on in-flight oxygen saturation in Figure 4. According to this plot, compared to age <65 years, age ≥65 is associated with a greater frequency of 5-minute average oxygen saturation measures below 90% (moderately hypoxic level and the level at which patients typically receive oxygen in the emergency room).

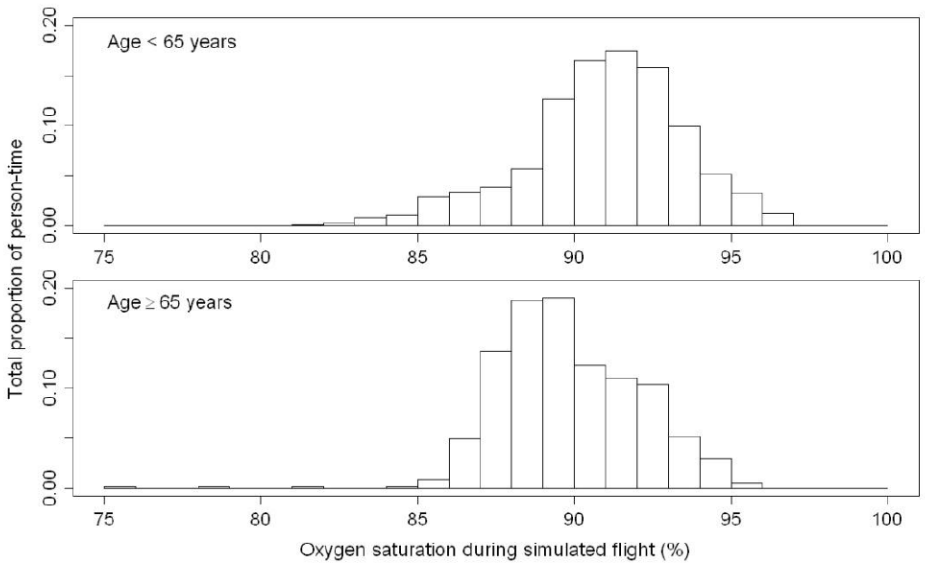


Figure 4. The distribution of 5-minute average SpO2 values according to age <65

While the plots displayed above point out the impact of baseline SpO2 and age on oxygen saturation in flight, the significance of these effects are clearly observed in the mixed model regressions (Table 3) that summarize the combined effects of age, health status, and baseline SpO2, and adjust also for day (exposure first day in the chamber or second day), gender, and other baseline groupings listed in the Table 3 and their interactions with a flight versus control day indicator variable.

Table 3. Effect of pre-flight subject characteristics on oxygen saturation during simulated flight, measured as both change compared to control day and absolute levels during simulated flight.

Period/group	Crude	Adjusted*
Difference in change in SpO_2 from control to flight days		
Healthy reference	Reference = -4.0	
Cardiac disease	-0.01 (-1.10, 1.08)	-0.02 (-1.10, 1.07)
Smoker	0.19 (-0.87, 1.24)	0.19 (-0.87, 1.25)
Baseline SpO_2 ≥96%	Reference = -3.9	
Baseline SpO_2 <96%	-1.16 (-2.32, -0.00)	-1.12 (-2.36, 0.12)
Age (per 10 years)	-0.63 (-1.16, -0.10)	-0.66 (-1.20, -0.13)
Difference in SpO_2 during flight		
Healthy reference	Reference = 90.6	
Cardiac disease	0.13 (-1.38, 1.64)	-0.17 (-1.49, 1.15)
Smoker	-0.27 (-1.96, 1.41)	-0.85 (-2.45, 0.76)
Baseline SpO_2 ≥96%	Reference = 90.9	
Baseline SpO_2 <96%	-2.11 (-3.94, -0.29)	-2.01 (-3.73, -0.30)

Period/group	Crude	Adjusted*
Age (per 10 years)	-0.79 (-1.55, -0.04)	-0.88 (-1.62, -0.13)

* Adjusted for day (exposure first day or second day in the chamber), gender, and other baseline groupings listed in the table. Values are estimates with 95% confidence intervals.

Interestingly, the difference in SpO2 from control to flight days was not related to whether the subject was in the healthy, cardiac or smoker group. The decline in SpO2 from control days to simulated flight days was similar for subjects in each of these subgroups. Baseline SpO2 below 96% as assessed independently by a physician, however, was associated with a greater decline in SpO2 between control and simulated flight days, and this association was borderline statistically significant after adjustment for potential confounders (p-value = 0.078). Each 10-year increase in age was significantly associated with a 0.66% (95% CI: -1.20, -0.13) greater decline in SpO2 from control to simulated flight days (p-value = 0.015). (Refer to the top of Table 3 for overall *change* from control to flight days)

The lower part of Table 3 shows the *absolute* difference in SpO2 during flight according to each of the categories. There was no evidence of a difference in the absolute value of SpO2 during flight between the healthy subjects, cardiovascular disease patients, and smokers. Baseline SpO2 below 96%, however, was associated with a 2.42% lower SpO2 during flight (p-value = 0.021). [Editor's note: see Errata, item 7.] Each 10-year increase in age was associated with a 0.88% lower SpO2 during simulated flight days (p-value = 0.040).

