Physiological Effects of Centrifuge-Simulated Suborbital Spaceflight

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BACKGROUND: High-G acceleration experienced during launch and re-entry of suborbital spaceflights may present challenges for older or medically susceptible participants. A detailed understanding of the associated physiological responses would support the development of an evidence-based medical approach to commercial suborbital spaceflight.

METHODS: There were 24 healthy subjects recruited into 'younger' (18-44 yr), 'intermediate' (45-64 yr) and 'older' (65-80 yr) age groups. Cardiovascular and respiratory variables were measured continuously during dynamic combinations of $+G_x$ (chest-to-back) and $+G_z$ (head-to-foot) acceleration that simulated suborbital G profiles for spaceplane and rocket/capsule platforms. Measurements were conducted breathing air and breathing 15% oxygen to simulate a cabin pressure altitude of 8000 ft.

RESULTS: Suborbital G profiles generated highly dynamic changes in heart rate, blood pressure, and cardiac output. G-induced hypoxemia was observed, with minimum arterial oxygen saturation < 80% in a quarter of subjects. Increased age was associated with greater hypoxemia and reduced cardiac output responses but did not have detrimental cardiovascular effects. ECG changes included recurrent G-induced trigeminy in one individual. Respiratory and visual symptoms were common, with 88% of subjects reporting greyout and 29% reporting blackout. There was one episode of G-induced loss of consciousness (G-LOC).

DISCUSSION: Suborbital acceleration profiles are generally well tolerated but are not physiologically inconsequential. Marked hemodynamic effects and transient respiratory compromise could interact with predisposing factors to precipitate adverse cardiopulmonary effects in a minority of participants. Medically susceptible individuals may benefit from expanded preflight centrifuge familiarization that includes targeted physiological evaluation in the form of a 'G challenge test'.

KEYWORDS: passenger health, fitness to fly, spaceflight participant, crew, ageing, +Gx and +Gz acceleration.

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Foundational knowledge of the physiological effects of commercial airline flights underpins the process of assessing and optimizing airline passenger fitness-to-fly and thereby facilitating safe travel.[12,24] Commercial suborbital spaceflights are now available for tourism and scientific research, and are ultimately anticipated to mature into extremely fast point-to-point travel (e.g., London-Sydney in less than 2 h).[22] Just as for air travel, a strong foundational knowledge of fundamental flight-related physiology is required to inform medical decision-making and maximize safe access to suborbital flights.

Stressors of suborbital spaceflight can include mild hypoxia from airline-style cabin pressure altitudes of 6000–8000 ft (1829–2438 m),[23,25,29] but also extend beyond the air travel paradigm to include dynamic high-G and zero G exposures. Flight profiles vary in detail and are specific to each platform

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but include a high-G launch phase followed by a period of microgravity and then a further high-G phase during atmospheric re-entry.[1] Physiological challenges associated with this environment may well be clinically relevant for a small subset of suborbital spaceflight participants, who more typically resemble airline passengers than professional astronauts or flight crew with respect to background health and fitness.[3,6,22] At least initially, suborbital participants are also more likely to come from older age groups, with a naturally higher prevalence of medical disease,[6] and ageing-related physiological changes could additionally contribute to the development of flight-related complications.

The high-G phases of suborbital flight combine variable degrees of $+G_x$ (chest-to-back) and $+G_z$ (head-to-foot) acceleration that depend on several factors including the spacecraft and launch platform, the flight trajectory and the orientation of the seat (upright or reclined). Suborbital $+G_x$ loads can exceed $+3\ G_x$ for periods of 20–30 s and peak at up to $+6\ G_x$ on re-entry, while $+G_z$ may exceed $+3\ G_z$ for similar periods and peak at up to $+4\ G_z$.[1,4,7]

Large centrifuge-based studies have simulated suborbital spaceplane profiles in volunteers across a wide range of ages and with multiple well-controlled medical conditions, and have established that these profiles are likely to be tolerable for the majority of participants.[5,7,8] However, in these studies approximately 5% of volunteers were unable to complete the G exposures, and transient physical symptoms were not uncommon.[6] Visual G symptoms were frequently reported,[7] and while there have been no reports of G-induced loss of consciousness (G-LOC), across several studies comprising 314 subjects there was one potential episode of almost loss of consciousness (A-LOC).[9] Several asymptomatic arrythmias were triggered by the G profiles including bigeminy, accelerated idioventricular rhythm and a short run of ventricular tachycardia, and the investigators advised that heightened caution is warranted in individuals with cardiopulmonary disease or taking cardiac medications.[27]

Our recent work has focused on the pulmonary response to extended periods of static $+G_x$ over the suborbital range, allowing detailed characterization of the underlying physiological response to relevant G loads up to $+6\ G_x$.[17,20] Increasing $+G_x$ caused substantial changes in respiratory function and progressive hypoxemia that was exacerbated by a simulated cabin pressure altitude of 8000 ft, and was accompanied by breathlessness and musculoskeletal chest pain at higher levels of $+G_x$.[17,20]

Suborbital flights will evoke these and other underlying responses to some extent, and could potentially interact with predisposing factors to precipitate detrimental sequelae. This prospect has obvious clinical implications for individual participants but also has broader implications for the industry. Regulatory bodies are currently considering the future framework for suborbital operations including the medical approach to flight crew and to prospective participants, and there is current military interest in developing a future suborbital medevac capability allowing extremely rapid repatriation of casualties. Together with the expansion of regular tourism and research flights, there is a growing requirement to establish how suborbital acceleration profiles affect the body. This physiology study aimed to generate boundary data relevant to both current and future suborbital platforms using representative acceleration profiles. We aimed to determine what physiological changes occur in response to simulated suborbital acceleration profiles, including the effect of simulated airline-style cabin pressurization, and additionally investigated how these responses are affected by age.

METHODS

Subjects

There were 24 healthy volunteers recruited in three age brackets: a 'younger' group aged 18–44 yr, an 'intermediate' group aged 45–64 yr, and an 'older' group aged 65–80 yr. Subject and group characteristics are shown in **Table I**. Subjects were required to be in good health, as evidenced by holding a UK Civil Aviation Authority (CAA) Class 2 Medical Certificate (as a minimum), which is the medical standard required for private pilots in the UK and includes an electrocardiogram (ECG). Subject recruitment therefore targeted pilots holding the requisite medical certificate who had an interest in commercial spaceflight or high-performance flying. Pregnancy and BMI > 35 $kg \cdot m^{-2}$ were additional exclusion criteria, and to satisfy relevant RAF standards subjects confirmed specifically that they did not have major cardiac or respiratory disease, significant back or neck pathology, retinal detachment or untreated hernias. The study was approved by the Ministry of Defense and King's College London Research Ethics Committees (2039/MODREC/21) and was conducted in accordance with the Declaration of Helsinki. All subjects provided written informed consent.

Equipment

The study was undertaken using a 7.5-m radius centrifuge at the Royal Air Force High G Training and Test Facility (RAF Cranwell, UK) with a representative F-35 Lightning cockpit installed in the gondola (seatback angle 22°). Acceleration was measured at head level in all axes. Subjects wore a Type P/Q military aircrew oxygen mask modified with a gas sampling port, from which oxygen and carbon dioxide were measured using an O_2Cap oxygen/CO_2 analyzer (Oxigraf Inc., Sunnyvale, CA, USA). Breathing gas was supplied via an Mk17F panel-mounted aircraft oxygen regulator with an inline flow transducer, and could be switched between air and 15% oxygen (balance 85% nitrogen) to simulate a cabin pressure altitude of 8000 ft (2438 m). Heart-level blood pressure was measured continuously using an NIBP Nano (AD Instruments, Oxford, UK) applied to a finger of the right hand, which was positioned at the side of the chest at heart level using a sling, and cardiac output was derived from the arterial pressure waveform using integrated pulse wave analysis.[16] Subjects held a marker button in the left hand and pressed this to indicate the onset of any visual G symptoms. Three-lead ECG, arterial oxygen saturation (S_pO_2),

Table I. Subject and Group Characteristics.

CHARACTERISTICS	YOUNGER GROUP	INTERMEDIATE GROUP	OLDER GROUP	ALL SUBJECTS COMBINED
N	8	8	8	24
Male:Female	5:3	5:3	6:2	16:8
Age (yr)	37 ± 5 (32–43)	55 ± 5 (49–63)	69 ± 5 (65–80)	54 ± 14 (32–80)
Weight (kg)	74 ± 12 (57–94)	80 ± 15 (56–98)	74 ± 18 (44–97)	76 ± 15 (44–98)
Height (m)	1.74 ± 0.09 (1.60–1.88)	1.75 ± 0.10 (1.57–1.85)	1.74 ± 0.10 (1.58–1.88)	1.74 ± 0.09 (1.57–1.88)
BMI	24.2 ± 2.4 (22.3–29.1)	26.2 ± 4.2 (20.6–32.6)	24.0 ± 4.3 (17.6–29.9)	24.8 ± 3.7 (17.6–32.7)
FEV_1 (l)	4.18 ± 0.68	3.50 ± 0.64	3.11 ± 0.67	3.59 ± 0.78
(FEV_1% Predicted)	(106 ± 9)	(102 ± 11)	(104 ± 15)	(104 ± 12)
FVC (l)	4.91 ± 0.82	4.37 ± 0.90	3.88 ± 0.79	4.39 ± 0.91
(FVC % Predicted)	(101 ± 9)	(100 ± 11)	(98 ± 10)	(100 ± 10)
Previous Experience of $+G_z$ on a Centrifuge	7 (88%)	1 (13%)	3 (38%)	11 (46%)
Previous Experience of $+G_z$ in an Aircraft	5 (63%)	5 (63%)	7 (88%)	17 (71%)

FEV_1: forced expiratory volume in the first second. FVC: forced vital capacity. Mean ± SD values and range are shown.

tidal volume and respiratory rate, breath-by-breath end-tidal partial pressures of oxygen ($P_{ET}O_2$) and carbon dioxide ($P_{ET}CO_2$), and beat-by-beat blood pressure were recorded continuously via PowerLab and LabChart 8 (AD Instruments, Oxford, UK).

Procedure

Centrifuge-naïve subjects received a familiarization session prior to the experimental day that included suborbital profiles of reduced magnitude and duration and one complete suborbital profile. All subjects were briefed on what to expect throughout the study, including the potential for partial visual loss (greyout) and complete visual loss (blackout). Subjects did not wear anti-G trousers or other G-protection and were instructed to remain relaxed in the absence of visual symptoms, and to perform leg muscle tensing and press the marker button immediately if greyout developed. Leg muscle tensing consisted of pushing down on the rudder pedals while tensing the leg muscles to clear vision. Subjects were not instructed in any other anti-G measures, and formal anti-G straining maneuvers were not part of the study.

Subjects undertook three different G profiles that were intended to be representative and relevant to current and future suborbital operations. The profiles were based on publicly available information[4,7] and accounted for seatback angles, and are shown in **Fig. 1**, **Fig. 2**, and **Fig. 3** together with the main results. All $+G_z$ and $+G_x$ values were relative to the subject axis. Two profiles represented an air-launched spaceplane, with a common launch phase in an upright seated position (seatback angle of 20° from vertical, 'head level' peak $+G_z$ 3.7, peak $+G_x$ 3.6) and re-entry in either a reclined (seatback angle 70°, peak $+G_z$ 1.2, peak $+G_x$ 5.9) or upright seated position (seatback angle 20°, peak $+G_z$ 4.0, peak $+G_x$ 4.5). A third profile represented a vertical rocket-launched capsule flight with both launch and re-entry in a recumbent position (seatback angle 70°, peak $+G_z$ 2.7, peak $+G_x$ 4.2). Between the high-G launch and re-entry phases $+G_x$ was off-loaded for approximately 30 s.

