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REVIEW ARTICLE

Oh G: The x, y and z of human physiological responses to acceleration

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Abstract

The desire to go higher, faster and further has taken us to environments where the accelerations placed on our bodies far exceed or are much lower than that attributable to Earth's gravity. While on the ground, racing drivers of the fastest cars are exposed to high degrees of lateral acceleration (Gy) during cornering. In the air, while within the confines of the lower reaches of Earth's atmosphere, fast jet pilots are routinely exposed to high levels of acceleration in the head–foot direction (Gz). During launch and re-entry of suborbital and orbital spacecraft, astronauts and spaceflight participants are exposed to high levels of chest–back acceleration (Gx), whereas once in space the effects of gravity are all but removed (termed microgravity, μG). Each of these environments has profound effects on the homeostatic mechanisms within the body and can have a serious impact, not only for those with underlying pathology but also for healthy individuals. This review provides an overview of the main challenges associated with these environments and our current understanding of the physiological and pathophysiological adaptations to them. Where relevant, protection strategies are discussed, with the implications of our future exposure to these environments also being considered.

KEYWORDS
acceleration, cardiovascular, flight, microgravity, motor racing, muscle, respiratory, space

1 | INTRODUCTION

With our evolutionary heritage developing in the presence of Earth's gravity (9.81 m/s^2), the human body is well adapted to the everyday rigours associated with gravity that life on Earth places upon it. Human nature has led to a drive to explore, first evidenced by the migration of *Homo erectus* out of Africa and, more recently, by the desire of modern-day humans to go further, higher and faster, pushing the boundaries of human endurance. Only in the last 100 years, with developments in internal combustion engines, jet engines and rockets, have we been able to place ourselves in gravity environments far exceeding the tolerance of the human body. On Earth, racing drivers of the fastest cars are exposed to high levels of lateral acceleration (Gy) during cornering. In the air, while within the confines of the lower reaches of earth's atmosphere, fast jet aircrew are routinely exposed to high levels of acceleration in the head–foot direction (Gz). During launch and re-entry of suborbital and orbital spacecraft, astronauts and spaceflight participants are exposed to high levels of chest–back acceleration (Gx), whereas once in space the effects of gravity are all but removed (microgravity, μG). These environments have profound effects on the homeostatic mechanisms within the body, which can be serious for healthy individuals, let alone those with underlying pathology.

Furthermore, an understanding of the physiological responses to altered gravity environments provides an opportunity for translational research when in a normal gravity environment. For example, the cardiovascular and baroreceptor responses to Gz can be used to help understand orthostatic intolerance, with anti-G trousers theoretically being a potential method to treat clinical orthostatic intolerance (Elizondo et al., 1996) and, occasionally, other clinical conditions (Pelligra et al., 1970). An understanding of the responses to Gz (and other acceleration vectors) is also important for the design of future aircraft, spacecraft and even rollercoasters. There is much we still have to learn about the function of the lung and, in particular, the influence of gravity on ventilation and perfusion (Galvin et al., 2007); exposure to microgravity and Gx could play a vital role in this. The physiological adaptations that occur in microgravity resemble those of inactivity and an accelerated ageing process and, as such, can provide a wealth of information that can help in understanding terrestrial issues, such as age-related deconditioning, frailty and poor bone health.

The aim of this review is to highlight the main (patho-)physiological challenges associated with each acceleration environment and, where relevant, the implications in both health and disease.

New Findings

- **What is the topic of this review?**
  This review focuses on the main physiological challenges associated with exposure to acceleration in the Gx, Gy and Gz directions and to microgravity.
- **What advances does it highlight?**
  Our current understanding of the physiology of these environments and latest strategies to protect against them are discussed in light of the limited knowledge we have in some of these areas.

2 | WHAT IS ACCELERATION?

Acceleration is defined as a rate of change in velocity and is a vector quantity, having both a magnitude and a direction. Therefore, acceleration can be experienced either through a change in velocity without a change in direction (linear acceleration), such as that during acceleration/breaking in a car or during a rocket launch, or through a change in direction without a change in speed (radial acceleration), such as that experienced during an aircraft turn/loop or in a race car going around a bend (Figure 1).

Newton's first law states that an any object in motion will remain in motion, in a straight line, until acted on by a force. The implication of this for a turning object (undergoing radial acceleration) is that the object will 'want' to continue in a straight line at every point during the turn; that this is not the case indicates a force acting on the object pulling it away from the straight line, which is termed the centripetal force. Newton's third law states that every action has an equal and opposite reaction; therefore, the centripetal force must be balanced by an equal and opposite force, which is termed the centrifugal force (Figure 1). It is this centrifugal force that is experienced by an individual and is responsible for the physiological effects of radial acceleration. Likewise, with linear acceleration it is the reactive force that an individual feels, a simple analogy of which would be the feeling of being pushed back into the seat when a car accelerates forwards. In acceleration physiology, it is these resultant inertial forces that exert their effects on the body, and acceleration physiologists use the term acceleration interchangeably with resultant inertial force.

When discussing acceleration, it is common to use the notation G, where 1 G is equivalent to acceleration attributable to Earth's gravity (i.e., 9.81 $\mathrm{m/s^2}$). The physiological significance of the effects of G are determined by the direction of application, which is described using a three-axis coordinate system, where the *z*-axis crosses the transverse plane (head–foot), the *x*-axis crosses the coronal plane (front–back) and the *y*-axis crosses the sagittal plane (left–right). In discussions of acceleration, a suffix is added to G to indicate the axis around which it acts (Gx, Gy and Gz; Figure 2). In addition, a prefix, either + or −, is also added to indicate the direction of the acceleration in that axis (Figure 2). This review will focus on long-duration G (> 1–2 s; N. D. C. Green, 2016) experienced as Gy, +Gz and +Gx.

A final thought on acceleration needs to be given to μG. Microgravity is considered to be synonymous with weightlessness or 0 G, although, in a stationary object, the effects of gravity are never truly removed until there is considerable distance between an object and other celestial bodies. The International Space Station (ISS) is currently the most easily recognizable environment where μG is experienced. The μG environment experienced here is attributable to the ISS being in low Earth orbit and effectively free falling around the Earth, causing the perception of weightlessness and the associated physiological adaptations.

3 | Gy: MOTOR RACING

Gy is the least common and least studied direction of acceleration. Short-duration exposures can occur during vehicle crashes or during impacts in some sporting events (e.g., rugby or American football). The focus of this review is on sustained exposures which, for Gy, tend to occur only when driving round corners, although generally the levels are minor and have no meaningful impact on the body. Only during motor racing do the levels become physiologically meaningful. Owing to the design of racing cars, they are able to corner at higher velocities than would be experienced in everyday road cars, meaning that the fastest cars produce 4–5.5 Gy (FIA Institute, 2011; Watkins, 2006). Interestingly, there are some disciplines, for example National Association for Stock Car Auto Racing (NASCAR), where 2–4 Gz can be experienced owing to the banked nature of race tracks (Reid & Lightfoot, 2019). Only the effects of Gy will be considered here.

3.1 | Implications of Gy

Although motor racing is extremely popular, there is a relative paucity of physiological and medical research relating to Gy. One of the primary