As further test of the effect of flight on oxygen saturation, we compared the oxygen saturation for each of the six chamber subjects who later flew aboard the commercial flights and observed similar results. We found no real differences between each subject's baseline oxygen saturation levels before and after all of the test periods, including the pre-post periods before the chamber sequence and each of the commercial flights. In addition, we observed no real differences in oxygen saturation levels during the simulated flight and each of the three actual flights (Table 4). Importantly, means tests for significant differences in this small sample do not rule out a chance finding.

Table 4. Comparison of chamber simulated and actual flight: summary of altitudes, oxygen

Measure	Chamber	Flight 1085	Flight 2861	Flight 1377
Before and after periods				
Number of 5-min measures	105	132	138	148
Altitude - test site (ft)	1,311	1,201	33	2,014
SpO_2 (%)	95.9 (1.4)	96.4 (1.4)	95.4 (1.6)	94.7 (1.3)
Flight period				
Flight Duration	4 h 20 m	2 h 45 m	5 h 9 m	2 h 12 m
Number of 5-min measures	287	96	268	80
Altitude (ft)	7,110 (146)	6,985 (68)	7,064 (150)	7,133 (0)
SpO_2 (%)	90.9 (1.7)	90.8 (1.7)	90.7 (1.5)	90.6 (1.6)

*All variables are analyzed only for 5-minute intervals for which a valid SpO2 measure was obtained. Measurements from commercial flight periods include those after 15 minutes of reaching a cruising altitude of over 6,000 feet up until 5 minutes before start of descent. Before and after periods include measures up to 2 hours before takeoff or 2 hours after landing for flight or simulated flight.

Breathing and Heart Rate in Control and Flight Conditions

Because the body works to maintain homeostasis in stressful environments, such as hypoxic conditions, we were interested in the impact of flight on breathing measures and heart rate. Table 5 shows the descriptive statistics for breathing and heart rate in the chamber according to the passenger categories of interest: age, health group, and baseline SpO2. Overall, breathing and heart rate appear to increase under flight conditions compared to control conditions.

Table 5. Breathing and Heart Rate Measures – Chamber Study.

Period/group	Control Days: Subjects (N)	Control Days: Mean (SD); Range	Flight Days: Subjects (N)	Flight Days: Mean (SD); Range
Breathing rate (breaths per minute)				
Overall	40 (2289)	20.4 (4.9); 6.8, 41.9	41 (2334)	22.0 (5.2); 7.3, 45.7
Healthy	14 (682)	20.7 (4.5); 6.8, 37.6	14 (696)	21.1 (5.1); 7.3, 45.7
Cardiac disease	12 (748)	22.6 (5.3); 10.9, 41.9	13 (798)	23.1 (5.8); 11.4, 45.3
Smoker	14 (859)	21.0 (4.7); 9.3, 40.8	14 (840)	21.6 (4.5); 11.3, 39.5
Baseline SpO2 ≥96%	34 (1954)	21.7 (5.1); 6.8, 41.9	35 (2021)	22.0 (5.4); 7.3, 45.3
Baseline SpO2 <96%	6 (335)	20.2 (3.0); 14.2, 32.3	6 (313)	21.7 (4.3); 12.3, 45.7
Age <65y	23 (1345)	21.5 (5.0); 9.3, 40.8	24 (1378)	21.9 (5.5); 10.8, 45.7
Age ≥65y	17 (944)	21.4 (4.8); 6.8, 41.9	17 (956)	22.1 (4.8); 7.3, 39.5
Tidal volume (ml)				
Overall	40 (2289)	612 (282); 55, 2218	41 (2334)	698 (286); 162, 2663
Healthy	14 (682)	611 (251); 164, 1526	14 (696)	671 (284); 187, 2663
Cardiac disease	12 (748)	624 (310); 185, 2218	13 (798)	678 (315); 162, 2153
Smoker	14 (859)	602 (281); 55, 1994	14 (840)	741 (254); 282, 2274
Baseline SpO2 ≥96%	34 (1954)	609 (291); 55, 2218	35 (2021)	715 (271); 202, 2274
Baseline SpO2 <96%	6 (335)	628 (225); 216, 1772	6 (313)	589 (353); 162, 2663
Age <65y	23 (1345)	581 (299); 55, 2218	24 (1378)	709 (320); 162, 2663
Age ≥65y	17 (944)	657 (251); 218, 1997	17 (956)	684 (229); 298, 2274
Minute ventilation (L/min)				
Overall	40 (2289)	13.5 (7.6); 0.9, 68.1	41 (2334)	15.8 (8.6); 3.4, 79.2
Healthy	14 (682)	12.6 (5.4); 2.4, 37.3	14 (696)	14.4 (7.7); 3.4, 78.9
Cardiac disease	12 (748)	14.5 (8.4); 3.0, 57.1	13 (798)	16.4 (9.9); 3.4, 67.4
Smoker	14 (859)	13.3 (28.9); 0.8, 296.1	14 (840)	16.5 (7.9); 5.5, 79.2
Baseline SpO2 ≥96%	34 (1954)	13.5 (7.8); 0.9, 68.1	35 (2021)	16.2 (8.4); 3.9, 79.2
Baseline SpO2 <96%	6 (335)	13.3 (6.4); 4.3, 52.9	6 (313)	13.2 (9.2); 3.4, 78.9
Age <65y	23 (1345)	13.1 (8.3); 0.9, 64.6	24 (1378)	16.2 (9.6); 3.4, 78.9
Age ≥65y	17 (944)	14.0 (6.3); 4.3, 68.1	17 (956)	15.3 (6.9); 5.2, 79.2
Heart rate (beats per min [bpm])				
Overall	40 (2287)	78 (11); 44, 109	41 (2288)	80 (12); 44, 119
Healthy	14 (681)	77 (11); 50, 109	14 (681)	81 (12); 54, 119