Profiles were undertaken twice, once breathing air and once breathing 15% oxygen, and subjects were blinded to the gas mixture. The order of the G profiles and gas mixtures was counterbalanced. There was a 5-min wash-in period when the gas mixture was changed, and exposures were separated by a minimum of 2 min at centrifuge baseline G level (+1.2 G_z). Normalization of physiology was confirmed before proceeding with each profile. Breathlessness intensity was recorded after each individual profile using the modified Borg (mBorg) scale,[10] and subjective data were captured using a symptom questionnaire.

Statistical Analysis

A repeated measure mixed model approach with Greenhouse-Geisser correction was used to analyze the effect of age and the effect of breathing 15% oxygen on physiological responses (GraphPad Prism 9.3.1). A Mann-Whitney U Test was used to compare the ages of subjects who did and did not experience visual symptoms. Statistical significance was assumed at $P < 0.05$. Data are reported as mean ± SEM unless otherwise stated.

RESULTS

There were 24 subjects (16 men, 8 women) with 8 in each age group. The overall age range was 32–80 yr. Subject and group characteristics are shown in Table I. The groups were well matched for body habitus and spirometry was normal across the groups. Most subjects had some prior experience of $+G_z$ (Table I). Several medical conditions were declared, particularly by the older subjects, and these are shown in **Table II**. All were well controlled in accordance with the CAA Class 2 Medical Certificate standard. Acceleration profiles (Fig. 1–3) were well tolerated overall, and all subjects completed all G exposures with the exception of one profile that was terminated shortly after peak G due to G-LOC.

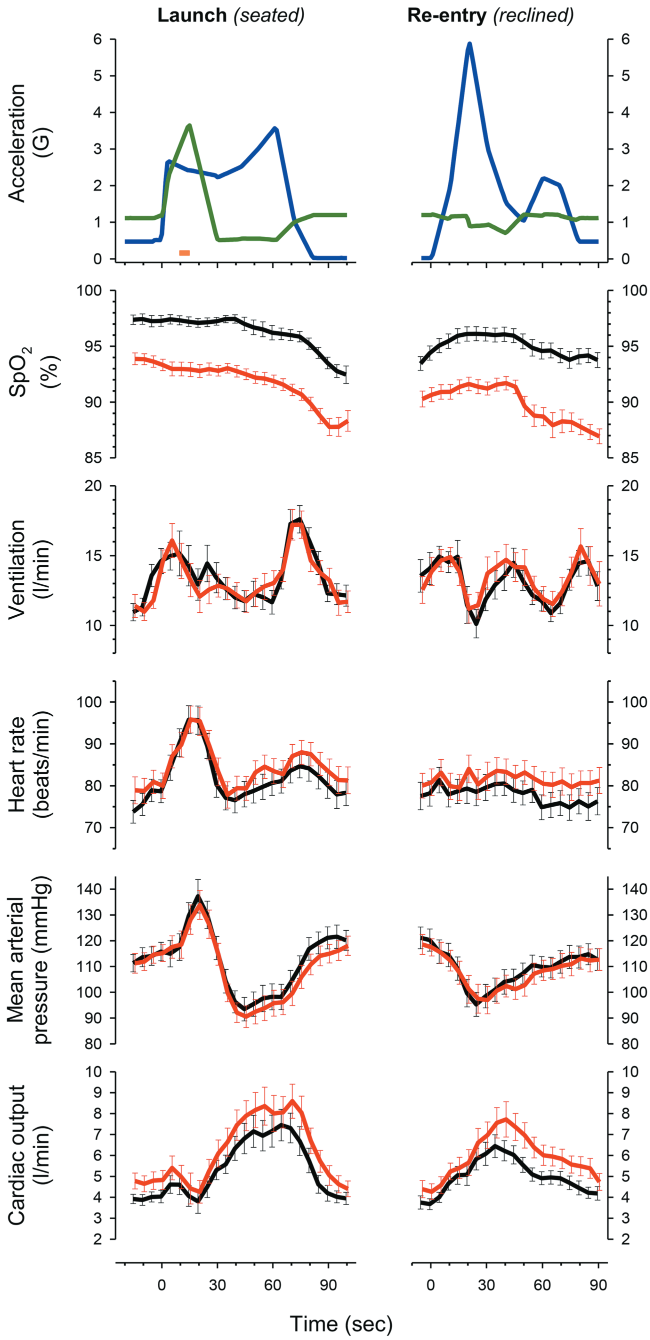

Fig. 1. Physiological responses to a simulated spaceplane profile with re-entry in a reclined position. The data shown are applied acceleration, arterial oxygen saturation (S_pO_2), ventilation, heart rate, mean arterial blood pressure measured at heart level, and cardiac output. The range over which the onset of visual G symptoms occurred is indicated with an orange bar on the acceleration profiles. Left panels show launch phase data and right panels show re-entry phase data. Data were obtained while breathing air and breathing 15% oxygen to simulate a cabin pressure altitude of 8000 ft. Data are mean ± SEM. Blue lines: $+G_x$; green lines: $+G_z$; black lines: breathing air; red lines: breathing 15% O_2.

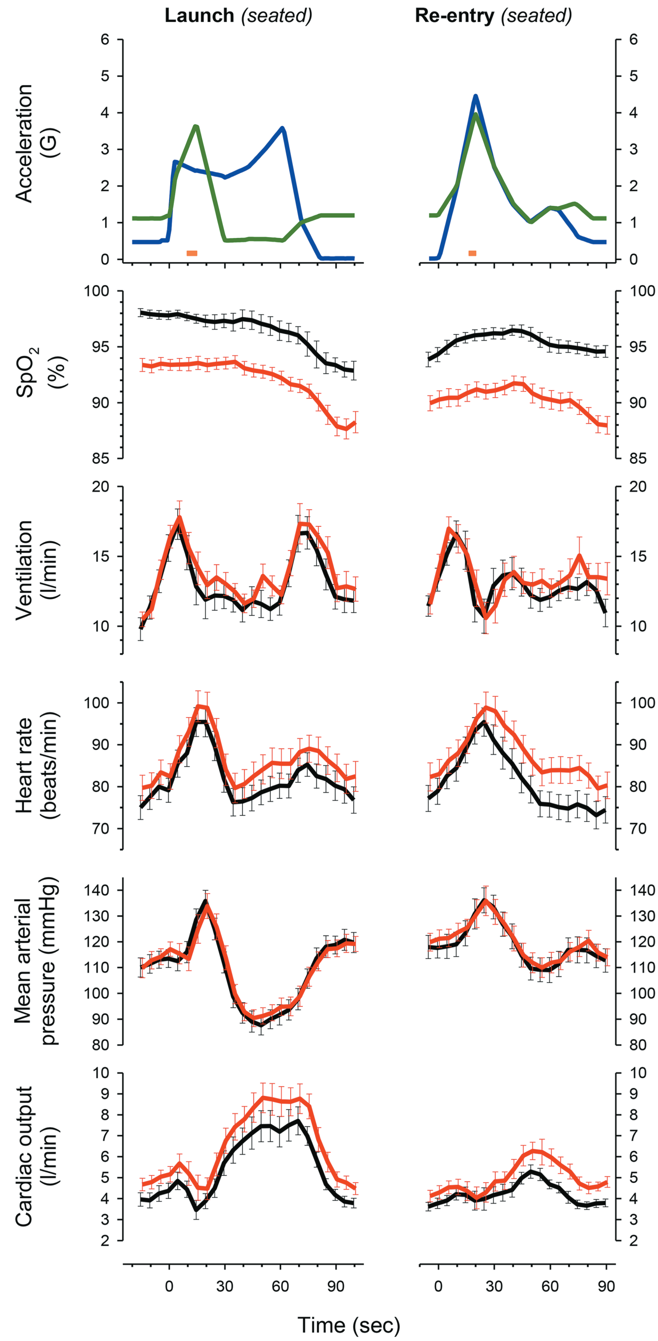

Fig. 2. Physiological responses to a simulated spaceplane profile with re-entry in an upright seated position. The data shown are applied acceleration, arterial oxygen saturation (S_pO_2), ventilation, heart rate, mean arterial blood pressure measured at heart level, and cardiac output. The range over which the onset of visual G symptoms occurred is indicated with an orange bar on the acceleration profiles. Left panels show launch phase data and right panels show re-entry phase data. Data were obtained while breathing air and breathing 15% oxygen to simulate a cabin pressure altitude of 8000 ft. Data are mean ± SEM. Blue lines: $+G_x$; green lines: $+G_z$; black lines: breathing air; red lines: breathing 15% O_2.

Symptom questionnaire data and mBorg breathlessness scores are shown in **Table III**. Approximately two-thirds of subjects reported transient chest heaviness that was 'unpleasant' and difficulty breathing. This was typically under peak $+G_x$, which also generated a sensation of throat 'constriction' obstructing airflow in two older subjects. Breathlessness was greatest during reclined spaceplane re-entry, when the highest magnitude of $+G_x$ was experienced, with a median mBorg score of 4 ('somewhat severe breathlessness') and a maximum of 5 ('severe breathlessness'). Nausea and occasional vomiting

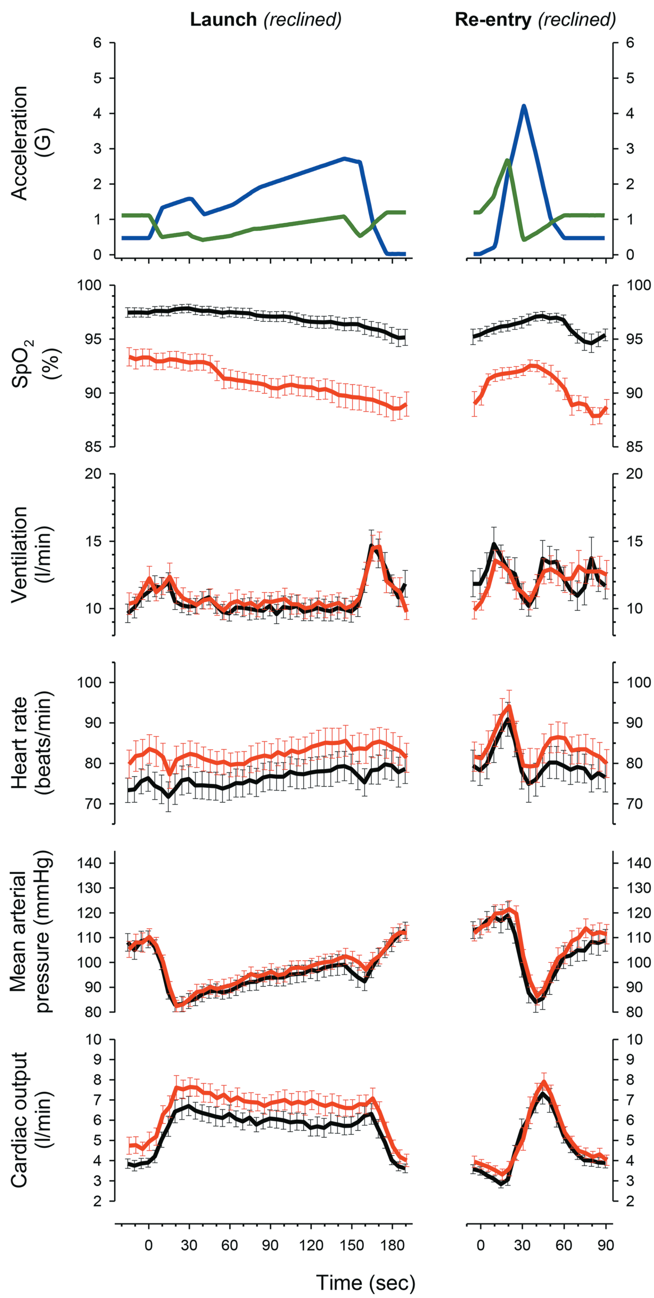

Fig. 3. Physiological responses to a vertical rocket-launched capsule profile with launch and re-entry in a recumbent position. The data shown are applied acceleration, arterial oxygen saturation (S_pO_2), ventilation, heart rate, mean arterial blood pressure measured at heart level, and cardiac output. Left panels show launch phase data and right panels show re-entry phase data. Data were obtained while breathing air and breathing 15% oxygen to simulate a cabin pressure altitude of 8000 ft. Data are mean ± SEM. Blue lines: $+G_x$; green lines: $+G_z$; black lines: breathing air; red lines: breathing 15% O_2.