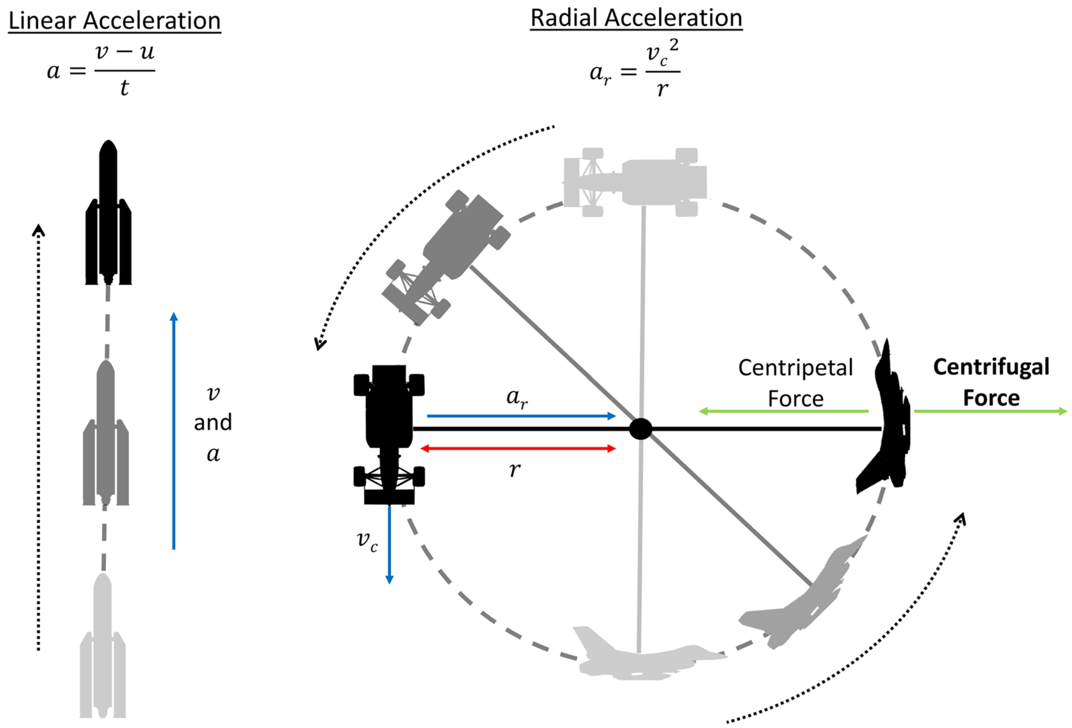
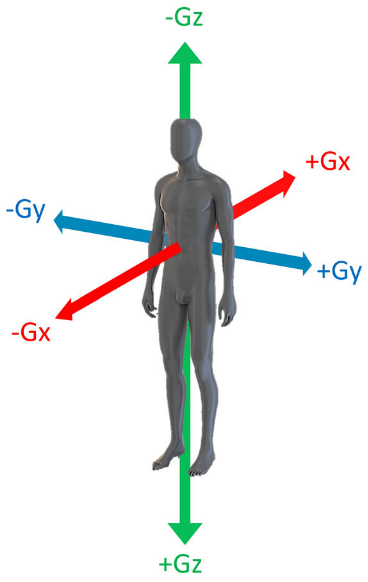


FIGURE 1 Depiction of linear and radial accelerations, with the equations used to calculate them. Linear accelerations occur with a change in velocity in the absence of a change in direction, whereas radial accelerations occur through a change in direction in the absence of a change in speed. Dotted arrows indicate the direction of travel, whereas continuous arrows indicate the direction of acceleration, force or velocity. Abbreviations: *a*, acceleration; a_r, radial acceleration; *r*, radius of turn; *t*, time for velocity change; *u*, initial velocity; *v*, final velocity; v_c, circumferential velocity

FIGURE 2 The three-axis coordinate system and terminology for describing the direction of acceleration and how the resultant force is perceived



Acceleration	Perceived Direction
+Gz	Head to Foot
-Gz	Foot to Head
+Gx	Front to Back
-Gz	Back to Front
+Gy	Right to Left
-Gy	Left to Right

concerns of Gy is the effect it has on the neck. Early reports indicated an incidence of cervical neck pain during and after Formula 1 races of 63–67%, attributable, in part, to the Gy forces experienced (A. Burton, 1983; A. Burton & Sandover, 1987). A similar incidence of 54% has been reported in a mixture of professional and amateur rally drivers, with co-drivers experiencing higher rates than drivers (Mansfield & Marshall, 2001). A recent study of 137 novice and experienced drivers from various disciplines found that 34% suffered cervical spine pain (Koutras et al., 2017). Although this lower incidence might be attributed to the range of abilities of the individuals studied, improvements in race car design, neck protection and awareness of neck injuries.

To reduce the risk of neck injury, it is important to understand the tolerance of the spine to lateral loading. Unfortunately, the work conducted in this regard focuses on the short-duration forces associated with impact (crash) and how cadaveric or spine segments respond to these (Whyte et al., 2020). The high incidence of neck pain and injury in racing drivers is perhaps unsurprising, given that a combined head and helmet mass of ~6.5 kg undergoing exposure to 4 Gy results in the application of a 26 kg load laterally to the head. This needs to be accommodated by muscles, ligaments, joints or other soft tissues in the cervical region, and if the associated mechanical stress exceeds what these structures can support, neck injury can occur (Sommerich et al., 2000). When loading to the neck occurs, particularly in a non-neutral position (Netto & Burnett, 2006), there is a greater reliance on the musculature to support the load. If these muscles become fatigued, their force generation capacity and ability to control head movement and position will become impaired, transferring greater loads to the spinal column and intervertebral discs, thereby increasing the likelihood of injury.

3.2 | Protecting against Gy

Strength training of the upper body and neck is important for racing drivers (Ebben, 2010; FIA Institute, 2011; Watkins, 2006). Despite neck and core training being identified as one of the most important physical demands faced by stock car drivers and head and neck injuries being one of the top three concerns in these drivers, not a single driver out of 40 studied performed specific neck-strengthening exercises (Ebben & Suchomel, 2012). The act of driving itself might help to strengthen the neck in race drivers, with neck strength of racing drivers being greater than that found in the general population and even in fast jet pilots (Backman et al., 2005). Furthermore, open-cockpit racing drivers have a greater neck strength than rally drivers, probably owing to the lower demand on lateral neck strength associated with rally driving, indicating that differences exist between racing disciplines (Backman et al., 2005). Further research is required to determine whether these differences are the result of the loads experienced through racing or because of specific training.

Other than neck strengthening, protection against the effects of Gy in racing drivers is achieved through engineering solutions. The use of lighter helmets can reduce neck pain in racing drivers (Mansfield & Marshall, 2001). Most racing cars now have some form of head protection system, such as foam padding on each side of the driver's head or integrated head support. This typically works in combination with the seatbelt/harness to control head acceleration and reduce neck strain (FIA Institute, 2011). As of 2003, Formula 1 introduced a head and neck support (HANS) device, which might be responsible, in part, for the lower rate of cervical spine injuries reported recently (Koutras et al., 2017). Although these protection systems are designed to protect against the forces associated with crash and impact, they might also reduce some of the burden associated with long-duration Gy exposure.

4 | +Gz: FAST JET FLYING

Exposure to +Gz can occur during motor racing, use of roller coasters and launch/re-entry of spacecraft, but the most common and greatest exposures occur in military fast jet pilots during turns and loops. Routinely, aircrew may be exposed to accelerations up to ~6 Gz, although the highest-performing aircraft can sustain ≤ 9 Gz, with onset rates of 10 G/s. Without mitigation, +Gz can lead to visual changes, almost loss of consciousness (A-LOC) and gravity-induced loss of consciousness (G-LOC), with the resulting loss of aircraft control having potentially fatal consequences. Fortunately, there are strategies and equipment that aircrew can use to help protect themselves against the negative effects of +Gz.

4.1 | The physiology of +Gz

Broadly speaking, the physiological effects of +Gz can be attributed to an increased head-to-heart hydrostatic pressure gradient and redistribution of blood to the lower limbs. In simple terms, arteries and veins can be considered as a column of fluid running from the head to the feet. For any column of liquid, the pressure exerted at a given point (the hydrostatic pressure, p) will be determined by the density of the liquid (ρ), the gravitational constant (g) and the height of the column (h) such that: $p = \rho gh$.

In an upright human, a pressure gradient exists down the body, with the lowest pressures at the head and the highest pressures at the feet. To ensure adequate head-level perfusion, the heart must generate sufficient pressure to overcome the hydrostatic effect of the weight of the blood above it. At 1 Gz (9.81 m/s), assuming a constant density of blood (1,060 kg/m^3), the hydrostatic pressure associated with a difference in height of 1 cm is 104 Pa (or 0.78 mmHg). Assuming 30 cm from heart to head, the head-level pressure will be ~23 mmHg lower than that at the heart. At 1 Gz, the heart generates sufficient pressure to overcome this difference. An increase in Gz will raise the pressure gradient such that at 4.5 Gz the pressure difference will be ~104 mmHg, roughly equivalent to mean arterial pressure; consequently, there will be minimal, if any, head-level blood pressure. This is exacerbated by Gz-induced descent of the diaphragm and heart, estimated to be ~5 cm when exposed to 5 Gz (N. D. C. Green, 2016; Rushmer, 1947).