Period/group	Control Days: Subjects (N)	Control Days: Mean (SD); Range	Flight Days: Subjects (N)	Flight Days: Mean (SD); Range
Cardiac disease	12 (717)	78 (9); 44, 106	13 (756)	80 (12); 44, 112
Smoker	14 (888)	78 (12); 56, 109	14 (851)	80 (11); 59, 115
Baseline SpO2 ≥96%	34 (1997)	78 (11); 44, 109	35 (2003)	80 (12); 44, 115
Baseline SpO2 <96%	6 (290)	75 (7); 59, 105	6 (285)	78 (9); 60, 119
Age <65y	23 (1361)	80 (11); 44, 109	24 (1391)	82 (12); 44, 119
Age ≥65y	17 (926)	75 (10); 50, 109	17 (897)	78 (10); 54, 111

In the fully adjusted multi-level mixed models (Table 6) breathing does in fact increase in flight with borderline significance and heart rate significantly increases 2.4 beats per minute over the flight also.

Table 6. Effect of flight on respiratory parameters and heart rate. Comparison of 5-min average measures during simulated flight at altitude and control days in the chamber*.

Measure	Crude: Effect (95% CI)	Crude: p-value	Adjusted for experimental order: Effect (95% CI)	Adjusted: p-value
Breathing rate	0.51 (0.02, 1.05)	0.060	0.64 (0.00, 1.28)	0.050
Tidal volume (ml)	79 (-18, 176)	0.107	66 (-50, 183)	0.258
Minute ventilation (L)	2.1 (-0.1, 4.3)	0.061	1.7 (-0.9, 4.3)	0.185
Heart rate (bpm)	-0.27 (-0.61, 0.06)	0.113	2.4 (0.7, 4.1)	0.007

* Models include random intercept for subject, random flight for subject for effect of flight, and autoregressive correlation among subsequent 5-minute measures.

Although we observed increased breathing rates and heart rates in flight, we were interested to know if these events were related to the passenger's level of hypoxia. These mixed model regression results are presented in Table 7.

Only breathing rate was borderline significantly positively associated with SpO2 levels during flight across the entire sample. Notably, cardiac patients showed significantly larger increases in all respiratory indices (rate, volume and minute ventilation) in association with SpO2 when compared to the other health groups. In addition, heart rate was inversely associated with oxygen levels in cardiac patients, although these changes were minor and insignificant.

We were surprised by the direction of these relationships if increased breathing rate and heart rate were expected to compensate for hypoxia (decreased oxygenation). The pattern we observed instead was that breathing rates increased when oxygen levels increased. Further, for cardiac patients specifically, that breathing response was exaggerated and followed the same unexpected pattern; the rise in all of the breathing indices (breathing rate, tidal volume and minute ventilation) was significantly associated with an increase in oxygen saturation.

This intensified breathing response in the cardiac patients may make more sense as hypoxic compensation if one considers that these heart patients may depend more on respiratory responses when compensatory cardiac stimulation is depressed under the influence of beta blocker medications prescribed for these patients. In addition, the contemporaneous associations

we observed would not account for lagged effects in hypoxic compensation. In this light, increased respiratory effort as SpO2 rises may be a logical compensatory response pattern in hypoxia.

Table 7. Association between SpO2 during simulated flight and cardiopulmonary indices. Effects expressed per 1% change in 5-minute average SpO2.

Measure	Crude: Effect (95% CI)	Crude: p-value	Adjusted*: Effect (95% CI)	Adjusted*: p-value
All				
Breathing rate	0.16 (-0.3, 0.36)	0.102	0.18 (-0.01, 0.37)	0.062
Tidal volume (ml)	6.0 (-5.3, 17.2)	0.298	6.8 (-3.8, 17.3)	0.207
Minute ventilation (L)	0.16 (-0.23, 0.55)	0.426	0.19 (-0.18, 0.56)	0.307
Heart rate (bpm)	-0.27 (-0.61, 0.06)	0.113	-0.27 (-0.60, 0.07)	0.120
Cardiac disease				
Breathing rate	0.40 (0.06, 0.75)	0.023	0.39 (0.05, 0.74)	0.027
Tidal volume (ml)	23.6 (4.5, 42.6)	0.015	20.4 (1.0, 39.8)	0.039
Minute ventilation (L)	0.82 (0.20, 1.43)	0.009	0.72 (0.07, 1.36)	0.029
Heart rate (bpm)	-0.30 (-1.04, 0.44)	0.423	-0.32 (-1.09, 0.44)	0.410

*Age, gender, time in chamber since start of flight or control conditions.