(Table III) were attributed to rotational acceleration on a centrifuge and are not necessarily translatable to suborbital flight.

A large proportion of subjects experienced visual symptoms at least once, with 88% reporting greyout and 29% reporting blackout. Apart from one greyout during vertical rocket launch, all visual symptoms occurred during upright seated spaceplane phases which involved greater $+G_z$ exposures. During spaceplane launch the incidence of visual symptoms was 67% (N = 16) breathing air and 58% (N = 14) breathing reduced oxygen. During spaceplane re-entry in a seated position the incidence was 71% breathing air (N = 17) and 63% breathing reduced oxygen (N = 15). Visual symptoms occurred within a tight range of $+G_z$ and $+G_x$ which is indicated on Fig. 1 and Fig. 2. The G threshold for visual symptoms was effectively identical whether breathing air or 15% oxygen, as shown in **Fig. S1** in the supplementary online **Appendix A** (https://doi.org/10.3357/AMHP.6153sd.2022). Those who experienced visual symptoms [mean age 50 ± 14 yr (SD)] were significantly younger than those who did not (66 ± 6 yr; U = 81, P = 0.015). There was one episode of G-LOC which occurred during the profile simulating spaceplane re-entry in an upright seated position while breathing 15% oxygen. The subject was an 80-yr-old man who noted afterwards that he had been concentrating on indicating the onset of visual symptoms with the marker button and, distracted by this, had then forgotten to perform muscle tensing. Greyout coincided with the combined $+G_x$/$+G_z$ re-entry peak and G-LOC occurred 9 s later. S_pO_2 was 86% at the time, and momentary breath-holding at peak G was observed.

Fig. 1, Fig. 2, and Fig. 3 show continuous data for S_pO_2, ventilation, heart rate, heart-level mean arterial blood pressure and cardiac output for the three respective suborbital profiles. Data are shown breathing air and breathing 15% oxygen. Peak physiological changes from baseline are quantified in **Table IV** for each age group. A fall in S_pO_2 was observed with all G exposures (Fig. 1**,** Fig. 2, and Fig. 3) and was more pronounced when simulating spaceplane profiles. The minimum S_pO_2 for each phase of each profile is shown in **Fig. 4**. Minimum values tended to cluster around 89–94% breathing air and 83–88% breathing reduced oxygen, but there were numerous outlying values below these ranges, and six subjects (including at least one from each age group) desaturated to an S_pO_2 value < 80% at some point. Ventilation appeared to be restricted during periods of $+G_x$, with subsequent recovery and overshoot as $+G_x$ returned to baseline demonstrated most clearly in Fig. 3. Respiratory rate and tidal volume data corroborated this and are shown in **Fig. S2, Fig. S3,** and **Fig. S4** in the supplementary online appendix (https://doi.org/10.3357/AMHP.6153sd.2022) together with $P_{ET}O_2$ and $P_{ET}CO_2$, which illustrated real-time impairment of ventilation/perfusion matching as they rose ($P_{ET}O_2$) and fell ($P_{ET}CO_2$), respectively, with high G.

Marked hemodynamic changes were observed during all three profiles. These were most pronounced during the upright seated launch phase, which was common to both spaceplane profiles and produced the same responses in both (Fig. 1 and Fig. 2). The initial $+G_z$ peak was associated with a rapid elevation in heart rate and blood pressure, then as the $+G_z$ reduced and $+G_x$ continued to build, heart rate returned toward baseline while blood pressure swung low, falling approximately 50 mmHg from its peak, alongside a large rebound increase in cardiac output. Cardiovascular responses to spaceplane re-entry in a seated position (Fig. 2) were somewhat similar although smaller in magnitude. The combined $+G_x$/$+G_z$ peak was associated with increases in heart rate and blood pressure, which were

Table II. Medical History of Subjects.

	YOUNGER GROUP	INTERMEDIATE GROUP	OLDER GROUP
Declared Medical Conditions	Hyperlipidemia	Hypertension	Hypercholesterolaemia ($N = 4$) Hypertension ($N = 2$) Gastro-esophageal reflux disease Mild coronary artery disease Prostate cancer Hypothyroidism
Regular Medications	Atorvastatin, fenofibrate	Amlodipine, lisinopril	Antihypertensives: ramipril, amlodipine, losartan Statins: pravastatin, lansoprazole Other: thyroxine, enzalutamide, aspirin

followed by a smaller post-G increase in cardiac output. Spaceplane re-entry in a reclined position caused less cardiovascular disturbance, although cardiac output was elevated during the $+G_x$ peak (Fig. 1). During vertical rocket launch (Fig. 3), offloading $+G_z$ together with increasing $+G_x$ was associated with a fall in blood pressure and increase in cardiac output, while the adjacent $+G_z$ and $+G_x$ peaks of capsule re-entry were accompanied by a rise in heart rate, a decrease in blood pressure and a corresponding increase in cardiac output. Premature atrial and ventricular complexes are common during high-G acceleration[19] and were frequently observed on ECG monitoring during all profiles, although G-related ectopy was much more common in the older age groups. One individual, a 67-yr-old man with no cardiac history, developed asymptomatic trigeminy that occurred consistently at peak G, lasting up to 40 s before reverting to sinus rhythm. The ECG rhythm strip showing trigeminy under G is reproduced in **Fig. S5** in the supplementary online Appendix A (https://doi.org/10.3357/AMHP.6153sd.2022).

Figs. S6, S7, and S8 in the supplementary online Appendix A (https://doi.org/10.3357/AMHP.6153sd.2022) show the continuous physiological data presented in Fig. 1, Fig. 2, and Fig. 3, but separated into the three respective age groups. There was a significant effect of age on S_pO_2, which was lowest in the older group [$F(2, 21) = 4.192$, $P = 0.029$]. There was also a significant effect of age on cardiac output [$F(2, 21) = 12.08$, $P < 0.001$]; taking the study as a whole, the increase in cardiac output during G profiles in the older group was approximately half that of the younger group, with the intermediate age group in between. There was no effect of age on ventilation [$F(2, 21) = 0.2$, $P = 0.8$], heart rate [$F(2, 21) = 0.1677$, $P = 0.8$], or blood pressure [$F(2, 20) = 0.9509$, $P = 0.4$]. Compared with breathing air, breathing 15% oxygen caused a decrease in S_pO_2 [$F(1, 46) = 76.60$, $P < 0.001$] as shown in Fig. 1, Fig. 2, and Fig. 3, but did not affect ventilation [$F(1, 46) = 0.1535$, $P = 0.7$], heart rate [$F(1, 46) = 1.317$, $P = 0.3$], blood pressure [$F(1, 46) < 0.001$, $P = 0.99$], or cardiac output [$F(1, 46) = 2.549$, $P = 0.1$].

Table III. Questionnaire Data and mBorg Breathlessness Scores.

	YOUNGER GROUP	INTERMEDIATE GROUP	OLDER GROUP	ALL SUBJECTS COMBINED
Symptoms Associated with G Profiles				
Greyout	8 (100%)	8 (100%)	5 (63%)	21 (88%)
Blackout	3 (38%)	2 (25%)	2 (25%)	7 (29%)
G-LOC	0	0	1 (13%)	1 (4%)
Presyncope or light-headedness	1 (13%)	2 (25%)	0	3 (38%)
Difficulty breathing	7 (88%)	5 (63%)	3 (38%)	15 (63%)
Unpleasant chest 'heaviness'	8 (100%)	6 (75%)	2 (25%)	16 (67%)
Throat 'constriction' at peak $+G_x$	0	0	2 (25%)	2 (8%)
Disorientation or vertigo	3 (38%)	3 (38%)	2 (25%)	8 (33%)
Nausea	2 (25%)	3 (38%)	4 (50%)	9 (38%)
Vomiting	1 (13%)	0	1 (13%)	2 (8%)
Palpitations	0	0	2 (25%)	2 (8%)
Modified Borg Breathlessness Scores				
Baseline Air	0 (0–0)	0 (0–0)	0 (0–0.5)	0 (0–0.5)
Hypoxia	0 (0–0.5)	0 (0–0.5)	0 (0–0.5)	0 (0–0.5)
Spaceplane profile (reclined re-entry) Air	4.5 (3–5)	5 (3.5–5)	2 (1–3.5)	4 (2–5)
Hypoxia	4 (4–4.5)	4 (3.5–4.5)	2 (1.5–3.5)	4 (2–4.5)
Spaceplane profile (seated re-entry) Air	3 (2–4.5)	3 (2.5–4)	1.5 (0.5–2.5)	3 (1–3.5)
Hypoxia	4 (2–4)	4 (3.5–4)	2 (1–3)	3 (2–4)
Capsule flight profile Air	2.5 (2–4)	3 (2–4)	1 (0–2.5)	2 (1–4)
Hypoxia	2.5 (1–4)	3 (2.5–4)	1 (1–2.5)	3 (1–4)

Number of subjects and percentage are shown. For modified Borg scores, median (IQR) is shown. Scores recorded while breathing 15% oxygen are denoted as Hypoxia. The mBorg scale runs from 0–10, where 0 is no breathlessness at all and 10 is the maximum severity of breathlessness imaginable. An mBorg score of 5 indicates 'Severe breathlessness'.

Table IV. Peak Changes in Main Physiological Variables During Simulated Suborbital Flights.