The hydrostatic effect causes an instantaneous fall in head-level blood pressure, but experiments show that blood pressure continues to decline for ≤ 5 s (Lambert & Wood, 1946), as shown in Figure 3. This is attributed to the high intravascular pressures generated in the lower limbs increasing vascular transmural pressures. This is thought to have two main effects: (1) vasodilatation in arterioles reduces peripheral resistance and blood pressure; and (2) vascular distension redistributes blood to the venous compartment of the lower limbs, termed blood 'pooling', impairing venous return and, consequently, reducing blood pressure. It is estimated that at 5 Gz, 60 ml of blood, mainly from the intrathoracic vascular compartment, pools in each leg (Sjostrand, 1953). This is considerably less than when moving from lying to standing (~500 ml; Maw et al., 1995), suggesting that the

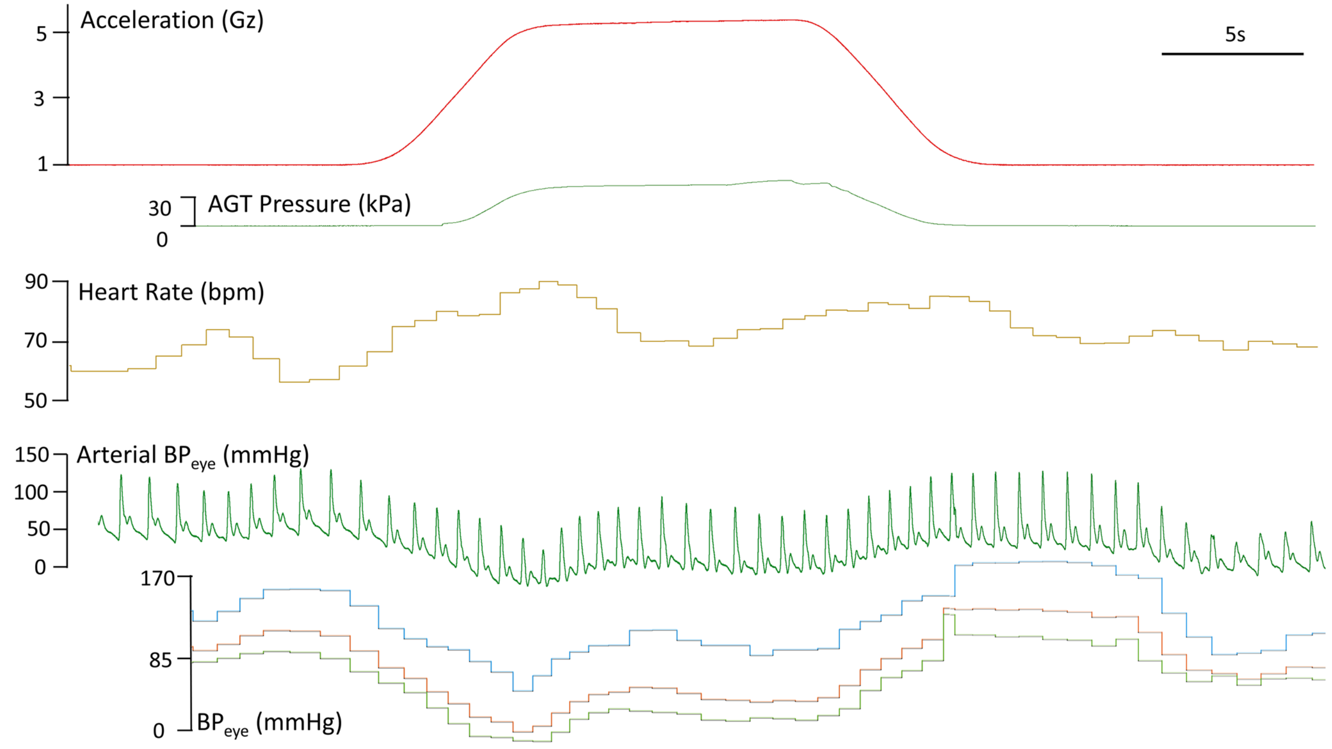


FIGURE 3 Representative physiological recording taken from a centrifuge exposure to the point where 60° peripheral light loss occurred (in this instance, 5.6 Gz with an onset rate of 1 G/s), while the participant was relaxed and wearing full-coverage anti-G trousers. The variables recorded are acceleration, anti-G trouser (AGT) inflation pressure, heart rate (in beats per minute, bpm), eye-level arterial blood pressure (BP_{eye}) waveform and, in the lower trace, systolic (blue), diastolic (green) and mean (red) arterial blood pressures at eye level

head-to-heart hydrostatic effect exerts a greater influence on the cardiovascular response to +Gz than blood pooling (N. D. C. Green, 2016).

4.2 | Visual changes and loss of consciousness

As +Gz increases and head-level blood pressure falls, a point will be reached when retinal circulation becomes compromised, resulting in visual changes described as 'greyout' or 'blackout'. Greyout refers to a progressive loss of peripheral vision which, with increasing +Gz levels, leads to loss of central vision, after which blackout occurs (N. D. C. Green, 2016); note that blackout refers to a complete loss of vision rather than loss of consciousness. The loss of peripheral vision before central vision is attributable to the end arteries of the retina losing blood supply at their periphery before central regions (Duane, 1954). Assuming a slow rate of onset, visual symptoms precede G-LOC owing to the cessation of blood flow that occurs when head-level blood pressure falls below the intraocular pressure of 10 - 20 mmHg (Eiken et al., 2017; Mertz, 2015). This has been demonstrated by increasing the +Gz level at which visual changes occur by applying suction to the eye (using goggles or a full helmet) to maintain blood flow (Glaister & Lenox, 1987; Lambert, 1945). Greyout and blackout will occur around ~3.8 and ~4.6 Gz, respectively, although there is considerable inter-individual variability, with the most susceptible individuals potentially experiencing visual symptoms at ~2.5 Gz (Kerr & Russell, 1944).

Exposure to +Gz greater than that eliciting blackout will result in G-LOC, on average at 5.2 Gz (Kerr & Russell, 1944). Approximately 15% of UK Royal Air Force pilots and weapons system operators have experienced G-LOC (Slungaard et al., 2017), which is in broad agreement with other Air Forces (Alvim, 1995; Cao et al., 2012). G-LOC results in ≥ 30 s (J. E. Whinnery & Forster, 2013) of incapacitation (unconsciousness followed by a state of disorientation/confusion), with full recovery in some instances taking > 1 min (Tripp et al., 2006). Almost loss of consciousness (A-LOC) can occur, which has been described as a disconnect between the desire and ability to act (Morrisette & McGowan, 2000), and manifests with amnesia, euphoria, confusion, difficulty in forming words and/or sensory abnormalities (Shender et al., 2003). The development of G-LOC and visual symptoms is dependent on the level of +Gz experienced and its onset rate; traditionally, this has been highlighted by the Stoll curve (Figure 4; Stoll, 1956), although alternative curves have been developed more recently (J. E. Whinnery & Forster, 2013). Assuming a slow onset rate (e.g., < 0.3 G/s), a progressive loss of vision followed by G-LOC will occur. A rapid onset (≤ 10 G/s in some aircraft) to a high level of Gz (e.g., > 6 Gz) causes instantaneous cessation of cerebral blood flow and, if maintained for > ~5 s, G-LOC occurs without any preceding visual changes. If, however, exposure is < 5 s neither G-LOC nor visual changes occur. This is attributable to a functional oxygen reserve in the cerebral tissues and eye, which can maintain vision and consciousness for ≥ 5 s after cessation of circulation (Rossen et al., 1943). Recently, the idea that G-LOC will occur within 5 s has been

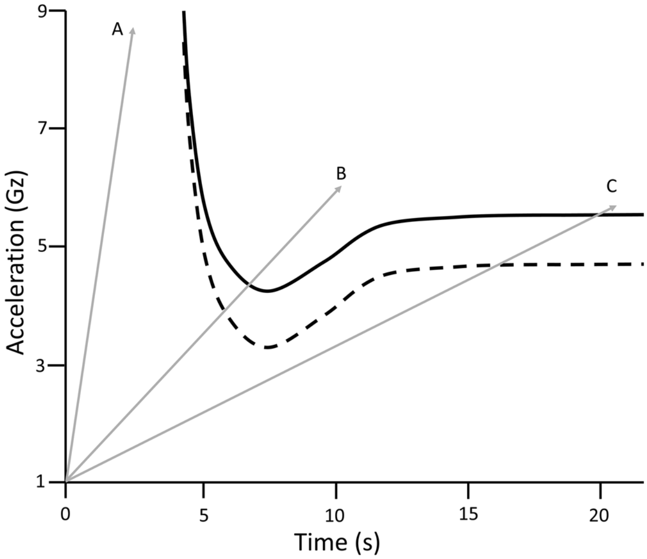


FIGURE 4 Re-creation of the Stoll curve, showing the interaction with +Gz level and time in relationship to when visual symptoms (dashed line) and gravity-induced loss of consciousness (G-LOC; black line) would occur. Line A represents an acceleration profile with a rapid acceleration to very high Gz, in which no visual symptoms or blackout occur, assuming rapid offset of Gz. If sustained at high Gz, immediate G-LOC would ensue without preceding visual symptoms. Line B represents a moderate acceleration onset rate, where visual symptoms would precede G-LOC. Line C represents a slow onset rate, where a baroreceptor response can develop, increasing the Gz level at which visual symptoms occur

challenged, with studies indicating that on average this might be closer to ~9 - 10 s (J. E. Whinnery & Forster, 2013).