As further test of the effect of flight on heart rate and breathing indices, we compared the chamber results to the findings from the commercial flights for each of the six chamber subjects who participated in these tests. Interestingly, we found the results were remarkably similar between both conditions (Table 8).

We found no real differences between each subject's baseline measures of breathing and heart rates (as measured before the test and included also the period immediately after the test), except for in the case of the Flight 2861. In this case, tidal volumes were higher at baseline *and* in flight. Flight 2861 was the longest low pressure exposure time by approximately one hour for the study participants, even when compared to chamber times. Given that the baseline measures for the commercial flights included readings from *both* pre and post flight periods, we considered that increased baseline tidal volumes for Flight 2861 may have captured residual spillover effects of increased tidal volumes *during* the flight in this composite baseline measure.

To understand what was happening to breathing during Flight 2861, we ran a mixed model with random intercepts accounting for autocorrelation to test for the slope over time during Flight 2861 among the six passengers. There is a statistically significant increase associated with time in flight of about 33 ml in tidal volume per hour (p-value = 0.019). This slope is only significant for this long flight and not the other two. Importantly, means tests for significant differences in this small sample do not rule out a chance finding.

Table 8. Comparison of chamber simulated and actual flight: heart rate, and breathing indices, including same-day comparison periods before and after flights*.

Measure	Chamber	Flight 1085	Flight 2861	Flight 1377
Before and after periods				
Number of 5-min measures	105	132	138	148
Heart rate	79 (8)	75 (14)	77 (12)	84 (14)
Breathing rate	22 (7)	29 (6)	28 (7)	28 (7)
Tidal Volume (ml)	712 (239)	763 (336)	1112 (383)	708 (294)
Minute ventilation (L/Min)	16 (8)	22 (13)	32 (16)	21 (13)
Flight period				
Flight Duration	4 h 20 m	2 h 45 m	5 h 9 m	2 h 12 m
Number of 5-min measures	287	96	268	80
Altitude (ft)	7,110 (146)	6,985 (68)	7,064 (150)	7,133 (0)
Heart rate	77 (12)	75 (12)	73 (11)	76 (12)
Breathing rate	22 (5)	22 (5)	21 (5)	21 (6)
Tidal Volume (ml)	642 (336)	579 (237)	780 (189)	569 (222)
Minute ventilation (L/Min)	14 (9)	13 (7)	17 (7)	12 (9)

*All variables are analyzed only for 5-minute intervals for which a valid SpO2 measure was obtained.

Increased Rates of Ectopic Beats in Flight

As discussed previously, we observed a significant effect of flight on heart rate. We found also a combined effect of flight and time in flight on heart rate (Figure 5). As seen below, the heart rate increases steadily over time only on flight days.

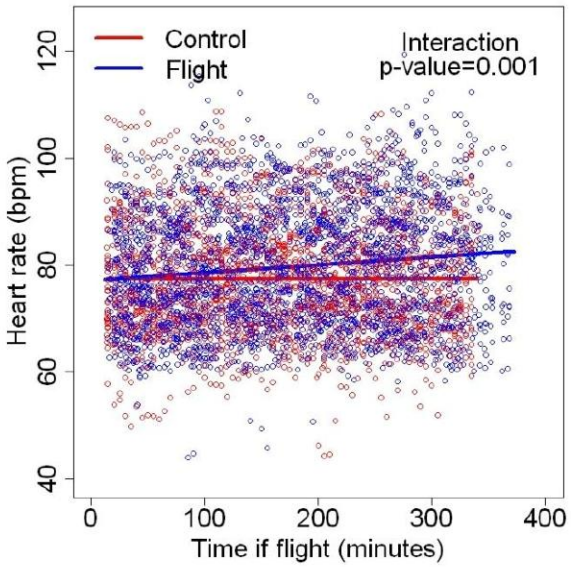


Figure 5. The effect of the interaction between the exposure of flight and the duration of flight on passenger heart rate

To further evaluate the consequences of cardiac stimulation in flight, we plotted the frequencies of ectopic (extra) beats in the control period versus flight periods from the chamber experiments. (Figure 6 and Figure 7)

We found that the odds of having any ventricular or atrial ectopy were not significantly different between simulated flight and control days. However the rate of ventricular couplets or runs of 3 or more beats were significantly higher during simulated flight compared to control conditions.

Importantly, arrhythmias occurred only in those subjects who had arrhythmias in the control period and all of these subjects were heart failure patients.

