

TOPICAL REVIEW

Plasticity of the heart in response to changes in physical activity

Eric T. Hedge^{1,2} , Tiffany L. Brazile^{3,4} , Richard L. Hughson¹  and Benjamin D. Levine^{3,4} 

¹Schlegel-UW Research Institute for Aging, Waterloo, Canada

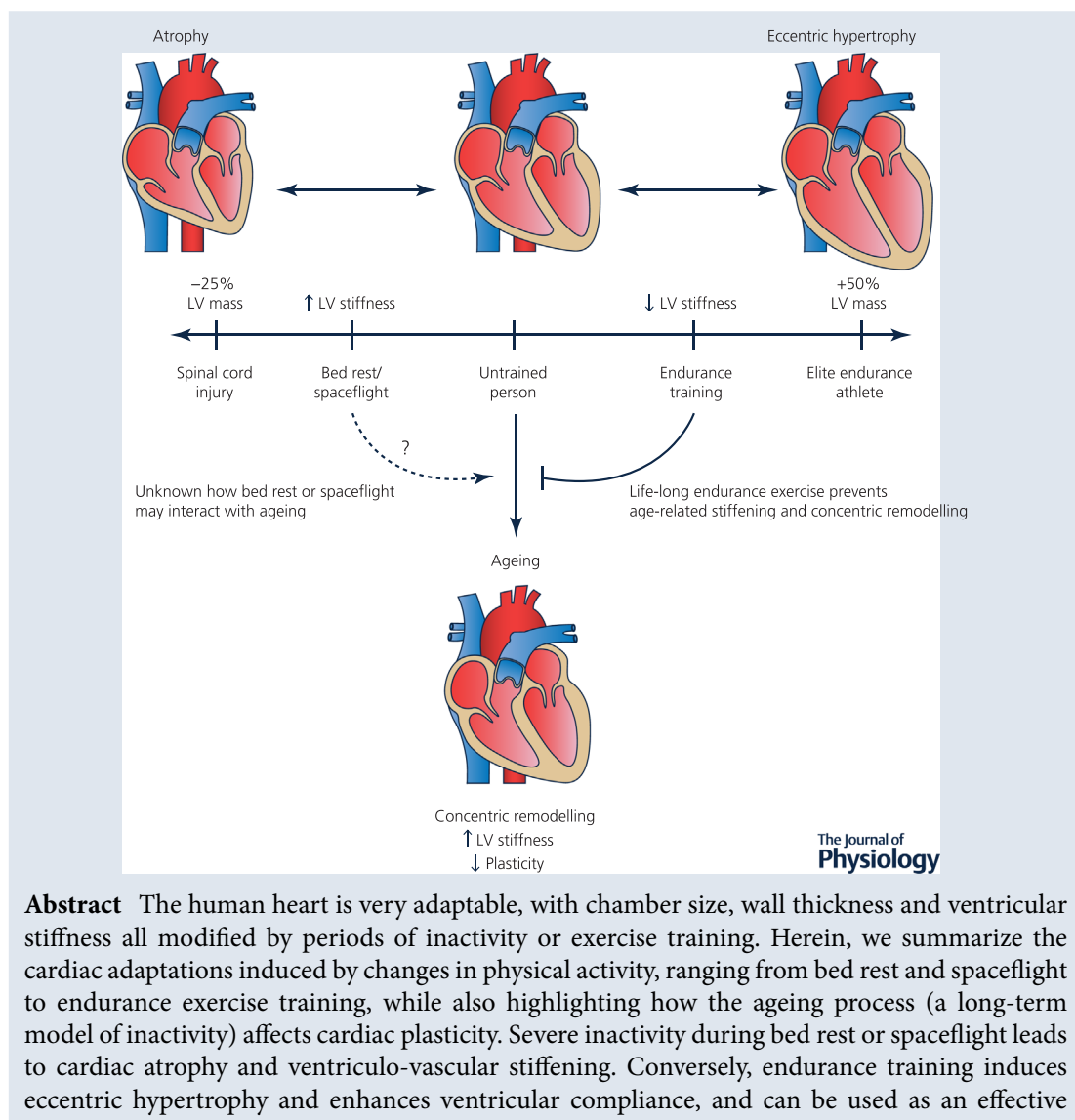
²Department of Kinesiology and Health Sciences, University of Waterloo, Waterloo, Canada

³Institute for Exercise and Environmental Medicine, Texas Health Presbyterian Hospital, Dallas, USA

⁴Division of Cardiology, University of Texas Southwestern Medical Center, Dallas, USA

Handling Editors: Laura Bennet & Paul Greenhaff

The peer review history is available in the Supporting Information section of this article (<https://doi.org/10.1113/JP284158#support-information-section>).