Declines in cerebral blood flow velocity (assessed by transcranial Doppler) of ~61% occur during exposure to 5 Gz. Despite this, cerebral blood flow declines less than cephalic arterial pressure (Ossard et al., 1994), indicating that there are mechanisms, such as a venous syphon and/or cerebral autoregulation, that maintain cerebral perfusion (N. D. C. Green, 2016; Ossard et al., 1994). Cerebral tissue oxygenation when fully conscious, during A-LOC and during G-LOC falls by 4.2, 5.3 and 6.0%, respectively (Ryoo et al., 2004), while blood volume and oxyhaemoglobin levels also decline (Glaister, 1988; Glaister & Jobsis-VanderVliet, 1988). Methodological limitations exist with the use of near-infrared spectroscopy (NIRS) to assess cerebral oxyhaemoglobin levels under +Gz, and there is considerable variability between individuals in the responses observed (Glaister & Jobsis-VanderVliet, 1988; Lange et al., 2020), making assessment of the variables described above difficult.

4.3 | Factors influencing G-tolerance

G-tolerance, commonly accepted to indicate the ability to withstand a certain level of +Gz, varies from day to day and is influenced by numerous factors. Although associations tend to be weak, it is generally accepted that taller individuals have lower G-tolerance (Park et al., 2015; Webb et al., 1991) and that weight is directly related to G-tolerance (Webb et al., 1991); overall, those with higher body mass index have an improved G-tolerance (Tu et al., 2020). Those with greater wall stiffness in precapillary leg vessels (Eiken et al., 2012) or stronger baroreceptor response (Sundblad et al., 2016) and, consequently, capacity for reflex vasoconstriction, generally have a higher G-tolerance, although it is unclear whether a causal relationship exists between the two.

Systolic and diastolic blood pressure are weakly associated with G-tolerance (Klein et al., 1969; Webb et al., 1991). Temperature, owing to effects on blood pressure associated with redistribution of blood flow and altered peripheral resistance, will change G-tolerance, with an increase in skin temperature of ~2°C lowering it by 0.3 Gz (Nunneley & Stribley, 1979). Dehydration, owing to its effect on circulating blood volume and blood pressure, can also lower G-tolerance, with a 3% reduction in body weight caused by dehydration reducing the duration of acceleration that can be tolerated by almost 50% (Nunneley & Stribley, 1979). Medications, particularly those lowering blood pressure or influencing the vascular system, also have the potential to impair G-tolerance (Mills et al., 2019). Given the effects of temperature and dehydration on G-tolerance, it is unsurprising that illness and alcohol consumption can lower G-tolerance, with alcohol being implicated in a number of G-related incidents (Mills et al., 2019).

4.4 | Protection against +Gz

The majority of the +Gz discussion above assumes a relaxed individual not using any G-protection. In reality, there are strategies and equipment that aircrew use to enhance their G-tolerance, the majority of which work by increasing blood pressure. Approximately 6 s into a sustained exposure to +Gz, head-level blood pressure begins to recover toward baseline levels (Eiken et al., 2017; Lambert & Wood, 1946), as shown in Figure 3. This is attributable to baroreceptors in the carotid sinus detecting the drop in head-level blood pressure, with the ensuing baroreflex increasing heart rate (owing to inhibited parasympathetic activity), contractility of the heart (owing to increased sympathetic activity) and vascular resistance (owing to sympathetically mediated vasoconstriction). These combined responses raise G-tolerance by ~1 Gz, although owing to the time taken for them to become established, they are not an effective means of increasing G-tolerance operationally.

The anti-G straining manoeuvre (AGSM) forms the basis of +Gz protection and consists of lower limb and abdominal muscle tensing, combined with a cyclical forced exhalation against a closed glottis for ~3 s followed by a rapid (< 1 s) breath exchange. Muscle contraction raises total peripheral resistance by exerting mechanical pressure on the arteries and arterioles surrounding the muscles while simultaneously limiting venous pooling and promoting venous return by compressing the veins. Contraction of the abdominal muscle helps to limit +Gz-induced descent of the diaphragm and heart (N. D. C. Green, 2016) and raises intra-abdominal pressure (Kobayashi et al., 2002), with contraction of the abdomen having one of the greatest

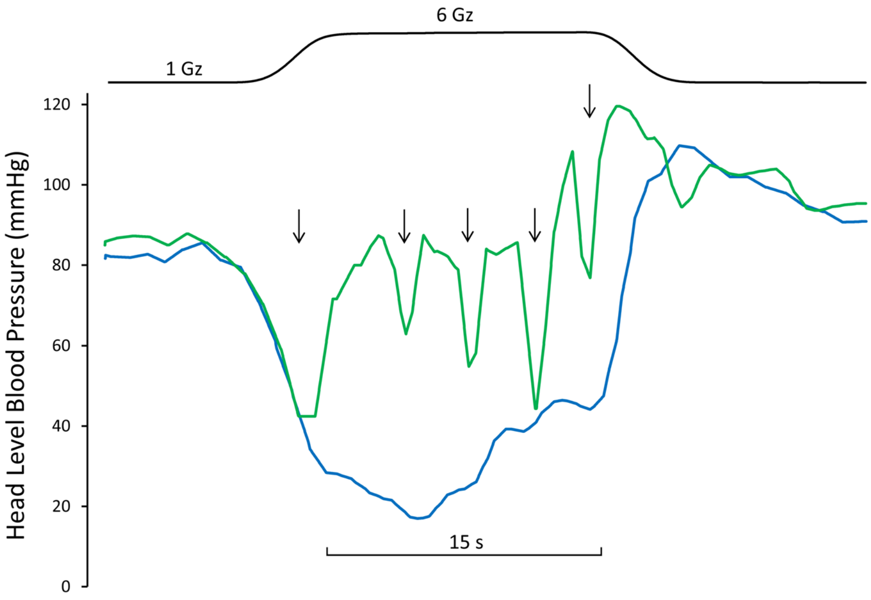


FIGURE 5 Head-level blood pressure response during a +6 Gz acceleration exposure when relaxed (blue line) and when performing the anti-G straining manoeuvre (AGSM; green line). Arrows indicate the point at which the rapid exchange of breath occurs during the AGSM

effects on cerebral blood volume (Kobayashi et al., 2002). Muscle contraction also enhances the protection provided by the breathing component of the AGSM, which on its own, via an increased intrathoracic pressure being transmitted directly to the heart, can raise blood pressure by 60–70 mmHg; however, when combined with muscle contraction this can reach ~90 mmHg (MacDougall et al., 1993). Cycling the breath every 3 s during the AGSM is essential, because it allows venous return to be maintained, which would otherwise be impaired by the raised intrathoracic pressure (Shubrooks & Leverett, 1973). The importance of a rapid breath exchange can be observed in Figure 5, where a substantial drop in head-level blood pressure occurs during the breath exchange, but the immediate resumption of the breathing manoeuvre raises blood pressure once more. If performed correctly, the AGSM can increase G-tolerance by 3–4 Gz, with poor performance being implicated in a number of accidents (R. Burton & Whinnery, 1985).

Anti-G suits represent an engineering solution that improves G-tolerance. Several types and variations of anti-G suits exist; the most common are pneumatic five-bladder partial coverage anti-G trousers (PCAGT) and full coverage anti-G trousers (FCAGT). These anti-G trousers (AGT) contain air bladders, which, when inflated (via pressurized gas delivered under +Gz), directly compress the underlying areas and tension the fabric in areas without bladders. Partial coverage anti-G trousers contain five bladders located over the abdomen, quadriceps and calves and provide ~30% bladder coverage. Full coverage anti-G trousers provide ~90% bladder coverage and exert pressure to most of the lower limbs and abdomen (Figure 6).