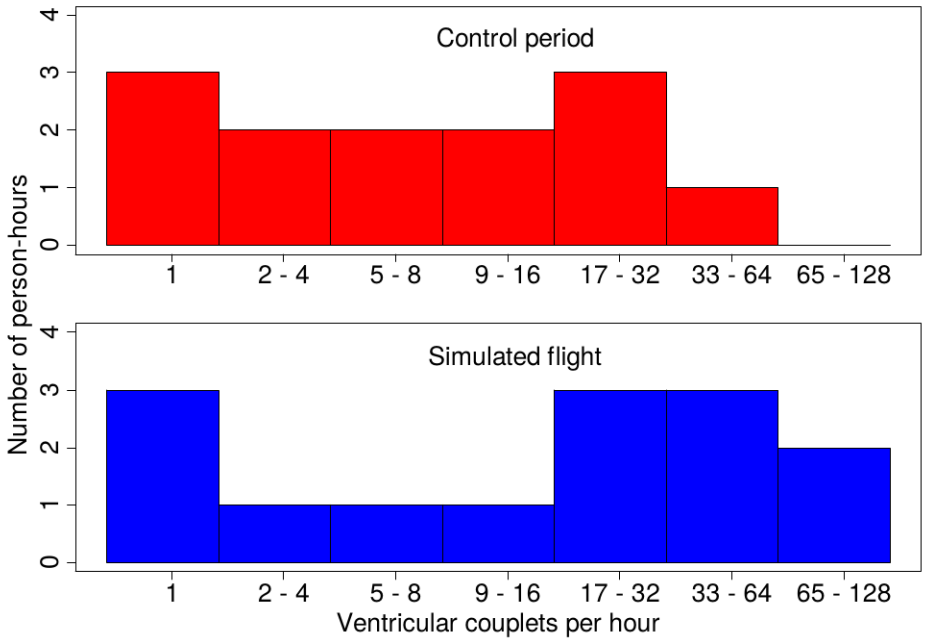


Figure 6. Frequency of ventricular couplets during flight compared to control (ground) conditions

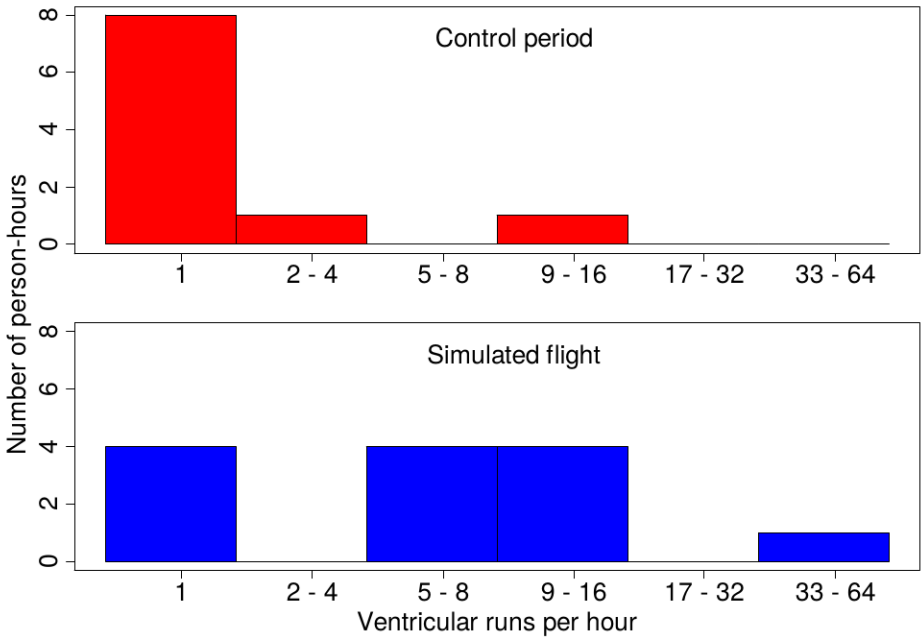


Figure 7. Frequency of ventricular runs (3 or more extra beats) during flight compared to control (ground) conditions

Ventricular ectopic beats occurred in couplets among eight of the subjects, during 32 subject-hour intervals, at an average rate of 22 (SD=33) within these intervals, and in runs of three or more among seven subjects, during 26 of the subject-hours, at an average rate of 9 (SD=19). Table 9 displays the counts of ectopy under control and flight conditions.

Table 9. Number of persons and person-hours with ectopic beat events and rates of events per hour during periods when events occurred.

Event	Subjects with any event (%): Control Period (n=38)	Subjects with any event (%): Simulated Flight (n=38)	Periods with any event (%): Control Period (n=172)	Periods with any event (%): Simulated Flight (n=182)	Rate per hour (SD)*: Control Period	Rate per hour (SD)*: Simulated Flight
VE couplets	4 (11)	5 (13)	13 (8)	14 (8)	15 (14)	33 (46)
VE runs	5 (13)	4 (11)	10 (6)	13 (7)	4 (4)	14 (25)
SVE couplets	9 (24)	11 (29)	15 (9)	20 (11)	1.4 (1.0)	1.8 (1.4)
SVE runs	5 (13)	3 (8)	7 (4)	5 (3)	1.5 (0.6)	1.2 (0.4)

VE – ventricular ectopy; SVE – supraventricular ectopy. * During person hours when events occurred.