		SIMULATED SPACEPLANE FLIGHT WITH RE-ENTRY IN RECLINED POSITION		SIMULATED SPACEPLANE FLIGHT WITH RE-ENTRY IN SEATED POSITION		SIMULATED CAPSULE FLIGHT	
		LAUNCH	RE-ENTRY	LAUNCH	RE-ENTRY	LAUNCH	RE-ENTRY
Minimum S_pO_2(%)							
Younger Group	Air	93 ± 4	94 ± 3	93 ± 3	94 ± 2	96 ± 2	95 ± 2
	Hypoxia	86 ± 3	85 ± 4	86 ± 4	83 ± 3	91 ± 3	87 ± 4
Intermediate Group	Air	91 ± 3	91 ± 3	88 ± 7	91 ± 3	94 ± 2	92 ± 3
	Hypoxia	86 ± 3	84 ± 1	87 ± 4	86 ± 4	86 ± 5	85 ± 5
Older Group	Air	90 ± 4	91 ± 3	90 ± 4	92 ± 3	93 ± 5	93 ± 5
	Hypoxia	83 ± 5	82 ± 6	82 ± 5	82 ± 5	84 ± 7	84 ± 4
Maximal increase in heart rate (bpm)							
Younger Group	Air	32 ± 10	9 ± 5	29 ± 7	24 ± 10	13 ± 11	20 ± 5
	Hypoxia	28 ± 7	11 ± 4	28 ± 10	25 ± 11	10 ± 5	20 ± 3
Intermediate Group	Air	21 ± 8	11 ± 7	22 ± 6	19 ± 11	11 ± 5	12 ± 3
	Hypoxia	19 ± 7	10 ± 6	22 ± 8	17 ± 7	8 ± 5	14 ± 7
Older Group	Air	16 ± 4	9 ± 5	13 ± 4	16 ± 7	11 ± 8	9 ± 4
	Hypoxia	14 ± 5	12 ± 7	17 ± 5	17 ± 7	12 ± 9	10 ± 2
Maximal decrease in mean arterial blood pressure (mmHg)							
Younger Group	Air	21 ± 8	33 ± 9	24 ± 11	12 ± 8	30 ± 10	31 ± 8
	Hypoxia	20 ± 11	20 ± 11	21 ± 12	16 ± 7	26 ± 8	21 ± 8
Intermediate Group	Air	28 ± 9	32 ± 14	26 ± 10	20 ± 4	21 ± 11	32 ± 7
	Hypoxia	32 ± 11	34 ± 12	29 ± 6	17 ± 6	20 ± 12	25 ± 6
Older Group	Air	21 ± 10	32 ± 21	31 ± 16	9 ± 6	23 ± 9	21 ± 7
	Hypoxia	21 ± 15	33 ± 16	26 ± 7	12 ± 9	31 ± 10	33 ± 10
Maximal increase in cardiac output ($L \cdot min^{-1}$)							
Younger Group	Air	6.0 ± 1.9	3.3 ± 1.1	6.3 ± 2.4	2.3 ± 2.5	4.0 ± 1.1	4.5 ± 1.2
	Hypoxia	6.5 ± 2.7	4.6 ± 3.6	6.5 ± 1.7	3.7 ± 2.8	4.7 ± 1.6	4.3 ± 1.6
Intermediate Group	Air	5.1 ± 2.6	3.7 ± 2.8	4.0 ± 2.3	1.7 ± 0.8	3.8 ± 1.1	4.0 ± 1.8
	Hypoxia	5.1 ± 2.9	4.5 ± 2.4	4.9 ± 1.7	1.8 ± 1.0	3.3 ± 1.3	3.7 ± 1.3
Older Group	Air	2.2 ± 1.8	1.9 ± 1.1	2.8 ± 0.6	1.5 ± 0.4	2.0 ± 0.6	2.3 ± 0.6
	Hypoxia	2.9 ± 2.4	3.0 ± 2.5	3.1 ± 0.6	1.2 ± 0.5	3.0 ± 0.4	3.7 ± 1.0

Maximal changes from baseline are shown for cardiovascular variables. Values are mean ± SD.

DISCUSSION

Commercial human suborbital spaceflight has opened a new frontier within aerospace medicine, and current understanding of the associated physiology remains limited.[3] This study provides a detailed description of physiological responses to simulated suborbital launch and re-entry, and has established that previously described respiratory effects[17,20] result in frequent symptoms and occasionally profound hypoxemia during these profiles. It has further demonstrated highly dynamic cardiovascular responses with recurring greyout and frequent blackout during simulated spaceplane profiles, and the episode of G-LOC we observed is, to our knowledge, the first reported in the suborbital context.

'G-tolerance' is defined as the ability to withstand a certain level of $+G_z$, most commonly in the context of visual loss, and is a crucial concept for military fast jet aircrew and for pilots of civilian high-performance aircraft.[19] Deliberate application of simultaneous $+G_x$ is unusual in these settings, but static addition of +2.5 G_x has been shown to reduce relaxed G-tolerance by approximately 0.25 G.[2] Suborbital spaceplane flights dynamically combine significant $+G_x$ and $+G_z$, and during representative simulated profiles we found that visual symptoms developed at lower levels of $+G_z$ than would typically be expected for pure $+G_z$ exposures,[19] consistent with impairment of G-tolerance by concurrent $+G_x$. The overall incidence of greyout was very high and more than a quarter of subjects experienced blackout. These results compare with a greyout rate of 69% in a previous centrifuge-based suborbital study, which also reported a protective effect of increasing age.[7] We likewise found that the small number of subjects who did not experience visual symptoms were significantly older than those who did. This is in contrast to the military $+G_z$ experience, where age is not a classic determinant of G tolerance, and we note that the single episode of G-LOC was in the oldest subject. The episode occurred during simulated spaceplane re-entry in an upright seated position while breathing 15% oxygen. A possible contribution from the simulated cabin conditions cannot be excluded, although S_pO_2 was not precipitously low at the time, and subconscious breath-holding under peak G may be a more likely factor. The subject attributed the G-LOC to his age, stating that he was confident his younger self would not have forgotten to perform leg muscle tensing, raising the question of what role nonphysiological aspects of ageing may play in responses to suborbital flight. A single case does not allow definitive etiological conclusions, but this episode does establish that G-LOC can occur during simulated suborbital G profiles. In doing so it also highlights the need for appropriately tailored

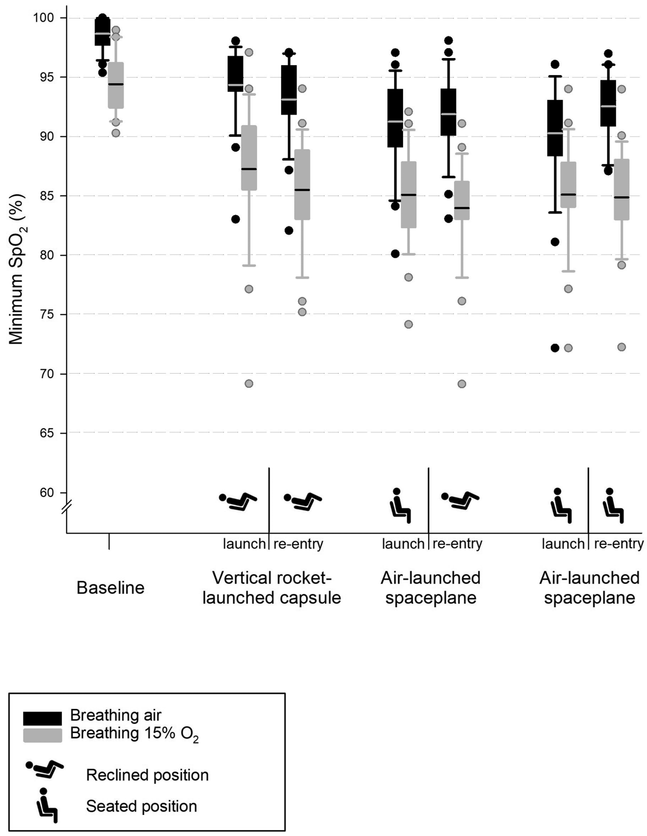

Fig. 4. Minimum arterial oxygen saturation during suborbital acceleration profiles. The minimum arterial oxygen saturation (S_pO_2) measured during each launch and re-entry phase of each suborbital profile is shown, including the mean (bar inside boxes), interquartile range (boxes), 10–90% range (whiskers) and individual outliers beyond this range (circles). Data were obtained while breathing air (black symbols) and breathing 15% oxygen to simulate a cabin pressure altitude of 8000 ft (gray symbols).

assessment and training to minimize the likelihood of G-LOC, which could be higher on actual flights due to a 'push-pull effect'-type phenomenon associated with transition from 0 G (rather than from 1 G) to high-G on re-entry.[18]

Visual G symptoms and G-LOC are closely linked to the underlying physiological responses that this study sought to characterize. The large hemodynamic fluctuations seen during upright seated spaceplane phases appeared to be driven primarily by $+G_z$, with reflex increases in heart rate and heart-level blood pressure attempting to maintain cerebral perfusion in the face of direct hydrostatic effects, dependent arteriolar distension and venous pooling, and reduced venous return.[19] As $+G_z$ eased, the presence of significant $+G_x$ appeared to amplify the recovery of venous return and cause a large rebound increase in cardiac output, possibly accentuated by the relative 'legs up' posture of a reclined seat. Although striking, this large surge in cardiac output reflects the confluence of fundamental cardiovascular processes playing out, rather than a specific protective response, and the fact that it was significantly lower in the older group is not necessarily of concern. This difference probably arises from age-related vascular stiffening and changes in peripheral vascular resistance,[15] with possible contributions from attenuation of cardiac contractility and autonomic function.[13] Age also affected S_pO_2, consistent with age-related deterioration in gas exchange,[28] but there were no other significant effects of age on physiological responses, and it is possible that chronological age per se may be less critical in suborbital fitness-to-fly considerations than previously thought.[20,22]

The current respiratory data extend our previous findings from static $+G_x$ exposures to confirm that impairment of gas exchange and consequent oxygen desaturation routinely develop to some degree during simulated suborbital profiles. We have previously established during $+G_x$ that this is caused by progressive G-dependent ventilation/perfusion mismatching alongside reversal in the relative distribution of regional lung ventilation, anterior gas trapping, increased work of breathing and neural respiratory drive, and limitation of ventilatory responses by impaired pulmonary mechanics (neuroventilatory uncoupling).[17,20] Overlaying mild hypoxia to simulate a cabin pressure altitude of 8000 ft unsurprisingly exacerbated the hypoxaemia associated with suborbital acceleration, but had no other effects. It is reassuring that, in the presence high G acceleration and its predominating responses, this additional reduction in arterial oxygenation is apparently insufficient to stimulate further effects on cardiopulmonary responses or visual symptom thresholds. On average, the fall in S_pO_2 during suborbital profiles was mild-moderate and well tolerated, and would not be concerning for the majority of participants. However, with outlying values in the 69–75% range, coupled with frequently reported respiratory symptoms, it is conceivable that susceptible individuals with pre-existing deficits in lung function could develop clinically meaningful effects. Transient sensations of chest heaviness, difficulty breathing and breathlessness during peak $+G_x$ were common and could be worse in those with pre-existing morbidity such as obesity or cardiopulmonary pathology, in whom greater hypoxemia may develop, increasing the risk of rare complications such as parenchymal lung damage, myocardial infarction, or serious arrhythmias.[11,27,30]

The arrhythmogenic potential of high/zero/high-G suborbital flight profiles is important because, although no doubt unlikely, an aberrant rhythm occurring in-flight could result in significant morbidity or even mortality. We observed repeated G-induced trigeminy in one individual, adding to the short list of rhythm disturbances that have been documented during suborbital G profiles.[27] None of these were associated with apparent hemodynamic compromise or adverse sequelae, and the propensity for benign ECG changes during centrifuge acceleration is well known.[19] Nevertheless, considering the rapidity and amplitude of the dynamic cardiovascular changes observed in this study, and the prevalence of diagnosed and undiagnosed cardiac pathology in the population, the latent risk of triggering a malignant rhythm is presumably not zero. Indeed, such swings in vital signs would be undesirable in clinical contexts such as anesthesia and critical care, where hemodynamic instability and coexisting hypoxia can be proarrhythmic and are considered best avoided.[22] The microgravity phase of actual suborbital flights could also interact with high-G and further challenge cardiopulmonary homeostasis. Transition to microgravity causes increased cardiac sphericity and changes the pressure/volume relationship, with decreased central venous pressure but increased left ventricular volume and cardiac output.[14] Whether this is problematic for older people with 'stiff' hearts is unknown, and in-flight studies are required to determine whether sudden transition from microgravity (rather than from 1 G) to hypergravity on re-entry intensifies the physiological effects sufficiently to cause concern.