Abstract The human heart is very adaptable, with chamber size, wall thickness and ventricular stiffness all modified by periods of inactivity or exercise training. Herein, we summarize the cardiac adaptations induced by changes in physical activity, ranging from bed rest and spaceflight to endurance exercise training, while also highlighting how the ageing process (a long-term model of inactivity) affects cardiac plasticity. Severe inactivity during bed rest or spaceflight leads to cardiac atrophy and ventriculo-vascular stiffening. Conversely, endurance training induces eccentric hypertrophy and enhances ventricular compliance, and can be used as an effective

countermeasure to prevent adverse cardiac changes during prolonged periods of bed rest or spaceflight. With sedentary ageing, the heart undergoes concentric remodelling and irreversibly stiffens at advanced age. Specifically, older adults who initiate endurance training later in life are unable to improve ventricular compliance and diastolic function, suggesting reduced cardiac plasticity with advanced age; however, lifelong exercise training prevents age-associated cardiac remodelling and maintains cardiac compliance of older adults at a level similar to those of younger healthy individuals. Nevertheless, there are still many knowledge gaps related to cardiac remodelling and changes in cardiac function induced by bed rest, exercise training and spaceflight, as well as how these different stimuli may interact with advancing age. Future studies should focus on understanding what factors (sex, age, heritability, etc.) may influence the heart's responsiveness to training or deconditioning, as well as understanding the long-term cardiac consequences of spaceflight beyond low-Earth orbit with the added stimulus of galactic cosmic radiation.

(Received 6 March 2024; accepted after revision 1 August 2024; first published online 20 August 2024)

Corresponding author B. D. Levine: Division of Cardiology, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390-8830, USA. Email: benjaminlevine@texashealth.org

Abstract figure legend The heart adapts to changes in physical activity, with inactivity (e.g. bed rest or spaceflight) causing cardiac atrophy and ventricular stiffening, and endurance exercise training leading to eccentric hypertrophy and improved ventricular compliance. The plasticity of the heart also decreases with increasing age, leading to interactions between the effects of exercise training or inactivity, and ageing. LV, left ventricle.

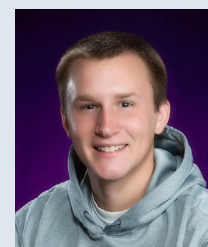
Introduction

The heart is a very adaptable organ, as it remodels based on stimuli ranging from physical inactivity to exercise training (Hill & Olson, 2008). Cardiac atrophy or hypertrophy result from reduced or increased loading, respectively. Cross-sectional comparisons of left ventricular mass between individuals with different physical activity levels clearly illustrate the heart's wide adaptive range (Fig. 1). When benchmarked against untrained healthy adults, an adaptive range of ~75% has been observed across different groups, spanning from individuals with a spinal cord injury that hinders their ability to exercise (−25%) (de Groot et al., 2006) to elite endurance athletes (+50%) (Milliken et al., 1988). Inactivity (Perhonen, Zuckerman, et al., 2001) or exercise training (Arbab-Zadeh et al., 2014) can also modify cardiac compliance. The functional importance of maintaining healthy heart size and compliant ventricles is highlighted by the outcomes of bed rest and early

spaceflight studies, as inactivity-associated remodelling of the heart contributed to reduced cardiorespiratory fitness and orthostatic intolerance following bed rest (Hastings et al., 2012; Levine et al., 1997; Perhonen, Zuckerman, et al., 2001; Shibata et al., 2010; Westby et al., 2016) and following spaceflight (Perhonen, Franco, et al., 2001). Maintaining a compliant heart is also clinically important, as adults with stiffer ventricles are at a higher risk for developing heart failure (Hieda et al., 2020).

Bed rest and spaceflight are two of the most severe forms of inactivity, providing strong stimuli for cardiac remodelling in healthy adults. In fact, −6° head-down tilt bed rest (HDBR) studies are often conducted to simulate the cardiovascular deconditioning associated with spaceflight (Hargens & Vico, 2016). These kinds of studies also provide strong evidence about the negative cardiac effects imparted by sedentary behaviour or immobility due to hospitalization. Some of the cardiac changes induced by these severe inactivity situations parallel those observed with ageing (e.g. ventricular and vascular

Eric Hedge is an integrative physiologist, with interests in studying the cardiovascular and respiratory adaptations to exercise, ageing, inactivity and spaceflight. He is currently a PhD candidate at the University of Waterloo, under the supervision of Professor Richard Hughson, and his PhD work is funded by a Banting and Best Canada Graduate Scholarship from the Canadian Institutes of Health Research. Outside of research, Eric enjoys playing basketball, farming and making maple syrup.



stiffening), but over a much shorter timespan (Hedge et al., 2022). Importantly, there are limited data currently available with respect to bed rest-associated cardiac effects in older adults. Conversely, exercise training imparts beneficial effects on heart size and function (Arbab-Zadeh et al., 2014), and can be used to counteract the deleterious effects of inactivity during bed rest (Hastings et al., 2012; Shibata et al., 2010) or spaceflight (Fu et al., 2019; Shibata et al., 2023). Life-long endurance exercise training also clearly attenuates age-associated increases in left ventricular stiffness (Bhella et al., 2014).

The aim of this review is to draw attention to the plasticity of the heart in response to changes in physical activity, with specific focus on how the heart remodels and how cardiac function changes following prolonged bed rest, endurance exercise training and spaceflight, as well as how these situations may interact with advancing age (Fig. 2). Additionally, we discuss important knowledge gaps related to cardiac remodelling and changes in function and propose areas of interest for future research.