Among subject-hours when couplets of ectopic ventricular beats occurred, the adjusted rate ratios were 3.5 (95% CI: 1.3, 9.5) for couplets and 9.4 (95% CI: 3.2, 27.3) for runs of three or more ventricular ectopic beats after removing one outlier in Model 2 in Table 10. Also adjusting for average heart rate during each subject-hour resulted in a similar rate ratio for couplets and a larger effect estimate for runs, but the confidence intervals were wider.

Table 10. Rate ratios for hourly counts of ventricular ectopic events associated with simulated flight versus control period in chamber.

Outcome	Subjects (N) and person-hours	Model 1[1]	Model 2[2]
Ventricular ectopic couplets	6 (27)	8.9 (1.7, 46.1)	3.5 (1.3, 9.5)
Ventricular ectopic runs	6 (23)	26.4 (6.2, 112.2)	9.4 (3.2, 27.3)

[1] Model 1: generalized estimating equations for Poisson counts of couplets or runs of ectopic beats, accounting for correlation within subjects and adjusting for week, time of day at start of each 1-hour interval. [2] Model 2: same as Model 1 except one outlier removed from simulated flight exposure.

Passenger Reports of Symptoms in Flight

The association between symptom reporting and altitude was not differentiated at the chamber pressures (7,000 feet). Either an increase in symptoms or an increase in the severity of symptoms, were not associated with flight versus control conditions. Instead, symptom reports were more closely associated with the passage of time.

Figure 8 is the plot of the mean scores across the different conditions of flight (7,000 feet) and control (sea-level), the time (hour), and the three different symptom measures ("feelingnow", fatigue, and ESQ). These scales were previously described under "Approaches" in the "Instrumentation: Measures" sub-section.

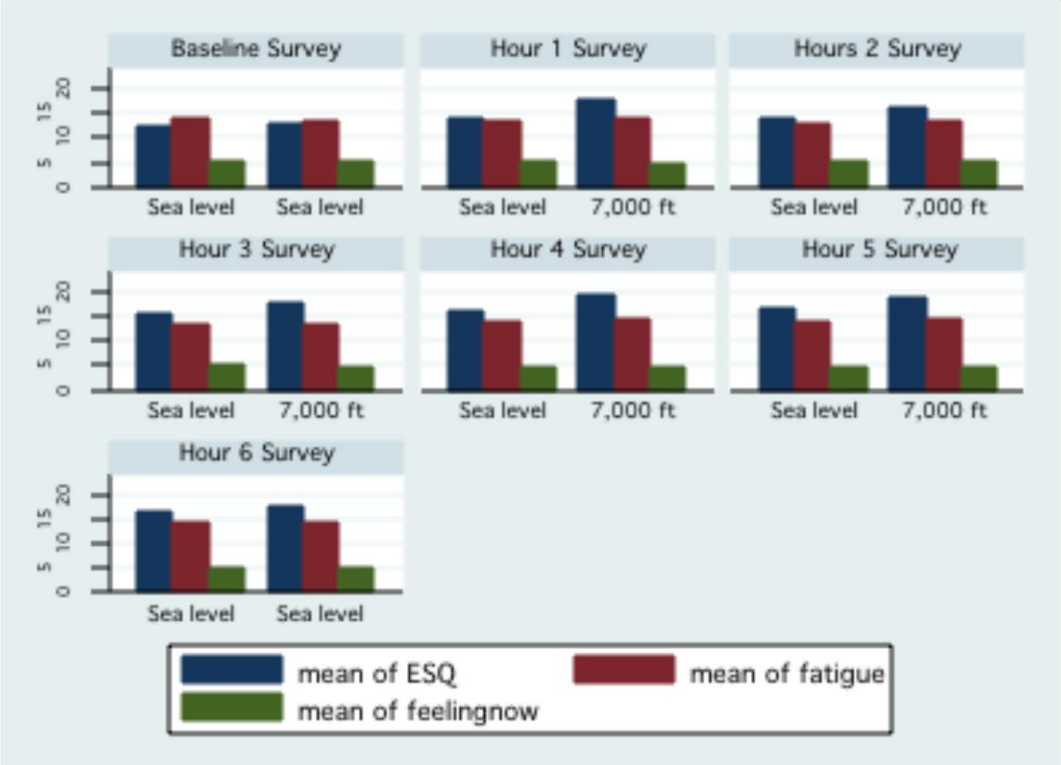


Figure 8. Survey scores by time period

None of these symptom outcomes were normally distributed. The feelingnow and fatigue outcome (based on Likert scales) were quite discrete, and so we fit these with a mixed cumulative logit model for ordinal outcomes. The resulting coefficients (Table 11) represent the log odds ratio of falling in a high category versus falling in a low category. For feelingnow, the main effect of flight was marginally insignificant (p=07), with flight associated with lower scores. The estimated odds ratio of falling in a higher category versus a lower category associated with flight (versus control) is 0.72 (95% CI: 0.51, 1.04). There were strong effects of time (i.e. survey number) overall (p<0.001), with later times associated with lower feelingnow scores. The estimated odds ratio for a higher (versus lower) score associated with each additional survey number is 0.76 (95% CI: 0.67, 0.86). There were no effects of flight on trends over time for feelingnow. There were no effects of flight (either overall or on trend over time) on fatigue.