Based on our findings, we believe routine preflight centrifuge familiarization, which is not currently mandated,[26] would be highly beneficial for prospective suborbital participants, providing helpful preparation for the physical and psychological challenges of high-G acceleration rather than experiencing these for the first time on an actual spaceflight. With the addition of appropriate monitoring, this centrifuge experience could also be tailored to allow relevant physiological assessment, and we suggest consideration of such a 'G challenge test' in medically susceptible participants.[19,20,22] While pre-existing disease, the likelihood of undiagnosed cardiac pathology, body mass, smoking history, and baseline fitness all form part of this balance, from the current results it seems advanced age may not necessarily be a critical independent factor in itself, although it is notably associated with greater hypoxemia and with a higher prevalence of comorbidities.

Responses differed between the three suborbital profiles investigated in this study. The vertical rocket-launched capsule profile, which involves the least exposure to $+G_z$, was less provocative physiologically although nevertheless stimulated the processes that were evident to a greater extent during spaceplane profiles. As well as fare-paying participants, our findings have some relevance for suborbital flight crew who experience launch and re-entry phases in an upright seated position during piloted spaceplane operations. Suborbital crew are carefully selected, highly experienced and professionally trained, but the passing of a Class 1 or Class 2 regulatory medical does not guarantee the absence of occult disease, and elite pilots can still be dangerously affected by high G.[18] It is therefore prudent to acknowledge the theoretical potential for intrusive effects in crew that, at the extreme, could cause in-flight incapacitation.

Detailed and continuous physiological measurements during high-G acceleration are challenging to conduct and rarely reported. The comprehensive, synchronous dataset is a strength of this study which, to our knowledge, is the first to present such data relating to suborbital high-G acceleration. The targeted recruitment process achieved a balance of male and female subjects across the desired age ranges, and also resulted in a high prevalence of prior $+G_z$ experience. Although it could be speculated that generic $+G_z$ experience protected the subjects in some way, such that even greater effects might be seen in inexperienced suborbital participants, in reality their experience is unlikely to have had any substantive effects on our findings. Standard technical limitations of acceleration research applied to this work, including the potential for changing hydrostatic gradients to confound blood pressure measurements, although this was minimized by carefully securing the hand at heart level. Noninvasive cardiac output techniques are subject to inherent limitations but are used widely in clinical practice and research, including on centrifuges.[16,21] The acceleration profiles and seating orientation used in the protocol closely approximated, but were not identical to, those used in current suborbital operations, in accordance with the aim of generating boundary data relevant to both current and future platforms. It remains possible that more subtle physiological effects may have been detected with a larger sample size.

The data reported here were obtained in healthy individuals across a wide age range, providing an important foundation that allows extrapolation to other individuals and populations. Ultimately, further research will be required to explore the equivalent responses in populations with diverse pathophysiology. Studies should investigate whether anticipatory 'pre-tensing' of the leg muscles can prevent visual symptoms (and thus also the risk of G-LOC) during suborbital G profiles, and evaluate the role of preflight centrifuge familiarization and judicious assessment using a G challenge test.

In conclusion, this study demonstrates that centrifuge-simulated suborbital G profiles generate highly dynamic cardiovascular responses and pronounced respiratory effects. Transient respiratory symptoms are common and G-induced hypoxemia can occasionally become substantial under air-breathing conditions, and more so under simulated airline-style cabin pressurization. Increasing age accentuated this hypoxemia but did not have detrimental cardiovascular effects, and overall our results are generally reassuring with respect to possible adverse effects of advanced chronological age per se. All effects were greater with spaceplane profiles, which caused frequent visual G symptoms and one episode of G-LOC, emphasizing that suborbital acceleration profiles are not physiologically inconsequential. The effects reported here are unlikely to trouble most suborbital participants but may impact on a minority who are medically susceptible. The continuing development of an evidence-based medical approach would benefit from further research investigating the potential role of preflight centrifuge-based familiarization and assessment, with the goal of enabling safe suborbital spaceflight for as many people as possible.

ACKNOWLEDGMENTS

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APPENDIX A. SUPPLEMENTARY RESULTS

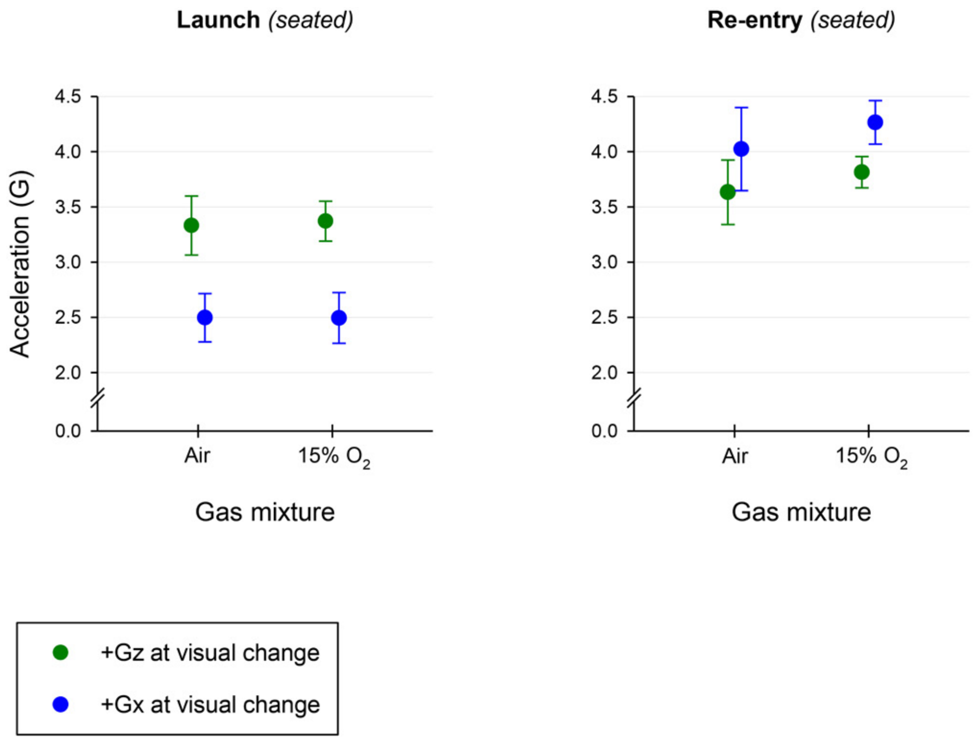

Fig. S1. Thresholds for onset of visual symptoms during simulated spaceplane profiles. The +Gz (green symbols) and +Gx (blue symbols) at which subjects indicated the onset of visual symptoms are shown. Data were obtained while breathing air and breathing 15% oxygen to simulate a cabin pressure altitude of 8,000 ft. Data are mean ± SD.

The following three figures (S2, S3, and S4) show additional respiratory data during suborbital acceleration profiles.

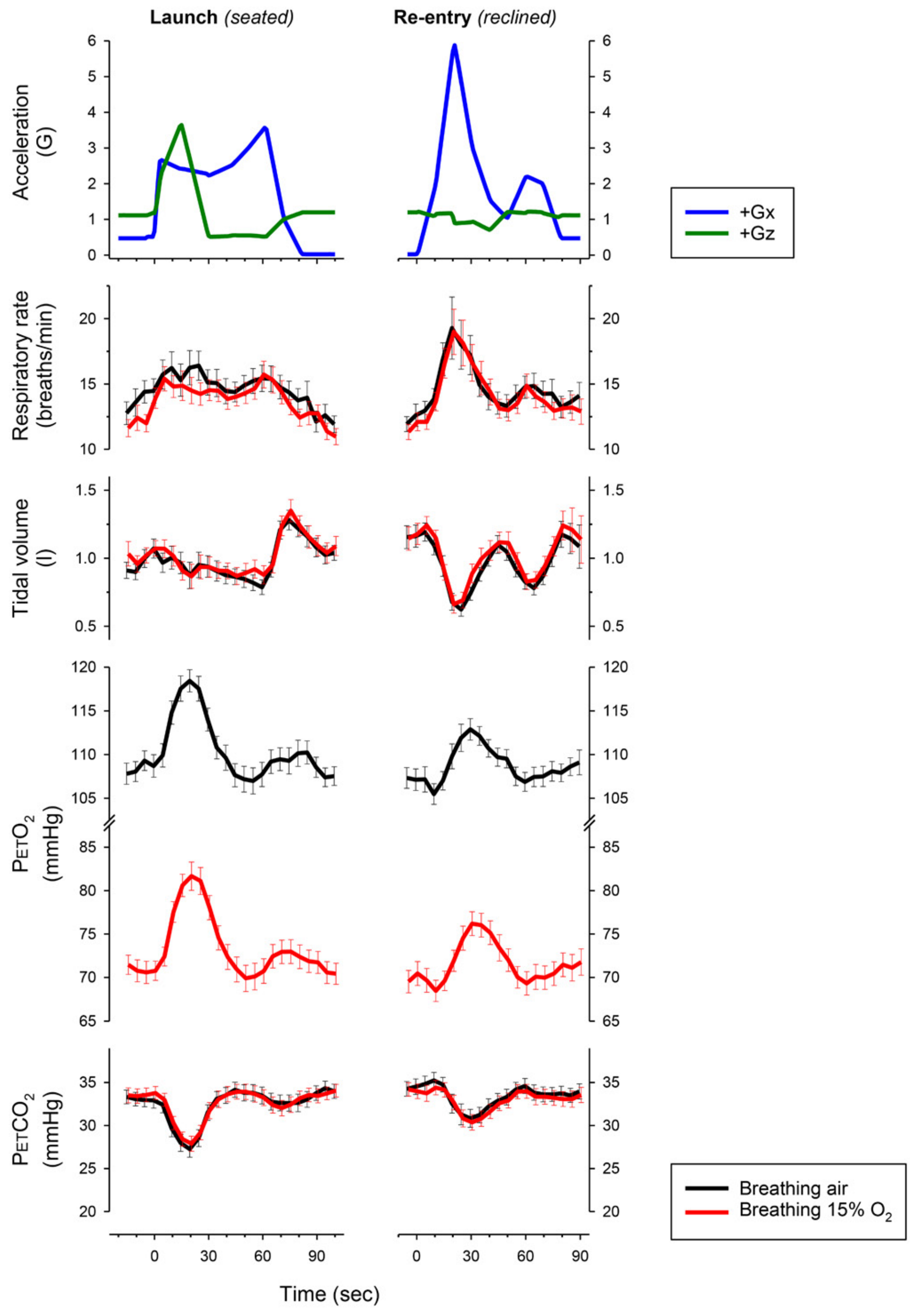

Fig. S2. Further respiratory data obtained during a simulated spaceplane profile with re-entry in a reclined position. The data shown are tidal volume, respiratory rate, and end-tidal partial pressures of oxygen ($P_{ET}O_2$) and carbon dioxide ($P_{ET}CO_2$). Left panels show launch phase data and right panels show re-entry phase data. Data were obtained while breathing air and breathing 15% oxygen to simulate a cabin pressure altitude of 8,000 ft, which naturally resulted in a lower $P_{ET}O_2$. Data are mean ± SEM.