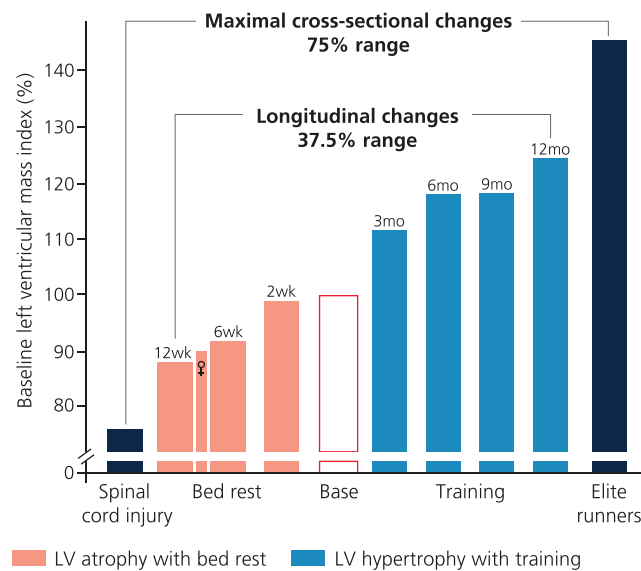


Figure 1. Comparison of left ventricular (LV) mass index relative to a healthy, untrained adult (white bar)
 Cross-sectional comparisons between adults with spinal cord injury (de Groot et al., 2006) and elite runners (Milliken et al., 1988) reveal an adaptive range for left ventricular mass index of ~75%. Longitudinal changes in mass index are also presented following 2, 6 and 12 weeks of bed rest (peach bars) (Perhonen, Franco, et al., 2001), and at 3 month intervals during 1 year of endurance exercise training in previously sedentary adults (blue bars) (Arbab-Zadeh et al., 2014). Comparable reductions in left ventricular mass index to men were observed in women following 60 days of bed rest (peach bar with ♀) (Dorfman et al., 2007).

Bed rest. It has been almost six decades since completion of a foundational investigation in the field of cardiovascular physiology: The Dallas Bed Rest and Training Study (Saltin et al., 1968), where large reductions in cardiorespiratory fitness and cardiac stroke volume were observed after bed rest, but were recovered with exercise training. This first demonstration of detrimental effects of inactivity altered clinical practice for the treatment of many acute and chronic health conditions. For example, standard treatment for myocardial infarction prior to the 1960s was absolute bed rest for several weeks, with few patients ever returning to normal physical activity levels out of fear of cardiac rupture and fatal complications (Braunwald, 2012). In the decades following the study, exercise training became widely recognized as a safe and essential part of cardiac care (Anderson et al., 2013; O’Gara et al., 2013), and its findings have inspired many investigations aimed at understanding the adaptability of the cardiovascular system in response to inactivity and exercise, with many experiments focusing on functional and morphological changes of the heart.

Hallmarks of bed rest-associated cardiac deconditioning are reduced left ventricular end-diastolic volume, reduced cardiac mass, increased ventricular

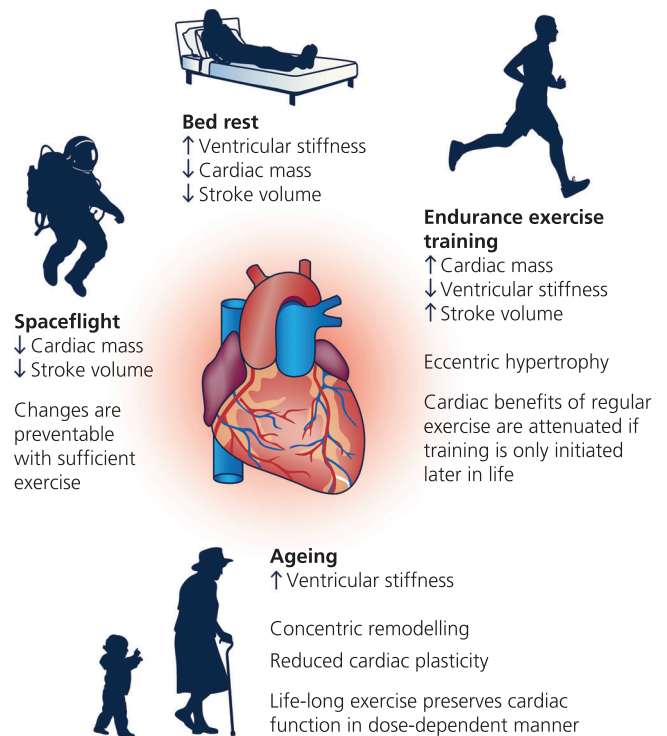


Figure 2. Summary of cardiac adaptations to bed rest, endurance exercise training, spaceflight and ageing

stiffness and, consequently, reduced stroke volume (Arbeille et al., 2001; Dorfman et al., 2007; Kozáková et al., 2011; Levine et al., 1997; Perhonen, Franco, et al., 2001; Westby et al., 2016); however, the time course of change for each of these cardiac properties is not uniform. Left ventricular end-diastolic volume decreased by 14% within the first 2 weeks of 12 weeks of sedentary bed rest, and was only reduced by an additional 8% in the following 10 weeks (Perhonen, Franco, et al., 2001), indicating that much of the early reduction in left ventricular end-diastolic volume occurred secondary to plasma volume losses due to a rapid diuresis following the onset of bed rest (Johansen et al., 1997). Conversely, left ventricular mass appears to decay relatively linearly over the course of prolonged bed rest at a rate of $\sim 1\%$ per week (Dorfman et al., 2007; Perhonen, Franco, et al., 2001; Westby et al., 2016), with no indication of a plateau in at least the first 12 weeks (Perhonen, Franco, et al., 2001). Performance of sufficient exercise while in bed can prevent the reduction in cardiac mass and increase in ventricular stiffness from occurring despite otherwise being sedentary during the bed rest period (Hastings et al., 2012; Shibata et al., 2010). This ability to offset the physiological consequences of extreme physical inactivity runs counter to suggestions that prolonged sedentary behaviours such as sitting may alter cardiovascular outcomes independent of exercise training (Madden et al., 2021). Recent population studies confirm that exercise training of sufficient dose is indeed sufficient to offset prolonged inactivity (Gao et al., 2024).