Due to the aggregation of multiple questions, the ESQ was approximately log-normally distributed. Therefore, we fit a linear mixed model for the transformed log(ESQ+1) outcome. There were no significant effects of flight on ESQ and no effect of flight over all times or with respect to trends over time. ESQ did decrease significantly over time, approximately a 5.6% increase in ESQ score per additional survey.

Table 11. Models of symptom outcomes, flight effect and time (surveynum), and interaction effects

Outcome and model	Term	Estimate	Std. Error	t or z value	Pr(>|z|)
Outcome: log(ESQ+1)					
Model 1. Flight only	(Intercept)	2.66879	0.09873	27.032 (t)	
Model 1. Flight only	Flight	0.03500	0.04455	0.786 (t)	
Model 2. Flight, surveynum, interaction	(Intercept)	2.505989	0.108435	23.110 (t)	
Model 2. Flight, surveynum, interaction	Flight	0.001369	0.076526	0.018 (t)	
Model 2. Flight, surveynum, interaction	surveynum	0.054351	0.014941	3.638 (t)	
Model 2. Flight, surveynum, interaction	Flight:surveynum	0.011676	0.021244	0.550 (t)	
Outcome: feelingnow					
Model 1 (location coefficients)	Flight	-0.3224	0.1827	-1.7649 (z)	.077584
Model 2	Flight	-0.4507	0.3250	-1.3867 (z)	0.1655419
Model 2	surveynum	-0.2740	0.0654	-4.1919 (z)	2.7657e-05
Model 2	Flight:surveynum	0.0335	0.0914	0.3661 (z)	0.7142647
Outcome: fatigue					
Model 1 (location coefficients)	Flight	0.1613	0.1601	1.0075 (z)	0.31369404
Model 2 (location coefficients)	Flight	-0.1972	0.2734	-0.7215 (z)	0.47060620
Model 2 (location coefficients)	surveynum	-0.0039	.0503	-0.0773 (z)	0.93837379
Model 2 (location coefficients)	Flight:surveynum	0.1250	0.0766	1.6307 (z)	0.10295707

The log(ESQ+1) models report t values; the feelingnow and fatigue models report z values and Pr(>|z|).

CONCLUSIONS AND DISCUSSION

This study is the first single-blind investigation we know to include a broad accounting of physiological effects of cabin pressure in older and susceptible passengers. The results suggest that a significant portion of older passengers may be moderately hypoxic (≤ 90% oxygen saturation) at 7,000 feet equivalent cabin pressures, pressures still slightly above the regulated limit to 8,000 feet.

Although we do not know the full extent of health impact for seniors from the hypoxia we observed in flight, several of the physiological markers that we tracked suggest that the flying experience may be more stressful than previously understood. In this sample, moderate hypoxia was common with almost half of the older passengers reaching SpO2 levels ≤90 for a significant amount of time during the flight in addition to changes in breathing rates. Further, cardiac stimulation was apparent by an average increase in heart rate of 2.4 beats per minute over the medium flight time (4- 5 hours). Also at these cabin pressures, the rate of ectopic beats increased in passengers with heart failure. Interestingly, according to current medical guidelines, most of the seniors in our study would have been considered low risk for moderate hypoxia according to their sea level oxygen saturations (Mortazavi et al., 2003; British Thoracic Society Standards of Care Committee, 2002).

Prior studies have found that in-flight oxygen saturations are typically higher than what we observed. One comprehensive study found a maximum decrease in oxygen saturation of 4.4% but the sample was younger and healthier than the participants in our study (Muhm et al., 2007). Another recent study with a sample matching our own, including cardiac patients, found that while the overall probability of achieving moderate hypoxia was low for the sample, the risk was higher in the 60 years and over age group (Grun et al., 2008).

Past studies have found, also, that hypoxic levels at cruise altitudes did dip as low as in our study (Kelly, 2009; Schacke et al., 2007; Seccombe et al., 2006; Akero et al., 2005; Dillard et al., 1989). However, some of these findings are limited pulse oximetry is the only outcome measure and often, only a single measurement of saturation (Humphreys et al., 2005) or small sample sizes (Kelly et al., 2006; Christensen et al., 2002; Christensen et al., 2000).

The results of studies that have looked at compensatory signs of cabin altitudes, such as cardiac and respiratory biomarkers, are mixed. However, many of these studies are limited to pulse rate only. In contrast, Akero et al. (2005) examined a number of cardio-pulmonary responses and found evidence for hypoxia induced sympathetic arousal including increased heart rate and evidence of hyperventilation after four hours with mean oxygen saturation drops to 87%, compared with 95% at ground level in the subjects. These results are in line with our findings and argue that at moderate saturation levels experienced at cabin altitudes over medium range flights (4-5 hours), seniors and vulnerable passengers are working harder to compensate. What this means for them over longer flights is still to be determined. Nonetheless, these signs

correspond to sympathetic arousal that may be worrisome in vulnerable passengers, such as heart failure patients (Silverman and Gendreau, 2009; Mortazavi et al., 2003).