Anti-G trousers raise arterial blood pressure by: (1) increasing total peripheral resistance through compression of the arteries and arterioles; and (2) promoting venous return by limiting venous pooling through compression of the veins. Partial coverage anti-G trousers have been shown to reduce the volume of blood that pools in the lower limbs, whereas FCAGT may prevent blood pooling entirely (Krutz et al., 1990; Pollock et al., 2019), helping to minimize declines in cardiac output and stroke volume (Tripp et al., 1994; Vettes, Vieillefond, & Auffret, 1980). Interestingly, despite being able to prevent blood pooling, FCAGT do not enhance stroke volume any more than PCAGT. This probably reflects a lesser decline in blood pressure with FCAGT, resulting in a less efficacious baroreflex response and, consequently, lower heart rate and cardiac contractility (Pollock et al., 2019).

The abdominal bladder of an AGT is one of its most important features (R. Burton & Krutz, 1975). When exposed to 5 Gz, it has been estimated to provide ~0.5 Gz of additional protection, in part owing to its ability to reduce downward displacement of the heart (Rushmer, 1947). Furthermore, it provides direct pressure transmission from the abdomen to the thorax (Eiken et al., 2011), where the increased thoracic pressure elevates blood pressure. The PCAGT and FCAGT increase G-tolerance by 1–1.5 and ~2.5 Gz, respectively (N. D. C. Green, 2016; Pollock et al., 2019), with the protection being additive to that of the AGSM (Stevenson & Scott, 2014).

In an aircraft capable of the highest levels of +Gz, positive pressure breathing for +Gz protection (PBG) may also be used. This involves the breathing of pressurized air via a facemask (Figure 6), with the resulting increased intrathoracic pressure being transmitted to the great vessels, raising blood pressure. PBG impairs venous return, therefore, lower-body counter-pressure (provided by AGT) is required during its use, with protection provided by PBG being additive to that of AGT (Eiken et al., 2007). A concern with PBG is the potential for overdistension of the lung and greater effort of expiration. For this reason, traditionally, chest counter-pressure, equal to the pressure being delivered via the facemask, has been used. Measurement of transpulmonary pressure during PBG with and without the use of chest counter-pressure reveals no effect of chest counter-pressure on transpulmonary pressure or work of breathing (Grönkvist et al., 2008), suggesting that chest counter-pressure might not be required with PBG. Overall, PBG use in combination with AGT increases G-tolerance by ~1 Gz (Shubrooks, 1973).

FIGURE 6 Clothing worn by Eurofighter Typhoon pilots, with G protection elements highlighted, including full-coverage anti-G trousers (FCAGT), facemask that can be used to deliver positive-pressure breathing for G and flight jacket incorporating integrated chest counter-pressure garment. Modified from © Crown Copyright 2021 image

4.5 | Pathophysiology of Gz

Fatigue and pain in the neck and back after air combat manoeuvring (ACM; Oksa et al., 1999) are often reported. Muscle activation increases during ACM and, in particular, when the head is moved to non-neutral positions (Sovelius et al., 2020). This is exacerbated by the use of a helmet and helmet-mounted equipment (Sovelius et al., 2019), with muscular and ligamentous injury possible with excessive loading. Furthermore, spinal shrinkage can occur, with 4.9 mm shrinkage reported after 40 min ACM sorties (Hamalainen et al., 1996), and premature intervertebral disc degeneration may occur in some aircrew (Hamalainen et al., 1993). For these reasons, it is important that aircrew perform neck strengthening to reduce the risk of injury and that attempts are made to minimize additional loading from head-mounted equipment.

Exposure to +Gz, particularly on a centrifuge, has been shown to cause premature ventricular contraction, bigeminy, trigeminy and sinus bradycardia (Chung, 2001; J. Whinnery, 1990; Zawadzka-Bartczak & Kopka, 2011). Typically, these are benign and resolve upon cessation of +Gz exposure. Although fast jet aircrew are generally healthy, caution is warranted if an individual with underlying cardiac pathology is exposed to +Gz.

Acceleration atelectasis can develop during exposure to +Gz, when the lower airways are compressed by the increased intrapleural pressure, the weight of the lung and AGT abdominal bladder inflation. This results in airway closure and extensive gas trapping in unventilated alveoli (Grönkvist et al., 2003). To protect against hypoxia, gas mixtures with elevated proportions of oxygen are breathed, but during +Gz exposure the ensuing rapid absorption of oxygen from unventilated alveoli and the lack of 'nitrogen splinting' can result in alveolar collapse (Dale & Rahn, 1952), which persists once +Gz is offloaded. This can cause cough, chest pain and breathing difficulties (I. Green & Burgess, 1962; Tacker et al., 1987). Furthermore, atelectasis is associated with pulmonary shunt (I. Green, 1963; Pollock, Gates, et al., 2021), potentially making aircrew hypoxaemic. In normal operation, this risk is minimal, because aircrew often breathe elevated oxygen levels; however, although unlikely, a hypoxic event (e.g., rapid decompression of aircraft) when atelectatic could exacerbate the effects of the shunt. Breathing gas mixtures containing $< 60\%$ oxygen has been assumed to protect against acceleration atelectasis

(Ernsting, 1965); however, there have been recent reports of aircrew developing symptoms of acceleration atelectasis (Monberg, 2013) that might contribute to 'physiological episodes' being reported by a number of Air Forces, including the United States Air Force (Flottmann, 2013). The reason for increased reporting remains unknown, although improved aircraft capabilities and AGT, in comparison to when the original research was conducted, might play a role. This is supported, in part, by shorter durations of acceleration than previously suggested causing atelectasis in some individuals when wearing FCAGT (Pollock, Gates, et al., 2021).

5 | +Gx: SUBORBITAL/ORBITAL SPACEFLIGHT LAUNCH AND RE-ENTRY

We are all familiar with the sensation of being pushed back into the seat when a car accelerates forwards; this is +Gx, sometimes termed forward, transverse or 'eyeballs in' acceleration. Astronauts experience +Gx during launch and atmospheric re-entry, when a recumbent position is typically used to avoid the undesirable effects of +Gz. However, even without applying additional G or leaving the Earth's surface, we all experience the effects of Gx. When we roll over in bed the Gx vector is reversed, from +1 Gx when lying supine to −1 Gx when lying prone. Greater body weight has the potential to magnify any associated effects, for example obesity (Steier et al., 2009) or under high G (which multiplies bodyweight), and, conversely, the prone position is used therapeutically in critically ill patients with respiratory failure in intensive care.

5.1 | The physiology of Gx

Even at 1 Gx, there are physiological advantages to breathing in the prone position, reflecting quadrupedal origins of humans. Functional residual capacity is increased, ventilation is more uniformly distributed owing to changes in lung density, and ventilation–perfusion matching is improved (Henderson et al., 2013; Lumb & White, 2021), and these differences are accentuated when G is increased (Rohdin et al., 2003). Mechanical ventilation in the prone position, known as 'proning', improves ventilation–perfusion matching, hence oxygenation, and improves outcomes in patients with severe hypoxaemic respiratory failure (Guérin et al., 2013). Proning of ventilated patients has been used extensively during the coronavirus disease 2019 pandemic, which has also seen the use of 'self-proning' by awake patients, although this latter practice has yet to undergo definitive trials (McNicholas et al., 2020).

As opposed to the acute cardiovascular and cerebral responses induced by Gz, Gx is best known for respiratory and cardiac effects caused by compression of the thorax. Overall, Gx has a reputation for being more 'tolerable' than Gz, although this naturally depends on the magnitude, rate of onset and duration of exposure. Trained centrifuge participants have tolerated 3 Gx for 30 min (Serrador et al., 2001), 8 Gx for 3 min (Steiner & Mueller, 1961), 12 Gx for 30 s, and 15 Gx for 10 s (Gillies, 1965; Torphy et al., 1966). As a basic guide, from the authors' experience, 2 Gx is comfortable, although it is hard to raise a leg, at 4 Gx moving and breathing feel noticeably more difficult and it is hard to raise an arm, and 6 Gx is uncomfortable, with substantial resistance to breathing and difficulty in moving. There have been rare reports of traumatic injury associated with +Gx, such as a case of parenchymal lung damage and mediastinal emphysema sustained at +5.5 Gx during a centrifuge experiment (Wood, 1992).