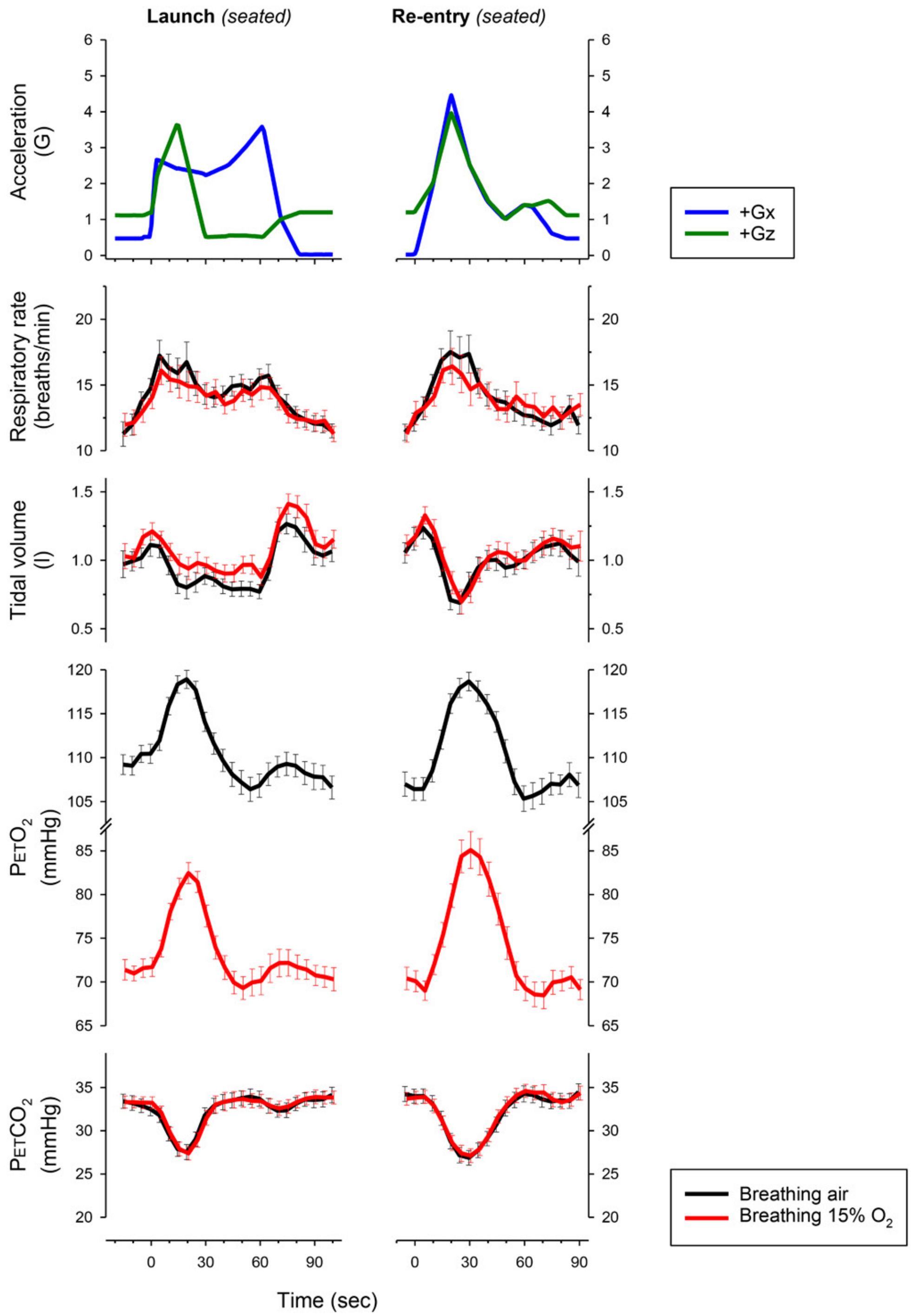

Fig. S3. Further respiratory data obtained during a simulated spaceplane profile with re re-entry in an upright seated position. The data shown are tidal volume, respiratory rate, and end-tidal partial pressures of oxygen ($P_{ET}O_2$) and carbon dioxide ($P_{ET}CO_2$). Left panels show launch phase data and right panels show re-entry phase data. Data were obtained while breathing air and breathing 15% oxygen to simulate a cabin pressure altitude of 8,000 ft, which naturally resulted in a lower $P_{ET}O_2$. Data are mean ± SEM.

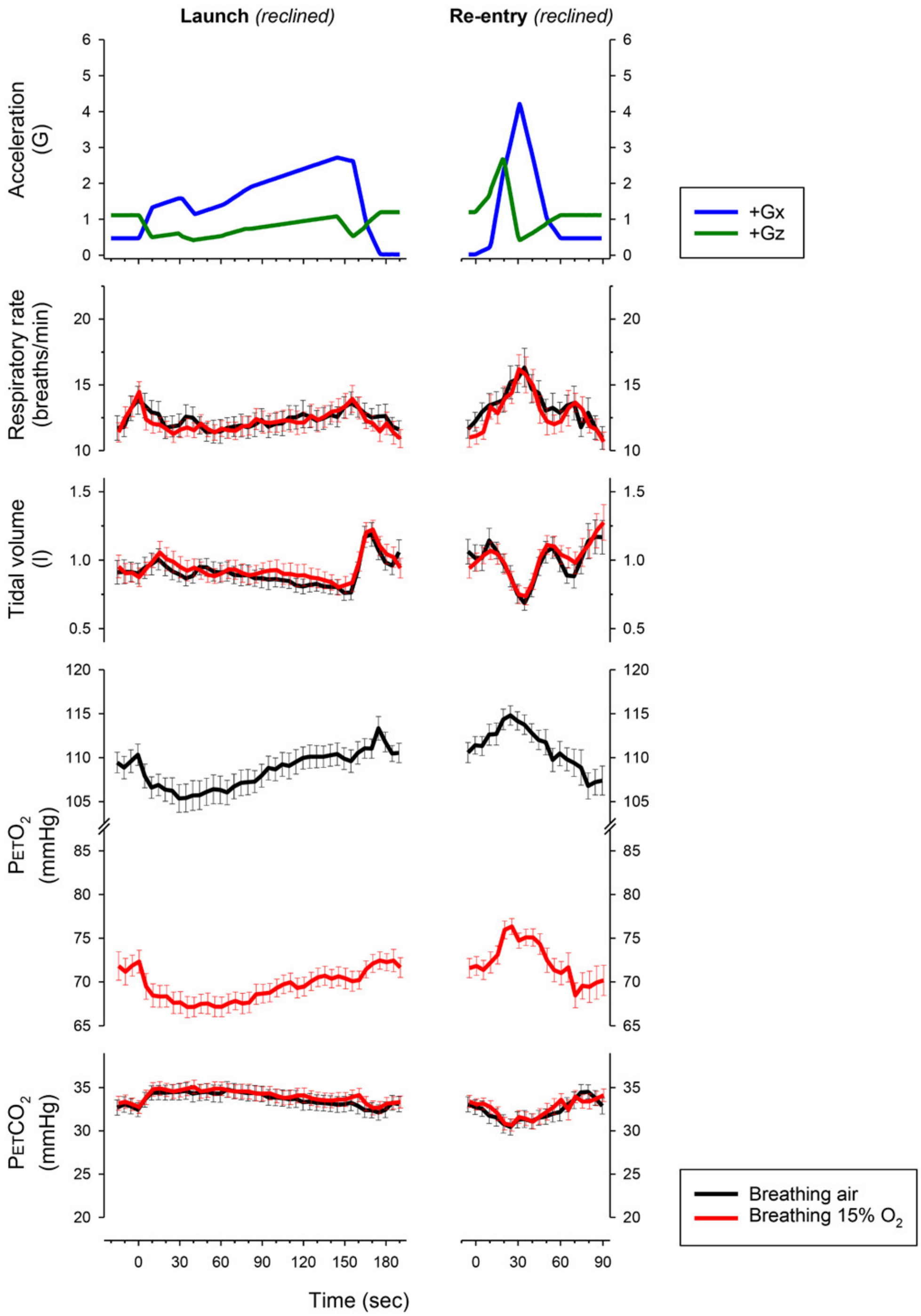

Fig. S4. Further respiratory data obtained during a vertical rocket-launched capsule profile with launch and re-entry in a recumbent position. The data shown are tidal volume, respiratory rate, and end-tidal partial pressures of oxygen ($P_{ET}O_2$) and carbon dioxide ($P_{ET}CO_2$). Left panels show launch phase data and right panels show re-entry phase data. Data were obtained while breathing air and breathing 15% oxygen to simulate a cabin pressure altitude of 8,000 ft, which naturally resulted in a lower $P_{ET}O_2$. Data are mean ± SEM.

Fig. S5. ECG rhythm strip of trigeminy induced by high G. The ECG shows trigeminy that was consistently triggered by peak G in a 67-yr-old man. The subject had no cardiac history and remained asymptomatic. Periods of trigeminy lasted up to 40 seconds before reverting to sinus rhythm.

The following figures (S6 A and B, S7 A and B, and S8 A and B) show physiological responses to suborbital acceleration profiles according to age group.