The independent effects of plasma volume status and cardiac remodelling on heart function were disentangled

by comparing changes in Starling and pressure–volume curves following 15 days of HDBR to those measured following acute plasma volume depletion with furosemide to a similar level as the bed rest condition (Fig. 3) (Perhonen, Zuckerman, et al., 2001). Despite both bed rest and acute hypovolaemia causing reductions in stroke volume, the changes for a given cardiac filling pressure were exacerbated in the bed rest condition. Bed rest induced a leftward shift in the pressure–volume curve and decreased the equilibrium volume of the left ventricle (i.e. volume of the ventricle when filling pressure is 0 mmHg), which was not observed with acute hypovolaemia, indicating that inactivity made the heart less distensible and further compromised ventricular filling beyond the simple plasma volume-linked reduction in venous return (Perhonen, Zuckerman, et al., 2001). Impaired ventricular filling after bed rest is supported by measures of slower diastolic untwisting rates following HDBR, suggestive of reduced diastolic suction (Dorfman et al., 2008). It is noteworthy that exercise countermeasures that prevent cardiac atrophy and stiffening during bed rest are able to preserve cardiorespiratory fitness, but are ineffective at maintaining orthostatic tolerance without being combined with a volume loading countermeasure to combat post-bed rest hypovolaemia (Hastings et al., 2012; Shibata et al., 2010). Importantly, volume loading without countermeasure exercise is not able to protect cardiorespiratory fitness (Shibata et al., 2010), nor orthostatic tolerance following bed rest (Hastings et al., 2012; Shibata et al., 2010), indicating independent and interactive effects of cardiac remodelling and filling pressures on functional cardiovascular outcomes.

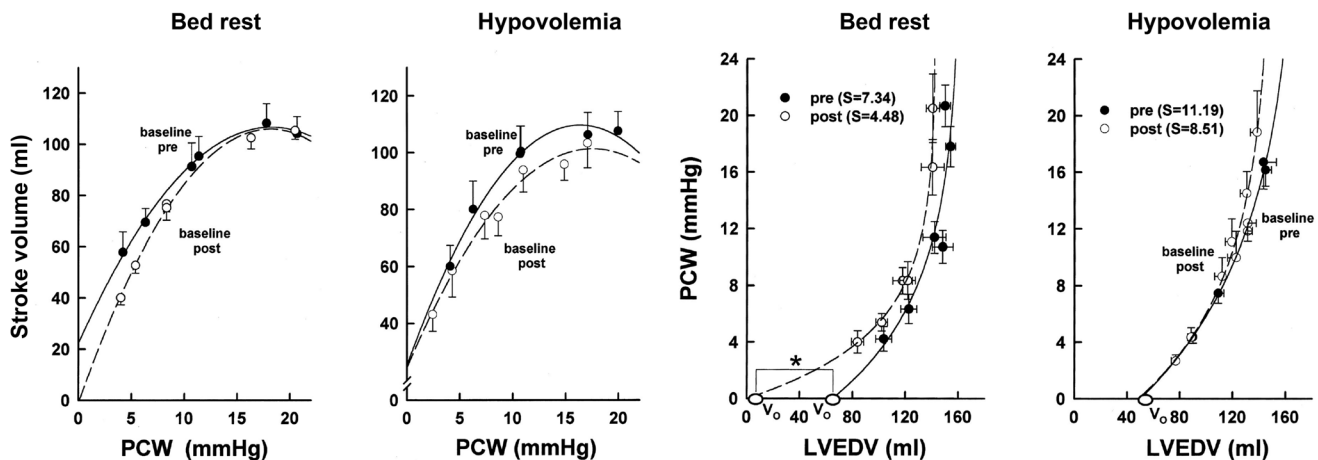


Figure 3. Comparison of Starling (left) and pressure–volume curves (right) before and after 15 days of head-down bed rest or acute hypovolaemia

Reductions in stroke volume for a given filling pressure were exacerbated with bed rest compared to hypovolaemia, and a leftward shift in the pressure–volume relationship with a reduction in the equilibrium volume was only observed following bed rest. LVEDV, left ventricular end-diastolic volume; PCW, pulmonary capillary wedge pressure; S, stiffness constant that describes the shape of the curve; V_0 , equilibrium volume (i.e., the left ventricular volume when filling pressure is 0 mmHg). Reproduced with permission from Perhonen, Zuckerman, et al. (2001).

The magnitude of cardiac remodelling induced by sedentary bed rest appears to be independent of sex, at least for young healthy individuals. The rate of cardiac atrophy observed in women following 60 days of HDBR (Dorfman et al., 2007) was comparable to those measured in men over 42 and 84 days of bed rest (Perhonen, Franco, et al., 2001). This conclusion is also supported by Westby et al. (2016), who found similar reductions in left ventricular mass for men and women in a mixed cohort (four men, three women) following 60 days of HDBR. That being said, the amount of data currently available to support the conclusion that sex does not influence cardiac remodelling following severe inactivity is rather limited and could be strengthened by the inclusion of more female participants in future bed rest studies where cardiac-based outcomes are assessed.