For spacecraft occupants in a typical recumbent position, the aerodynamic loads of rocket launch and re-entry are experienced mostly as +Gx and vary between vehicles and flight profiles. Early Mercury programme flights in the 1960s peaked at ∼6 Gx on launch and 12 Gx on re-entry, considerably higher than subsequent Apollo programme flights (M. R. Barratt, 2019). More recently, Space Shuttle launches plateaued at 3 Gx, compared with peaks of ∼4.5 Gx during ascent and descent for the Russian Soyuz, although emergency launch abort and ballistic re-entry profiles can generate greater G loads in the Soyuz (M. R. Barratt, 2016). At the extreme, in rare contingencies, cosmonauts have been exposed to exceptionally high maximal loads of ≤ 20 Gx that are believed to have caused some lasting injury (M. R. Barratt, 2019).

Research investigating the physiology of +Gx has tended to focus on the respiratory system. Pulmonary physiology is well known to be gravity dependent, although the precise role of gravity and its interaction with other factors is not completely understood (Glenny, 2008; Hughes & West, 2008; Prisk, 2011). Regional ventilation and blood flow, which are normally greater in the dependent region of the lung, become more inhomogeneous as increasing Gx is applied, resulting in ventilation–perfusion mismatching and hypoxaemia. Perfusion decreases in the non-dependent region of the lung, and within dependent lung regions there is reduced ventilation, airway closure and shunt secondary to compression of lung tissue and displacement of mediastinal contents (Ax et al., 2013; Glaister, 1970; Nolan et al., 1963; Prisk, 2011). Alongside worsening impairment of gas exchange and hypoxaemia, recent centrifuge experiments ≤ 6 Gx, sustained for 2 min, have demonstrated very high work of breathing and neural respiratory drive, in addition to a progressive reversal in the normal relative distribution of regional lung ventilation (from posterior to anterior), accompanied by anterior gas trapping (Menden et al., 2021; Pollock, Jolley, et al., 2021). In these experiments, ventilatory responses were limited by impaired pulmonary mechanics, with dose-dependent neuroventilatory uncoupling and pronounced breathlessness, and most participants reported musculoskeletal chest pain at higher G levels (Pollock, Jolley, et al., 2021). These effects were analogous to a very short-lived form of respiratory failure and were well tolerated by young, healthy volunteers but might have greater impact in other populations.

Cardiovascular effects of +Gx have not been as extensively investigated as those on the respiratory system. Early studies established that the heart is displaced posteriorly at 5 Gx (Sandler, 1966), and there is an increase in both right atrial pressure (to ∼20 mmHg) and mean aortic pressure (Lindberg et al., 1962). Heart rate can be increased with +Gx, although there is classically a reduction in heart rate when the body is fully supine (N. D. C. Green, 2016). Aortic flow measurements in anaesthetized dogs suggest that cardiac output might be reduced despite an increase in blood pressure (Stone et al., 1971). Cardiac arrhythmias are common during exposure to +Gx and consist mainly of premature atrial and ventricular contractions, with ectopy arising primarily in the atria (Rogge et al., 1969; Suresh et al., 2017; Torphy et al., 1966). Other ECG abnormalities have occasionally been reported, such as paroxysmal atrial tachycardia (Torphy et al., 1966). Rhythm disturbances induced by +Gx have been attributed to distension of the right atrium and are generally considered to be benign and self-limiting in healthy individuals (N. D. C. Green, 2016; Rogge et al., 1969; Torphy et al., 1966).

5.2 | Commercial suborbital spaceflight

To date, exposure to high +Gx acceleration during space operations has largely been confined to professional astronauts. This is changing with the advent of commercial suborbital spaceflight for paying customers, who experience several minutes of μG between high G loads that may exceed 3 Gx for 20 - 30 s and peak at $\leq$ 6 Gx on re-entry (Blue Origin, 2018; Blue et al., 2014; Stepanek et al., 2019). These flights are targeted at tourists and scientific researchers but are ultimately expected to develop into extremely fast point-to-point travel (T. G. Smith & Buckey, 2021). Parallels have been drawn between the emerging suborbital spaceflight industry and the early days of air travel a century ago, which began as joyrides for those who could afford them and eventually transformed global transportation.

Private space travel introduces the interesting question of how 'normal' members of the public, as opposed to astronauts or military pilots, are affected by relevant high-G acceleration, and over the past decade pioneering centrifuge studies have begun to explore this new frontier of physiology and medicine. Many individuals of varying ages ($\leq$ 88 years) and with various stable medical conditions have safely tolerated simulated suborbital G profiles (Blue et al., 2012, 2014; Blue, Bonato, et al., 2017), including a small number with cardiac pacemakers (Blue et al., 2015), indwelling insulin pumps (Levin et al., 2015) and corrected congenital heart disease (Blue et al., 2015). Among the self-selected volunteers in these studies, ~5% were unable to complete the exposures owing to physical or psychological intolerance (Blue et al., 2014). Relative bradycardia was commonly observed, as were a number of other asymptomatic arrythmias, including sinus pause, couplet premature ventricular contractions, bigeminy, accelerated idioventricular rhythm and a short run of ventricular tachycardia (Blue et al., 2014; Suresh et al., 2017). These episodes were not associated with clinically apparent decompensation, although blood pressure was not recorded contemporaneously, and transient haemodynamic compromise cannot be excluded. The investigators concluded that heightened caution is warranted with respect to potential arrythmias during suborbital hypergravity in individuals who have cardiopulmonary disease or are taking cardiac medications (Suresh et al., 2017).

Limited measurements during simulated suborbital profiles also indicated a degree of arterial oxygen desaturation (Blue et al., 2012, 2014) that is consistent with the hypoxaemia demonstrated during previous and subsequent work studying various magnitudes and durations of +Gx (Alexander et al., 1966; Ax et al., 2013; Glaister, 1970; Nolan et al., 1963; Pollock, Jolley, et al., 2021; Prisk, 2011; Rohdin et al., 2003). Any in-flight hypoxaemia is likely to be exacerbated by the use of mildly hypoxic airline-style cabin pressurization, which is anticipated on some suborbital vehicles (Pollock, Jolley, et al., 2021). Other factors that could compound the effects of +Gx during suborbital flights include the intervening μG phase and the simultaneous exposure to +Gz that is anticipated during some flight profiles (Albery, 2004; Blue et al., 2014).

Overall, the physiological effects of +Gx have the potential to cause adverse sequelae in a minority of predisposed passengers, such as those with cardiac or respiratory disease or obesity. Doctors are familiar with the concept of determining fitness to fly in airline passengers and, more broadly, in assessing and then optimizing the capacity of a patient to withstand major surgery. Suborbital spaceflight likewise presents a significant physiological challenge for some prospective passengers, and similar principles of evaluation and risk modification can be applied (T. G. Smith & Buckey, 2021). Undertaking a preflight 'G challenge test' on a centrifuge might be beneficial in this regard and warrants investigation (Pollock, Jolley, et al., 2021).

In summary, suborbital high G peaks are brief, and it is likely that most people will be able to tolerate flights safely. Underlying physiological responses to +Gx will nevertheless be triggered to some extent and might become clinically meaningful in some medically susceptible passengers (Pollock, Jolley, et al., 2021; T. G. Smith & Buckey, 2021; Suresh et al., 2017). Detailed physiological studies in relevant passenger groups are required to support the development of an evidence-based medical approach that ultimately minimizes morbidity while maximizing access to suborbital flights (T. G. Smith & Buckey, 2021; Stepanek et al., 2019).

6 | MICROGRAVITY: SPACEFLIGHT

In space, while orbiting around the Earth, the body is in a state of continual freefall, floating freely in what is termed μG. With the development of space stations, such as Mir and the ISS, humans can be exposed to long-duration μG, with missions in some instances lasting > 1 year. Spaceflight exposes the body to many different stressors that affect all systems (Figure 7; Aubert et al., 2016; Hodkinson et al., 2017; Williams et al., 2009). In this review, we aim to highlight adaptations most clearly related to the μG component of the spaceflight environment.