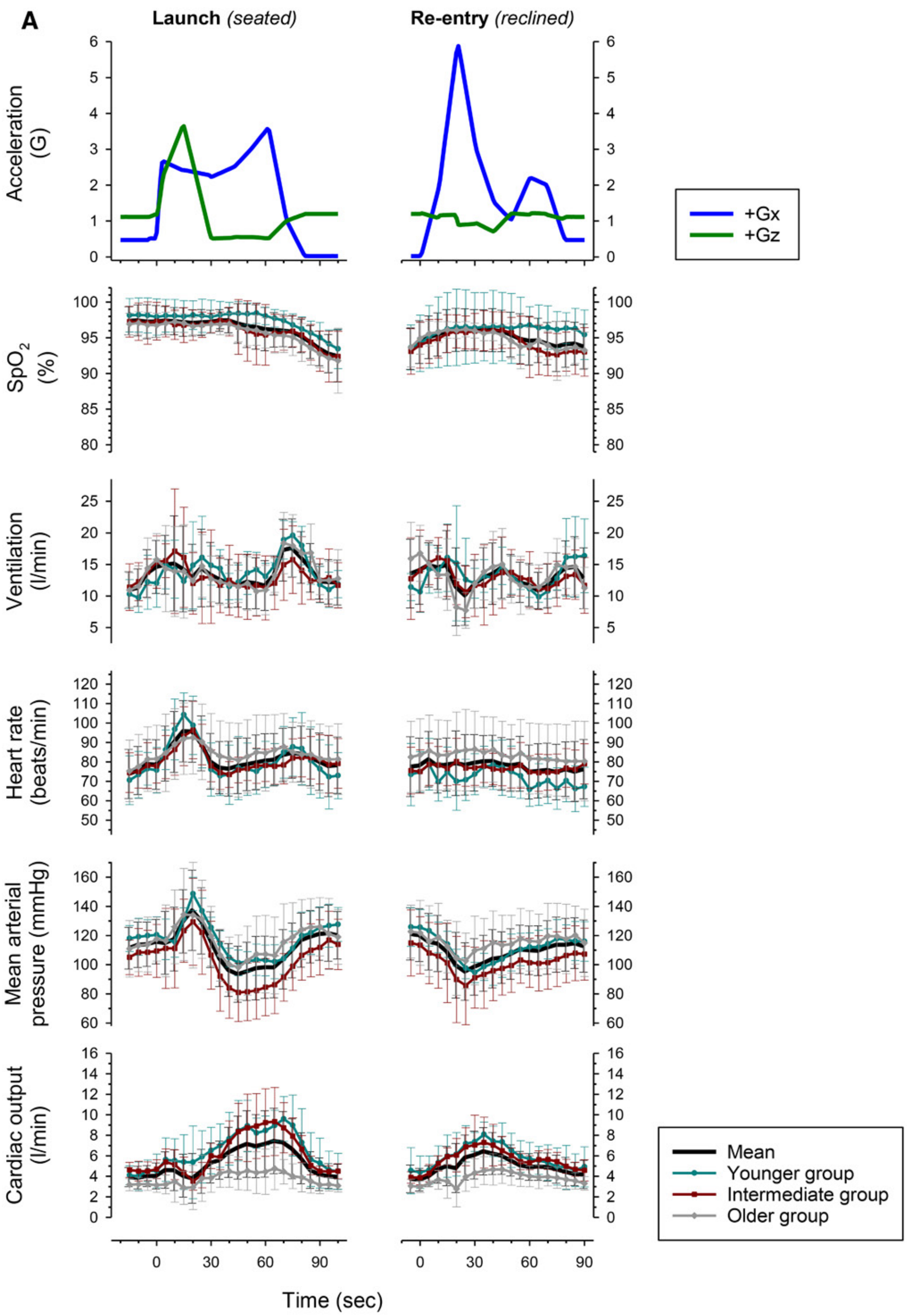

Fig. S6. Physiological responses according to age group during a simulated spaceplane profile with re-entry in a reclined position. Fig. S6A shows data breathing air and Fig. S6B shows data breathing 15% oxygen. The data shown are applied acceleration, arterial oxygen saturation (S_pO_2), ventilation, heart rate, mean arterial blood pressure measured at heart level, and cardiac output. Left panels show launch phase data and right panels show re-entry phase data. Data are mean ± SD.

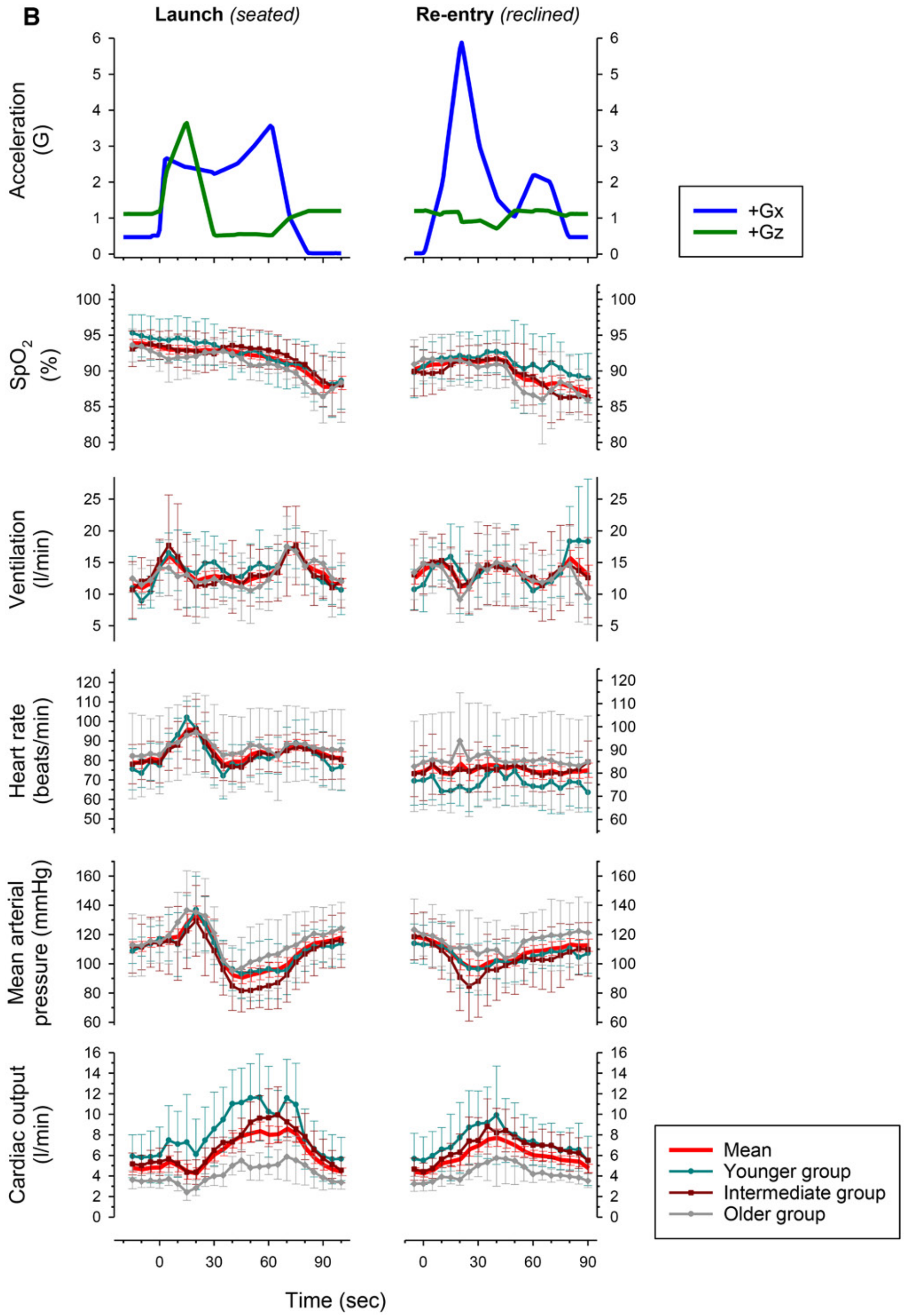

Fig. S6. (*Continued*)

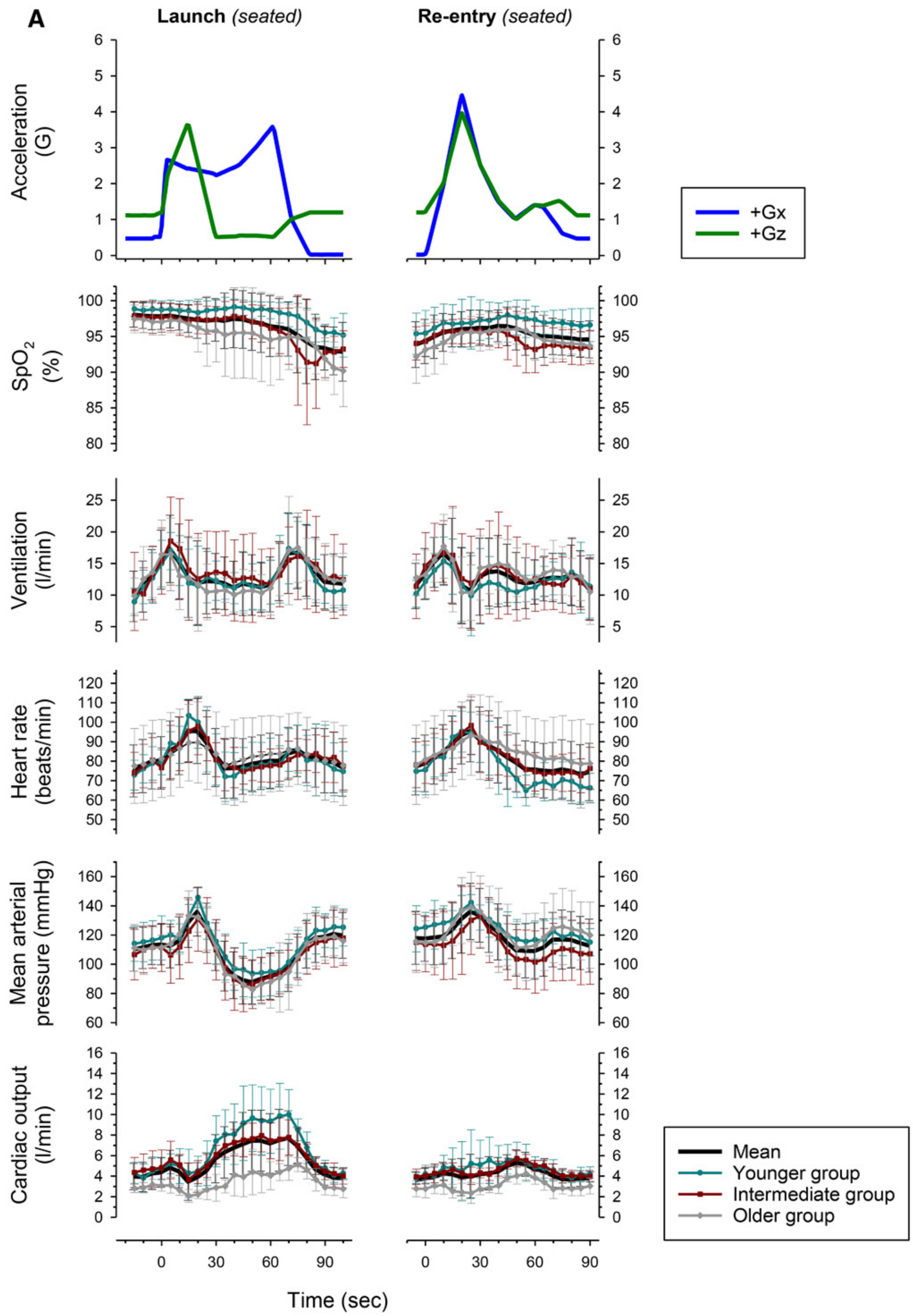

Fig. S7. Physiological responses according to age group during a simulated spaceplane profile with re re-entry in an upright seated position. Fig. S7A shows data breathing air and Fig.S7B shows data breathing 15% oxygen. The data shown are applied acceleration, arterial oxygen saturation (S_pO_2), ventilation, heart rate, mean arterial blood pressure measured at heart level, and cardiac output. Left panels show launch phase data and right panels show re-entry phase data. Data are mean ± SD.