Endurance exercise training. Endurance exercise training is a potent stimulus for cardiac remodelling (Martinez et al., 2021), with changes occurring in proportion to the training impulse (Arbab-Zadeh et al., 2014). Highly trained endurance athletes present with larger, more compliant hearts and operate on a steeper Starling curve than untrained individuals, leading to larger stroke volumes (Levine et al., 1991). However, cardiac adaptations to endurance exercise rapidly regress (though not completely) with cessation of training (Ehsani et al., 1978), and even trained competitive athletes experience variation in cardiac adaptation during the competition season (Baggish et al., 2008).

Cardiac adaptations to endurance exercise training occur on a continuum based on training status, with responses differing between previously sedentary individuals who are first starting to exercise regularly (Arbab-Zadeh et al., 2014), trained individuals over the course of a competitive season/off-season (Weiner et al., 2015) and elite athletes over their competitive careers (Nybo et al., 2014; Pelliccia et al., 2010). One year of progressive exercise training in previously sedentary young adults increased right and left ventricular mass, end-diastolic volume and stroke volume, as well as improved left ventricular compliance (Arbab-Zadeh et al., 2014). Interestingly, the right and left sides of the heart followed different pathways of adaptation to endurance training over time, with the right heart presenting with balanced increases in mass and volume throughout training, whereas the left heart presented with concentric hypertrophy (i.e. wall thickening) first followed by eccentric hypertrophy (i.e. chamber volume expansion) second to restore the mass–volume ratio to pre-training levels (Arbab-Zadeh et al., 2014). The different patterns of remodelling demonstrate how the left and right sides of the heart can experience different pressure and volume stresses driving adaptation during exercise training. The

pattern of concentric followed by eccentric hypertrophy in response to endurance training in previously sedentary adults (Arbab-Zadeh et al., 2014) contrasts with reported initial eccentric remodelling followed by eccentric hypertrophy in the 36 months following initiation of a varsity rowing training programme in already-trained competitive athletes (Weiner et al., 2015). Notably, cardiac characteristics of the varsity rowers at the beginning of their training programme (Weiner et al., 2015) were approximately similar to the cardiac characteristics of the previously sedentary adults following 1 year of training (Arbab-Zadeh et al., 2014). The great disparity in the process of how the heart remodels in response to these two endurance exercise training programmes for initially sedentary *versus* athletic populations raises important questions about how the pathway to increasing ventricle chamber size and mass differs based on the cardiac characteristics prior to initiation of endurance training. The concept of a continuum of cardiac remodelling in response to endurance exercise training based on initial training status is reinforced by data collected from world-class endurance athletes who trained uninterrupted for years, and presented with no significant changes in left ventricular mass or end-diastolic volume across multiple Olympic cycles (Pelliccia et al., 2010). Another important factor to consider when evaluating how the heart remodels in response to endurance training is the type of exercise being performed. For example, the Valsalva-like manoeuvre that is performed with the catch of each rowing stroke creates large fluctuations with higher peaks in arterial and central venous pressures than other aerobic exercise modalities, such as running or cycling (Clifford et al., 1994), imparting different pressure and volume stresses on the heart to drive adaptation.

Despite progressive endurance exercise training increasing cardiac mass of previously sedentary young adults (Arbab-Zadeh et al., 2014) to levels close to those seen in endurance athletes (Milliken et al., 1988; Riley-Hagan et al., 1992), the improvements in ventricular compliance with training did not approach the level of compliance observed in elite endurance athletes (Levine et al., 1991). This observation suggests that left ventricular filling may have been limited by the pericardium and that further improvements in ventricular compliance may take several years of intense training to occur, or that there may be important interactions between cardiac plasticity and training during critical periods of growth and development (Arbab-Zadeh et al., 2014) or limits imposed by biological variation and heritability (Sarzynski et al., 2017). When comparing cardiovascular adaptations following an exercise training programme to levels attained by endurance athletes, it is also critical to consider that the exercise training stimuli (i.e. exercise dose and duration) delivered in most interventional training studies of previously sedentary individuals are

rather modest in comparison to the decades of high-level training performed by athletes often since childhood.

Investigating the role of cardiac plasticity on between-person differences in cardiorespiratory fitness trainability may be particularly useful in building on the work of Montero & Lundby (2017), who demonstrated that a wide range of training responses are observed for a given dose of exercise. Determining the independent effects of baseline left ventricular stiffness and its magnitude of change with endurance exercise training, as well as the degree of eccentric hypertrophy observed with training, could be particularly useful in explaining inter-individual variation in improvements in maximal stroke volume – the key limiting factor for maximal oxygen uptake in healthy trained humans (Levine, 2008; Sutton, 1992).

Spaceflight. The microgravity environment of spaceflight uniquely modifies the daily challenges to the cardiovascular system. The absence of the normal head-to-foot gravitational gradient removes the arterial pressure differential along the body. Brachial arterial blood pressure was unchanged from resting pre-flight supine or seated values in some reports (Hughson et al., 2017; Marshall-Goebel et al., 2019), while other investigations noted reductions in systolic (Fu et al., 2019) or diastolic pressure (Norsk, 2020). Without gravitational loading, the venous blood volume is redistributed toward the central circulation triggering reflex mechanisms to reduce total blood volume (Diedrich et al., 2007). Unexpectedly with the greater central blood volume, there is a reduction in central venous pressure (Buckey et al., 1996). This latter observation, made by direct measurements during launch and microgravity entry, was explained by the unloading of the organs around the vascular system and heart resulting in an increased transmural pressure gradient that increases cardiac filling and stroke volume when referenced to upright seated posture (Hughson et al., 2017; Norsk et al., 2015). This removal of external constraint (by the lungs, pericardium and chest wall) also acutely changes left ventricle chamber pressure–volume relations, which is the only mechanism by which there can be both a decrease in pressure referenced to the atmosphere, but an increase in left ventricle chamber volume (Fig. 4). Drastically reduced physical demands of normal daily tasks while in space compared to Earth (Fraser et al., 2012) could also result in dramatic cardiovascular deconditioning.