6.1 | Physiology of and protection from μG

One of the first adaptations in exposure to μG is the loss of the hydrostatic pressure gradient from the head to the feet. This causes a headward fluid shift, with loss of volume in the lower limbs and an

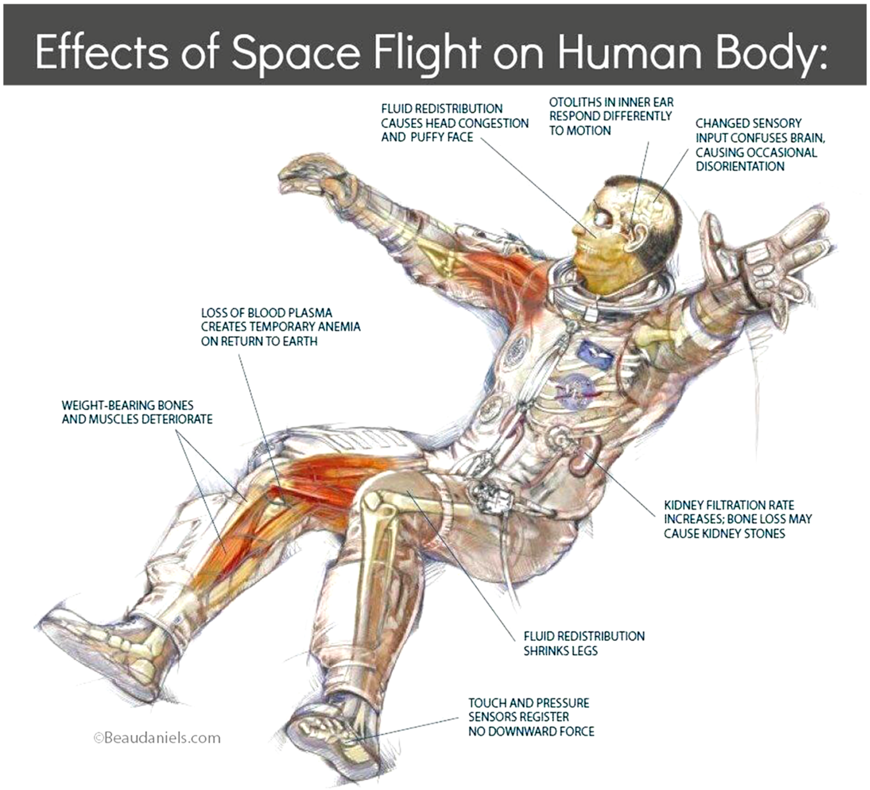


FIGURE 7 The effects of spaceflight on the human body. With permission: Beaudaniels.com

engorged and visibly oedematous head; however, rather than causing a diuresis as would be expected on Earth, a reduction in plasma volume occurs owing to fluid shifting to extravascular and extracellular compartments (Drummer et al., 2000; Leach et al., 1996). In the initial 2–3 days in μG, 50–80% of astronauts (Heer & Paloski, 2006) experience neurovestibular disturbance, part of a space adaptation syndrome, with risk of space motion sickness. Despite symptoms similar to terrestrial motion sickness, space motion sickness differs in aetiology and susceptibility, with anti-emetic medication routinely being used to prevent the worst of the effects. The longer-term neurovestibular adaptive responses to microgravity contribute to impaired manual dexterity and motion perception and degraded ability to operate a vehicle in the first days on Earth after a 6-month exposure to μG (S. T. Moore et al., 2019). This will have implications for the tasks that individuals might be required to perform on arrival at the surface of Mars after exposure to 6 - 9 months of μG on the transit flight from Earth.

Some of the greatest effects of μG occur in the musculoskeletal system. In μG, the body adopts an almost fetus-like position, with ambulation principally driven by the upper body, while the lower limbs are used predominantly for restraint. This has brought about unanticipated challenges, such as callous formation on the top of the feet caused by restraint straps and the need for slippers to protect the top of the feet. More significantly, owing to unloading and disuse, μG has a profound effect on muscle. After as little as 17 days in μG, reductions in muscle volume of 10% (ankle extensors and intrinsic back muscles), 57% (quadriceps and psoas) and 3% (hamstrings and ankle extensors) have been noted (LeBlanc, Lin, et al., 2000). Missions lasting 115–197 days have been found to reduce lower limb muscle volume by 10–17%, the intrinsic back muscles by 16% and the psoas muscle by 4%, despite performing an exercise countermeasure programme, although compliance varied markedly between astronauts (LeBlanc, Lin, et al., 2000). Interestingly, the neck musculature does not appear to be affected. During early 6-month ISS missions, peak power of the calf declined by 32%, also despite 5 h per week of aerobic exercise (cycle ergometer and treadmill) combined with resistance training on 3–6 days per week using the interim resistive exercise device (Trappe et al., 2009).

A classic study on long-duration spaceflight (4–14 months) revealed reductions in bone mineral density of 1.06, 1.15, 1.56 and 1.35%/month in the spine, femoral neck, trochanter and pelvis, respectively (LeBlanc, Schneider, et al., 2000). Again, this occurs even with regular use (1–1.5 h daily) of a treadmill, cycle ergometer and resistive exercise with bungees. For further detailed reviews on these topics, see: Grimm et al. (2016), Juhl et al. (2021) and Vico & Hargens (2018). The effect of μG on muscle and bone is strongly influenced by nutrition (S. M. Smith et al., 2012), and bone remodelling has associated effects on an individual's biochemistry and renal system (Pietrzyk et al., 2007). There is also great interest in the effect of μG on spinal unloading and the spinal elongation and low back pain associated with this (D. A. Green & Scott, 2018), with parallels for what is also a widespread terrestrial healthcare challenge (Bailey et al., 2018).

These musculoskeletal changes are a normal adaptive response to μG, which are largely not problematic in space; however, they are a significant health concern on return to Earth's gravity or for arduous activities, such as extra-vehicular activity (e.g., spacewalks) (Chappell et al., 2017; A. D. Moore et al., 2014). The changes are often used as a basis for translational research into ageing on Earth; therefore, much attention has been given to potential countermeasures to mitigate these adaptive responses. Early exercise countermeasures were effective only in part in mitigating musculoskeletal changes in μG. More recently, newer exercise devices (e.g., the advanced resistive exercise device) largely prevent bone changes when combined with bisphosphonate use (Sibonga et al., 2019). Although these interventions are highly effective, they come with the costs of astronaut time, oxygen usage and space that are unlikely to be available on future exploration spacecraft. Therefore, there remains a need for a more effective and space-efficient solution to counteract the musculoskeletal changes in μG, or a shift in perspective to accept the changes, perhaps with a greater focus on post-flight rehabilitation.

Adaptations are not confined to the musculoskeletal system, with cardiac remodelling, in the form of atrophy, also occurring, again despite the arduous physical training routine undertaken by astronauts in space (MacNamara et al., 2021; Perhonen et al., 2001). This raises new concerns about the risk of atrial fibrillation from the enlarged left atria (Khine et al., 2018). On return to Earth, the cardiovascular adaptation in space leads to orthostatic intolerance in the first hours or days of return (Buckey et al., 1996). Attempts to counter this through fluid loading before re-entry or use of AGT have shown variable efficacy and compliance (Perez et al., 2003).

Recently, a new pathophysiological finding associated with spaceflight was identified during a study of venous flow in μG (Marshall-Goebel et al., 2019). In one individual, complete occlusion of the internal jugular vein with thrombus was noted and required anticoagulation treatment in space (Auñón-Chancellor et al., 2020). This was a previously unrecognized hazard of spaceflight, highlighting the relative inexperience we have in this field and the potential for further issues to be identified in the future as more people travel to space or undertake different flight profiles.

Over the past decade, a key challenge has emerged in the form of spaceflight associated neuro-ocular syndrome (SANS), which was first recognized as microgravity ocular syndrome and then visual impairment intracranial pressure syndrome. Spaceflight associated neuro-ocular syndrome results in increased choroidal thickness, optic disc oedema and visual impairment (hyperopic shift) that requires optical correction (glasses) (Mader et al., 2011; Marshall-Bowman et al., 2013). The pathophysiological basis for this condition is currently unclear, and multiple groups are working to address different potential explanations and countermeasures. One potential contributory factor is the loss of daily shifts in pressure associated with moving from supine to standing, which occur on Earth. This has revived interest in the potential for lower-body negative pressure as a spaceflight countermeasure (Harris et al., 2020).

6.2 | Going forward in space

As we look to the future, there will be increased interest in personalized medicine and insight offered by the various '-omics' for space medicine and its terrestrial benefits. Fascinating insights have been revealed through these diverse approaches, including the National Aeronautics and Space Administration (NASA) twin study (Garrett-Bakelman et al., 2019) and associated NASA Gene LAB developments, amongst others (da Silveira et al., 2020; Madrigal et al., 2020; Rutter et al., 2020). There are also sex differences in the effects of human spaceflight (Figure 8), although our understanding of this is undermined by the disparity in the sex distribution of space travellers [total space travellers as of 2020: 64 female and 498 male (M. G. Smith et al., 2020)], and there is a recognized need for further research and greater representation in astronaut selection (Mark et al., 2014).