Despite this evidence for system loading, such as cardiopulmonary arousal in flight, researchers still disagree about the level of "tolerable" hypoxia. Some authors have argued that because passengers reported "feeling fine", that the decreased oxygen saturations were tolerable (Muhm et al., 2007). We caution about this interpretation based on our finding that symptom reports do not differentiate between control or flight conditions. Thus, symptom reports may be an insensitive indicator of the physiological load of flight and results from at least a few other studies would support this finding (Schwartz et al., 1984; Kelly et al., 2006).

Ours is not the first study to find that diagnostic categories are not particularly helpful in predicting oxygen saturation levels in flight (Robson et al., 2008). We found no difference in oxygen saturations for the healthy seniors compared to the cardiac and smoker groups. A more important differentiator between groups was how individuals *responded* to hypoxic states physiologically and this response was related to their disease state. The ability to compensate for hypoxia was notably different for the cardiac patients. In particular, the heart rate and breathing changed more with oxygen saturations in this group compared to healthy seniors and senior smokers.

Taking note of the *difference in the responses* to hypoxia underscores the subtle but important point that most of what we know about cabin pressure effects is based more on oxygen saturation levels than on the sequelae. But this is beginning to change. We believe our own study is a step in this direction by following signs of compensatory mechanisms in the presence of hypoxic conditions. More recent studies are looking at health outcomes in the 48-hour time span after air travel to show health impacts ranging from exacerbation of symptoms in COPD patients to myocardial infarction (Edvardsen et al., 2011; von Klot et al., 2011).

Finally, the evaluation of in-flight hypoxia has been limited in the past to young and healthy passengers on the one hand, and very sick, usually pulmonary patients, on the other. Our study has attempted to consider other sources of risk that apply to a broader spectrum of the flying public, and that include a more informed understanding about how senior age affects responses at cabin altitudes. The study of risk related to hypoxia at usual cabin altitudes is not well understood for other groups, especially for cabin crew that expend more energy at altitude and may present with concomitant occupational problems like sleep deprivation secondary to shift work that would further complicate hypoxia. This issue in particular has not been studied. Therefore, future studies should target this group in particular.

In summary, this study found moderate hypoxia, sufficient to produce compensatory mechanisms, to be prevalent in senior passengers. The study is a first of this kind to profile a full range of physiological signs, however, more work still needs to be done. For instance, we still know little about the health of passengers following long flights. The research on the risks of

thromboembolism after travel is a good template for investigations about other health outcomes after flight (Gallus, 2005; Kelman et al., 2003).

Our study was innovative in that we collected comprehensive, continuous, and repeated measures from passengers over several days (prescreening, chamber days and for some subjects, additional in-flight days). However, we wish to acknowledge several limitations. First, the sample size was small, especially with regard to the cardiac patients and the number of passengers that were tested aboard commercial flights. Also we recognize that pulse-oximetry is an indirect measure of oxygen saturation and may not have been accurate for the smokers in our sample. In any case, the problem would be to overestimate the level of oxygen saturation.

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ERRATA

The corrections and notes below were made when this report was prepared for republication through the National Transportation Library. Minor typographical, spelling, and punctuation errors were also corrected and are not listed individually.

Corrections Made in This Edition

1. Tables 1 and 5: oxygen saturation labels "SaO_2" corrected to "SpO_2". Per the Methods and Limitations, all oxygen saturation values were measured by pulse oximetry (SpO2), not arterial blood sampling (SaO2).
2. Table 1: body mass index (BMI) units corrected from "kg/m^3" to "kg/m^2".
3. Table 11: the second log(ESQ+1) model, originally labeled "Model 1. Flight, surveynum, interaction," relabeled "Model 2," consistent with the feelingnow and fatigue model labels.
4. Figure 5 caption: "the duration of flight passenger on heart rate" corrected to "the duration of flight on passenger heart rate."
5. References: third author of Akero et al. (2005) corrected from "Advardse A" to "Edvardsen A."
6. Technical Report Documentation Page (Form DOT F 1700.7): title corrected from "Pressure for Older and Vulnerable Passengers" to "Pressure in Older and Vulnerable Passengers," consistent with the report cover.

Discrepancies Noted but Not Changed

7. Results, oxygen saturation: The text reports that baseline SpO2 below 96% "was associated with a 2.42% lower SpO2 during flight (p-value = 0.021)." Table 3 reports a difference of -2.11 percentage points (crude; 95% CI -3.94, -0.29) and -2.01 (adjusted; 95% CI -3.73, -0.30). The reported p-value is consistent with the adjusted estimate. The value of 2.42 could not be reconciled with the tabulated results and is retained as originally published. Similarly, the reported effect of age (0.88% per 10 years) matches the adjusted estimate, while its p-value (0.040) matches the crude estimate.
8. Table 6: the crude heart-rate result, -0.27 (-0.61, 0.06), p = 0.113, is identical to the crude heart-rate result for all subjects in Table 7 and may have been entered in error. Retained as originally published.
9. Table 7: the crude 95% confidence interval for breathing rate (all subjects), "(-0.3, 0.36)," may contain a typographical error (possibly -0.03). Retained as originally published.