Early short-duration spaceflights were characterized by busy task schedules with little opportunity for formal exercise sessions. As a result, the heart quickly adapted to the lower cardiac workload and astronauts returned to Earth with reduced left ventricular end-diastolic volume (Bungo et al., 1987) and mass (Perhonen, Franco,

et al., 2001). Comparisons of changes in heart function of astronauts from early shorter and longer duration spaceflight missions revealed that the magnitude of change in cardiac function was linked to mission duration (Martin et al., 2002). However, recent evidence from long-duration spaceflight astronauts suggests that with the inclusion of more effective exercise countermeasures in-flight, left and right ventricular masses are maintained following ~6 months in space (Shibata et al., 2023). Amongst the more recent cohort of astronauts, strong relationships were found between relative changes in left ventricular mass and estimated daily total cardiac output and work (Shibata et al., 2023), reinforcing that exercising is essential to maintain heart mass while living and working in microgravity. Furthermore, preservation of cardiac mass and function after spaceflight could contribute to improved orthostatic tolerance once back on Earth in more recent astronauts when combined with a fluid loading countermeasure (Fu et al., 2019); however, orthostatic hypotension was still experienced during a 3 min stand test by some astronauts after spaceflight (Wood et al., 2019).

Although effective exercise countermeasures during spaceflight prevent ventricular remodelling, and associated changes in cardiac mass, left and right ventricular end-diastolic volumes, and stroke volume (Shibata et al., 2023), it did not prevent changes in left atrial structure and electrophysiology (Khine et al., 2018).

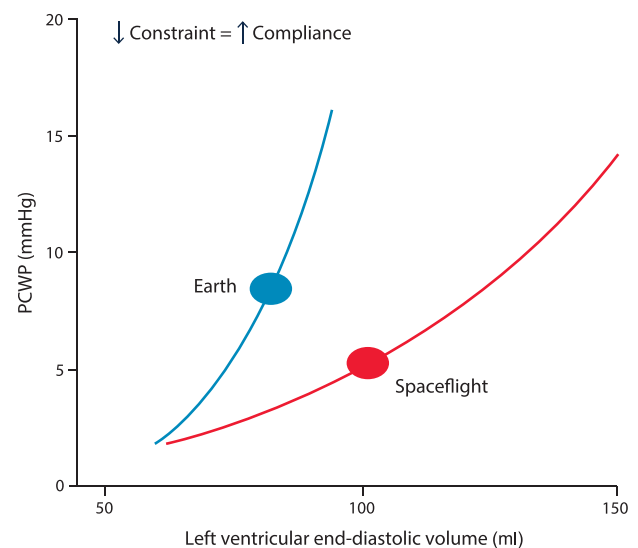


Figure 4. Conceptual illustration depicting how the left ventricular pressure–volume relationship changes from being on Earth (blue) to in space (red)

Removal of external constraint from around the heart in microgravity increases left ventricular filling despite the filling pressure being reduced. PCWP, pulmonary capillary wedge pressure.

Left, but not right, atrial size was increased after 6 months of spaceflight, which on Earth would be considered a risk factor for developing atrial fibrillation (Psaty et al., 1997). Importantly, the left atrium did return back to its pre-flight size within several weeks of returning to Earth, and no astronauts were reported to develop atrial fibrillation during nor immediately after long-duration spaceflight (Khine et al., 2018). Nevertheless, more continuous monitoring of cardiac electrophysiology for prolonged periods throughout and following future long-duration spaceflight missions may be necessary to detect any potential clinically relevant consequences of these changes in atrial size and function.

Looking to the future of space travel, humans are preparing to return to the Moon and conduct extended missions beyond low-Earth orbit with plans to colonize Mars. As humans explore beyond the Van Alan Belt that partially protects astronauts on the International Space Station, they will lose the shielding against protons and high-energy heavy ion radiation and experience greater levels of galactic cosmic radiation. It is estimated that the radiation dose to humans will increase over 300-fold beyond low-Earth orbit leading to increased risk of radiation-induced cardiovascular disease (Hughson et al., 2018). The effects of radiation could be expected to manifest as valvular heart disease, cardiomyopathy, conduction abnormalities, pericarditis and coronary artery disease with a marked increase in oxidative stress (Hughson et al., 2018). Concerns about oxidative stress as a trigger for cardiovascular disease (Lee et al., 2020) and recent observations of increased arterial stiffness in astronauts returning from the International Space Station (Baevsky et al., 2007; Hughson et al., 2016) suggest a need for enhanced monitoring during and following spaceflight missions as humans explore beyond Earth.