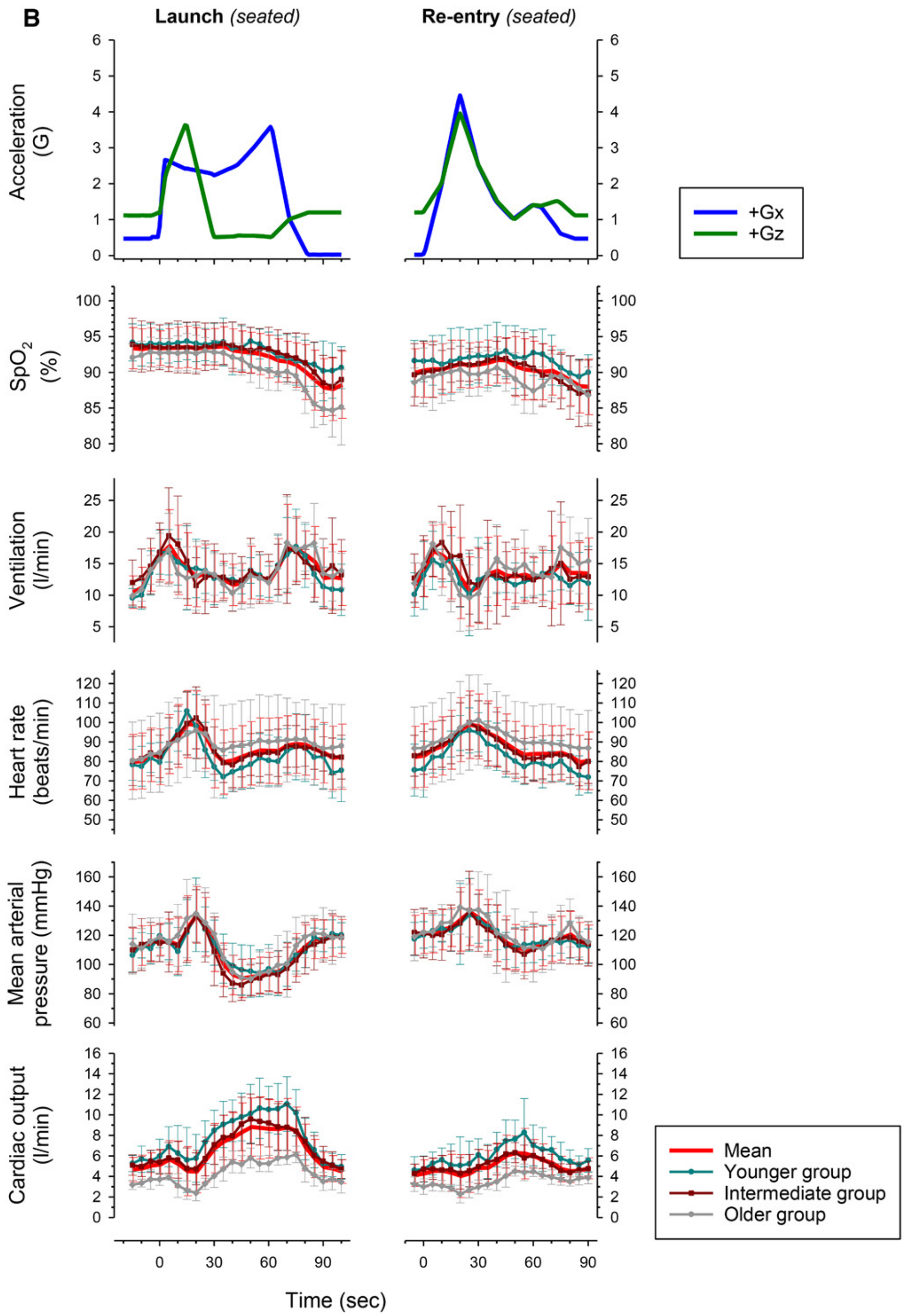

Fig. S7. (*Continued*)

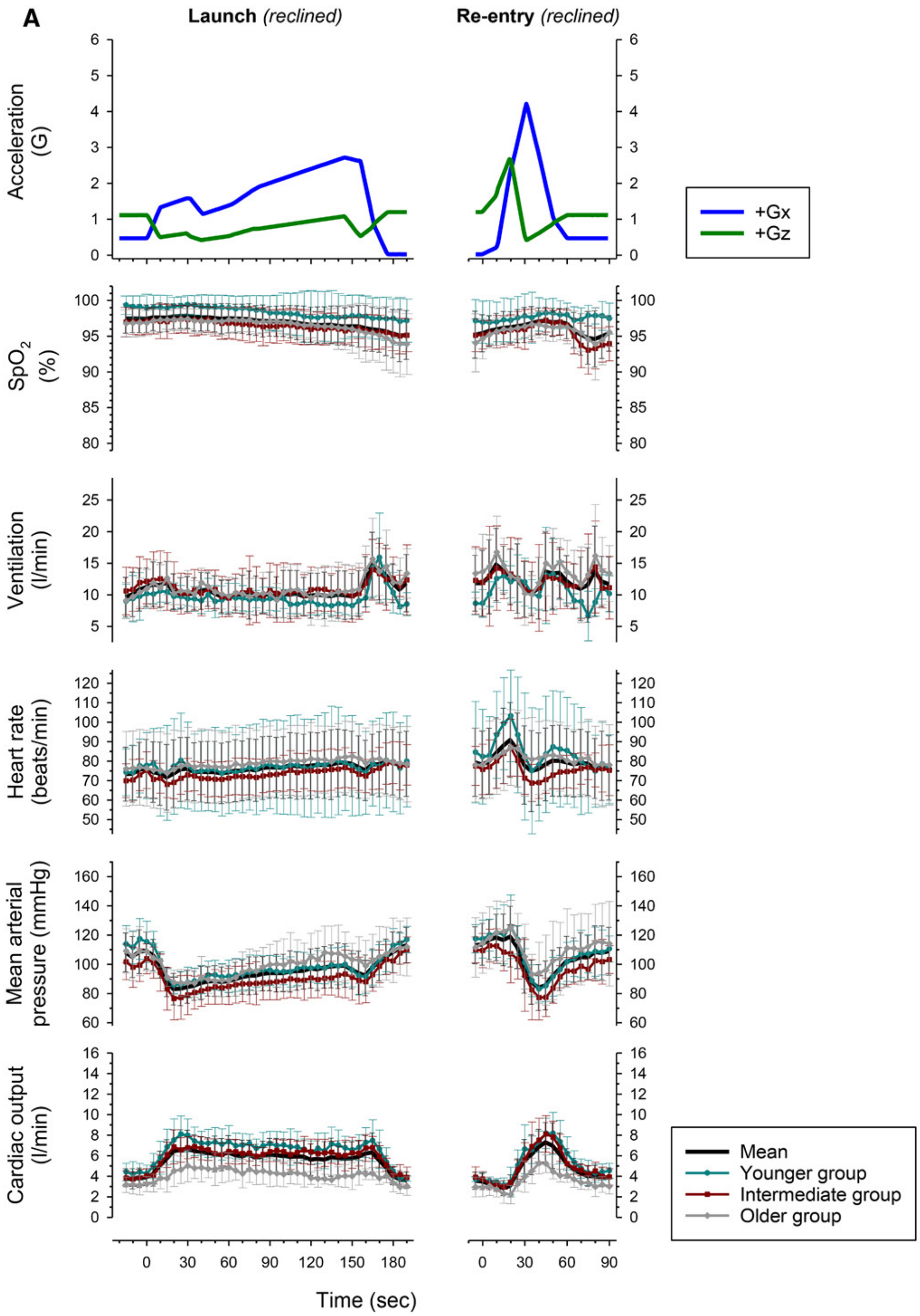

Fig. S8. Physiological responses according to age group during a vertical rocket-launched capsule profile with launch and re-entry in a recumbent position. Fig. S8A shows data breathing air and Fig. S8B shows data breathing 15% oxygen. The data shown are applied acceleration, arterial oxygen saturation (S_pO_2), ventilation, heart rate, mean arterial blood pressure measured at heart level, and cardiac output. Left panels show launch phase data and right panels show re-entry phase data. Data are mean ± SD.

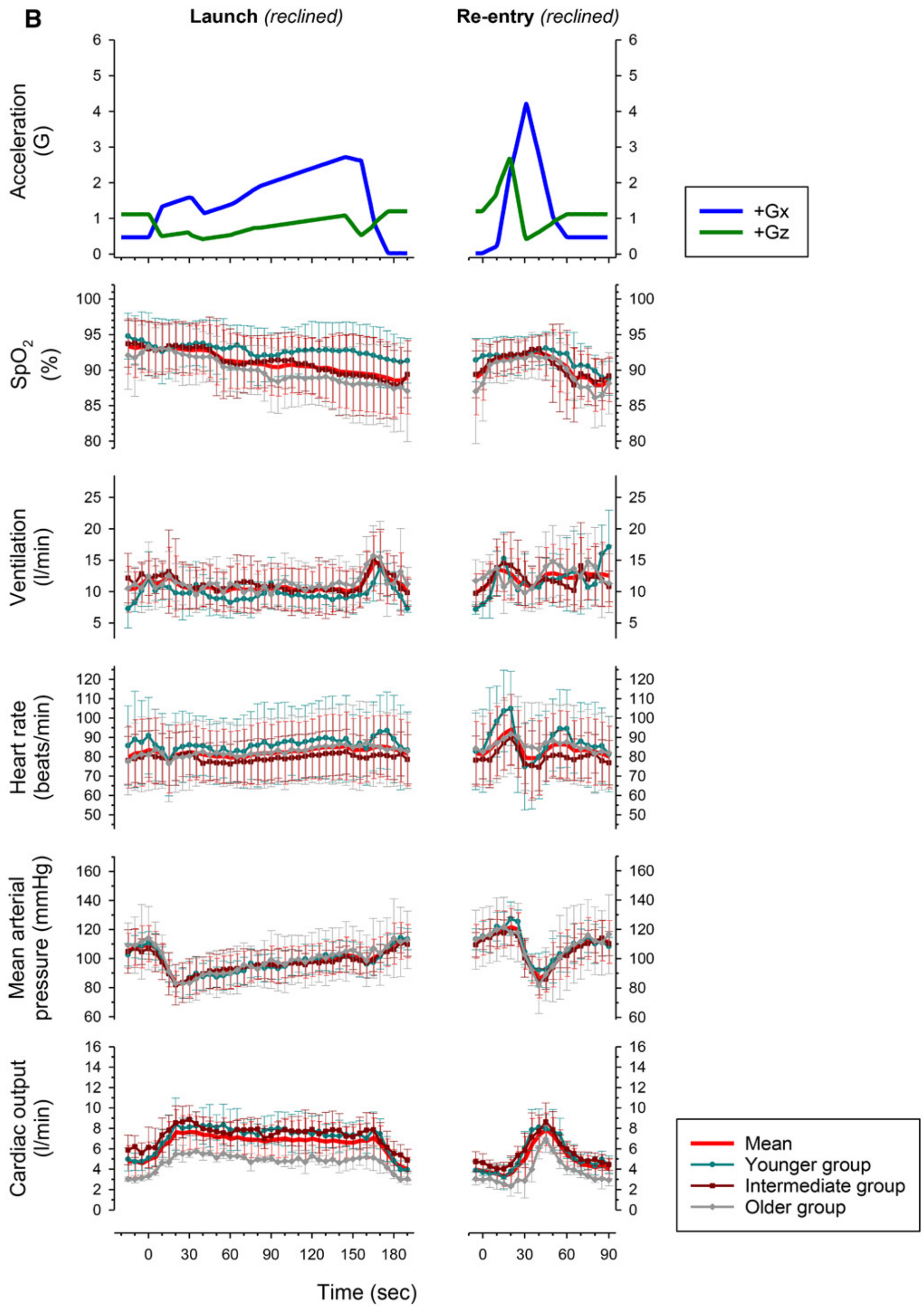

Fig. S8. (*Continued*)