Future physiological challenges might include the additional stressor of chronic mild hypoxia as part of a proposed exploration atmosphere (Norcross et al., 2015) that might modulate the adaptation to μG described above. Artificial gravity might be a valuable countermeasure to some aspects of μG, which is being studied actively in the form of short-arm centrifuges (Clément et al., 2015), but also for the potential of a longer-arm rotating module as part of future space vehicles or habitats. A fascinating physiological challenge is the interest in and potential to induce hibernation or torpor in humans for long-duration spaceflight to avoid the adaptation to μG or associated life support and logistic footprint to support the exercise countermeasure (Cerri et al., 2016). This is an area that has received some attention and development in terrestrial health care over the last decade, albeit with a different focus, and is something that could lead to a step change in clinical care for prolonged bed-bound patients in addition to an option for long-duration spaceflight. However, it is far from being an implementable solution at present.

7 | CONCLUSIONS

With advancements in technology and the desire to push the limits of human endurance, we have been able to place the human body in extreme acceleration environments. Our understanding of how the body responds to these environments is variable depending on the nature of the accelerations being experienced.

Gy is predominantly experienced by racing drivers and can result in neck discomfort, although little research has been conducted in this area owing to the relatively minor issues associated with it.

In contrast, there has been extensive research of Gz owing to the dangers is poses for fast jet pilots. Despite this and the use of multiple strategies to protect individuals from its negative effects, ultimately G-LOC, we are still unable to provide complete protection from Gz. With the development of future crewed aircraft, it remains important to identify how best to improve current protection strategies, which requires a detailed understanding of the physiological mechanisms of action of protection equipment.

The emergence of commercial (sub)orbital spaceflight will place people in an environment where elevated Gx can be experienced. Given the effect this can have on the respiratory and other systems, it is important for us to understand how the general population, potentially

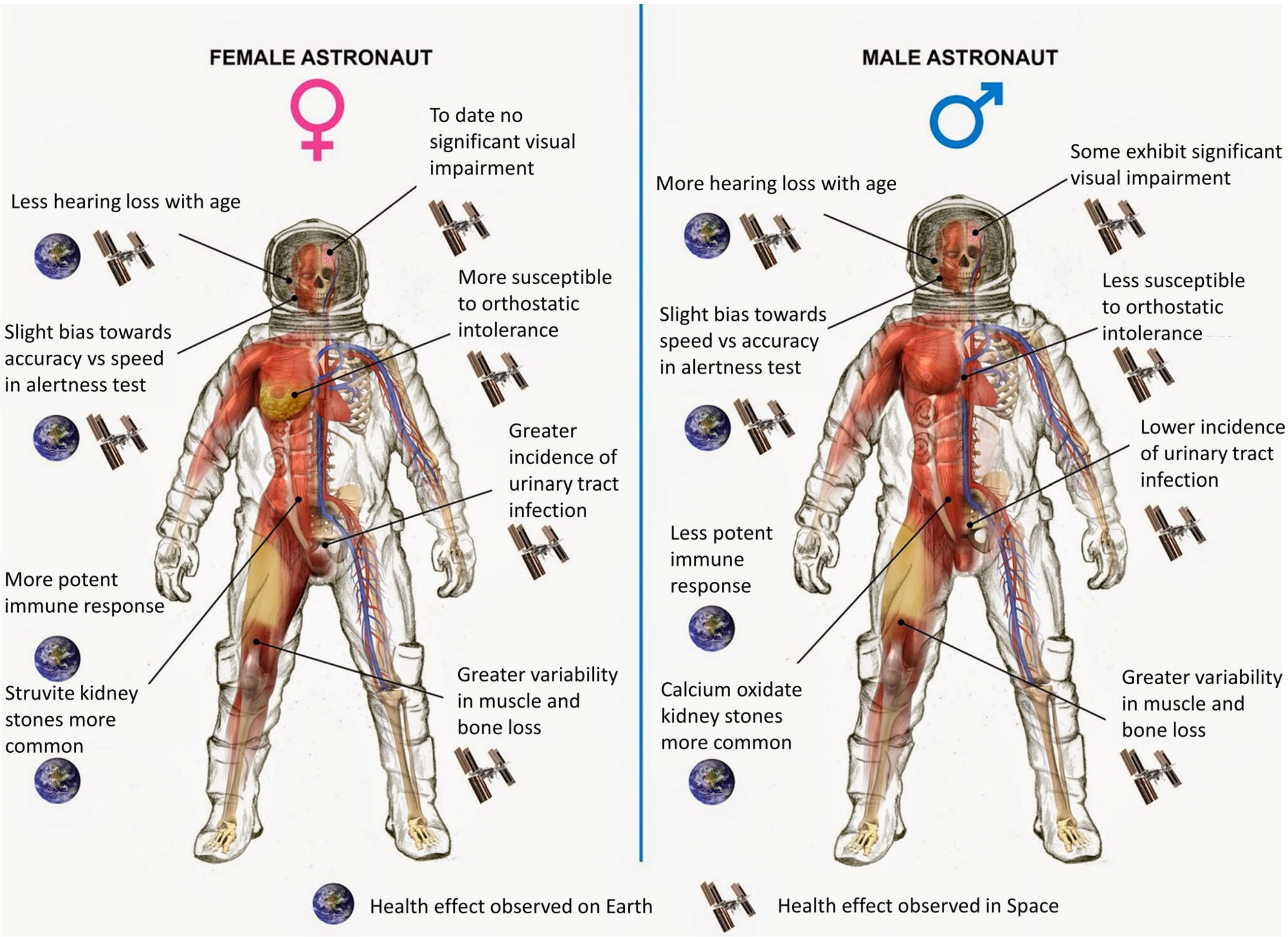


FIGURE 8 Key differences between men and women in cardiovascular, immunological, sensorimotor, musculoskeletal and behavioural adaptations to spaceflight. Credit NASA/NSBRI (modified)

with underlying pathology, will be affected by this, in order to ensure the safety of these ventures.

Finally, μG represents a unique environment where the effects of gravity are all but removed. This leads to numerous physiological adaptations in almost every body system, and we have much still to learn to identify how best to counter these. This remains a top priority, with future missions being planned to Mars, where an individual must not only arrive safely, but must also be able to perform various physical tasks immediately upon re-entry to a gravity environment with limited support and resources.

7.1 | Future recommendations

There is much still to learn about many of the acceleration environments being discussed. Meaningful effects of Gy are predominantly limited to motor racing, with relatively little study in the area. Gz has been researched extensively over the past 100 years and, although crewed fast jets will remain, increases in automation and the technology for remotely piloted aircraft will eventually reduce the need for detailed research in this field to inform the protection of fast jet pilots. With the anticipated increase in the number of people completing suborbital and orbital spaceflights and the endeavours of humankind to leave Earth's atmosphere there will be a growing need for research in the μG and Gx environments. As such, there is a wealth of future research avenues in each of these fields. A list, but by no means extensive, of some of these avenues is given to finish:

- What is the potential for physical conditioning, particularly of the neck, to reduce the impact of Gy acceleration in motor racing?
- Can anti-G suits be modified or redesigned to provide greater protection against +Gz?
    - How do anti-G suit inflation schedules alter levels of protection?
    - Can pressure transmission to the pilot be modified or improved through anti-G suit design to give enhanced protection?
- Are the levels of Gx experienced during suborbital spaceflight tolerated by those not in optimal health, and how should they be managed?
- Does the combination of Gx and Gz experienced with some suborbital spacecraft alter an individual's G-tolerance?

- What are the (patho)-physiological responses to the transition from the high-G to μG and back to the high-G environment associated with suborbital spaceflight?
- There is a need to understand and mitigate the risks associated with SANS and cardiac remodelling.
- There is a need to explore new drugs to complement exercise and nutrition countermeasures used in spaceflight.
- Can we develop more effective and efficient exercise and nutrition strategies to counter the effects of μG?
- There is a need for development/use of artificial gravity to counteract μG-related deconditioning.
- There is a need for research into hibernation/torpor to counteract the deconditioning that could occur during long-duration spaceflight.

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AUTHOR CONTRIBUTIONS

R.D.P. was responsible for the concept of the review. All authors contributed to the design and writing of the manuscript. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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