Ageing. Cardiac remodelling occurs with advancing age, especially in the absence of performing lifelong aerobic exercise. Sedentary older adults have a less compliant left ventricle than sedentary younger adults, which impairs diastolic filling (Arbab-Zadeh et al., 2004). Left ventricular hypertrophy is also often reported with ageing, which is further exacerbated by hypertension, while stroke volume is maintained (Lakatta & Levy, 2003); however, others have reported modest cardiac atrophy relative to body size and decreased stroke volume of sedentary older adults compared to younger adults (Arbab-Zadeh et al., 2004; Cheng et al., 2009). Importantly, concentric remodelling of the heart is linked to age-associated increases in arterial stiffness and afterload (Ohyama et al., 2016), highlighting the importance of maintaining vascular health for healthy heart function.

The timing of cardiac remodelling and stiffening appears to happen in the transition period from youth to middle-age (Fujimoto, Hastings, et al., 2012). Increased

left ventricular stiffness compared to young healthy adults was most apparent in those >50 years, with an intermediate phenotype observed in early-middle age (Fujimoto, Hastings, et al., 2012). Left ventricular stiffening is followed by concentric remodelling and a substantial leftward shift in the pressure-volume relationship, especially for those older than 65 years (Fujimoto, Hastings, et al., 2012). Mechanisms underlying the age-associated cardiac stiffening and impaired diastolic function include: cardiac myocyte hypertrophy with a reduction in overall cardiac myocyte number, and increased collagen deposition with non-enzymatic cross-linking (Lakatta & Levy, 2003).

The plasticity of the heart is reduced with increasing age. Unlike with young healthy individuals, where left ventricular compliance was improved with exercise training (Arbab-Zadeh et al., 2014), 1 year of progressive aerobic exercise training was unable to reverse the cardiac stiffening of healthy sedentary older adults (>65 years) (Fujimoto et al., 2010) or those with heart failure with preserved ejection fraction (Fujimoto, Prasad, et al., 2012). Despite exercise training being unable to improve left ventricular compliance of older adults, it still conferred cardiovascular benefits, such as increasing cardiac mass (+10%) and arterial compliance (+24%), and improving cardiorespiratory fitness (+19%) (Fujimoto et al., 2010). However, the reduced cardiac plasticity of older adults attenuates the cardiorespiratory fitness improvements from aerobic exercise training compared to fitness-matched young adults, as older adults have smaller increases in peak cardiac output (Wang et al., 2014).

In order to combat the myocardial stiffening associated with sedentary ageing, exercise training must be started, at the latest, in middle age before irreversible modifications occur. Two years of consistent aerobic exercise training (30 min per day for 4–5 days per week) in previously sedentary 45- to 64-year-old adults was able to shift the pressure-volume curve to the right, reduce left ventricular stiffness and increase left ventricular end-diastolic volume, while still conferring similar benefits as exercise training for older adults [e.g. cardiorespiratory fitness (+18%) and arterial compliance (+21%)] (Howden et al., 2018). Similar improvements in fitness and cardiovascular structure can occur during this 'sweet spot' in cardiovascular ageing, even in the face of cardiovascular risk factors that increase the risk for diseases such as heart failure with preserved ejection fraction (Hearon et al., 2022; Hieda et al., 2021). Nevertheless, lifelong exercise training can prevent this age-associated remodelling of the heart and maintain a compliant left ventricle in both men and women (Arbab-Zadeh et al., 2004; Carrick-Ranson et al., 2020). In fact, Master's endurance athletes present with similar left ventricular masses, stroke volumes and left ventricular stiffness indices as

young healthy adults (Fig. 5) (Arbab-Zadeh et al., 2004). However, the benefits of performing life-long exercise on left ventricular stiffness are dose-dependent, such that low doses of ‘casual’ exercise throughout life provide no benefit (Bhella et al., 2014)

Given that natural sedentary ageing already leads to cardiac remodelling and that older adults demonstrate reduced cardiac plasticity to exercise training compared to younger individuals, there are considerable concerns related to the acute and potentially chronic effects induced by periods of severe inactivity or immobility (e.g. bed rest or prolonged hospital in-patient stay) on older adults. Limited longitudinal data exist with regard to cardiac atrophy during hospitalization or bed rest; however, a 7% reduction in left ventricular mass was reported in older patients (61 ± 19 years) who were admitted into an intensive care unit for a median of 11 days (Kumaresan et al., 2022), suggestive of a rapid decline in cardiac mass while confined to bed.

Recently, there has been an increased interest in understanding the cardiovascular implications of bed rest and weightlessness in late-middle-aged and older adults (Limper et al., 2021). Bed rest studies ranging from 10 to 14 days with older participants have revealed marked functional cardiovascular deconditioning following bed rest (e.g. reduced peak oxygen uptake, orthostatic intolerance) (Hedge et al., 2023; Kortebein et al., 2008; Mastrandrea et al., 2023; Pišot et al., 2016), with the limited number of published studies suggesting that

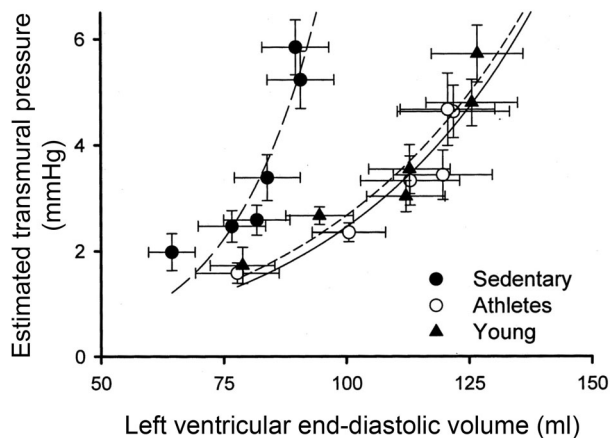


Figure 5. Comparison of pressure–volume curves from young adults (black triangle), older sedentary adults (black circle) and Master’s athletes (white circle)

Older sedentary adults have a leftward shift and a steeper curve than young adults and older adults who performed lifelong endurance exercise training, reflecting their increased left ventricular stiffness and reduced diastolic function. Importantly, Master’s athletes’ pressure–volume curves were superimposable with those of younger adults, demonstrating the benefits of exercise for maintaining ventricular compliance throughout the lifespan. Reproduced with permission from Arbab-Zadeh et al. (2004).

cardiovascular effects of bed rest in older adults may be exacerbated compared to younger participants. Importantly, there are still significant knowledge gaps, as the effects of bed rest on cardiac compliance or stiffness, chamber mass, dimensions and electrophysiology of older adults are largely unknown.

A report of two late-middle-aged men presenting with atrial fibrillation in the days immediately following 2 weeks of sedentary HDBR with unknown causality (Haji-Boutros et al., 2023) reinforces the need to improve our understanding of how the older heart responds to fluid shifts and periods of severe inactivity. The observation of atrial fibrillation following bed rest is notable, as individuals with low levels of physical activity were at 19% higher risk of developing atrial fibrillation later in life than those who were moderately active (Morseth et al., 2016). Determining how much and how rapidly the hearts of older adults remodel and atrophy during bed rest, and how these cardiac properties recover following bed rest, may enhance our understanding of older adult-specific mechanisms of cardiovascular deconditioning and plasticity. Given that sedentary ageing leads to a stiffer left ventricle that cannot be improved with exercise training in older adults, and that bed rest induces ventricular stiffening in younger adults, it will be particularly insightful to determine if potential stiffening of the left ventricle of older adults during prolonged bed rest is reversible.

Clinical implications. In a clinical context, periods of bed rest or inactivity following illness and hospitalization, surgery, or during transitions in care can be very problematic for cardiac health. The acute insult of bed rest can be further exacerbated by reduced physical activity levels upon returning to daily living (Kortebein et al., 2008), potentially initiating a spiral decline in health (Venturelli et al., 2012). Rapid reductions in cardiac mass occur during hospitalization (Kumaresan et al., 2022) and manifest functionally as large reductions in cardio-respiratory fitness upon discharge (Jensen et al., 2011). Given that most inpatients in hospital spend greater than 90% of their time being sedentary in bed – even if they can walk unassisted (Baldwin et al., 2017) – it is not surprising that cardiac atrophy and large reductions in fitness are observed. The hospitalization-associated reduction in fitness can be particularly concerning for older individuals when superimposed upon the age-related reduction in fitness (Fleg et al., 2005). Critically, these reductions in fitness may combine to push some individuals to the threshold of being able to live independently (Shephard, 2009), and highlights the importance of ‘pre-habilitation’ exercise training to minimize post-surgery complications and mortality (Ross et al., 2016). Accordingly, interventions aimed

at performing physical activity during inpatient stays (Martínez-Velilla et al., 2019), and rehabilitation exercises – especially for individuals with heart failure (Bozkurt et al., 2021) – should be part of standard care in order to minimize the effects of inactivity in the clinical setting.

Conclusions

Many research studies aimed at understanding the plasticity of the heart have been completed since the seminal Dallas Bed Rest and Training Study (Mitchell et al., 2019). The heart has an enormous adaptive range that can be manipulated by inactivity, exercise and environmental stimuli such as spaceflight. Severe inactivity, including that associated with ageing, causes cardiac atrophy and ventricular stiffening, while endurance exercise training leads to beneficial cardiac adaptations, such as eccentric hypertrophy and improved ventricular compliance. However, the heart becomes less plastic with advancing age and exercise training is less effective at improving ventricular compliance and diastolic function, highlighting the importance of performing habitual endurance exercise throughout life in order to maintain heart health. Despite this extensive research base, there are a few important questions that should be considered in future research:

- (1) Do men and women respond similarly, especially during ageing (Carrick-Ranson et al., 2023)? This question highlights the scarcity of invasive measures of cardiac function in women, as well as the exclusion of women in many past bed rest studies.
- (2) What factors influence cardiac plasticity besides or in conjunction with physical activity (heritability, age, etc.), and do between-person differences in baseline left ventricular function and plasticity lead to heterogeneous cardiorespiratory training and deconditioning responses?
- (3) Do hearts of older adults atrophy and stiffen more than younger individuals' hearts during prolonged inactivity or bed rest, and are they less resilient upon resuming normal daily life? This question is relevant for understanding long-term cardiac consequences of prolonged hospitalization or immobility, which are more likely to be experienced by older adults.
- (4) Does space travel by astronauts beyond low-Earth orbit affect heart plasticity and function later in life? Although exercise of adequate intensity and duration during spaceflight on the International Space Station maintains cardiac mass and function (Shibata et al., 2023), space missions beyond low-Earth orbit will have new challenges affecting the heart. Future exercise programmes for exploration missions will be limited by availability of exercise devices as

well as requirements for supplying nutrients and water to complete the volume and intensity of exercise prescribed for cardiac health. An unknown challenge to cardiovascular health will come from the oxidative stress and cellular damage caused by greater exposure to galactic cosmic radiation (Hughson et al., 2018). Extensive investigations will be required to establish exercise, dietary manipulations, nutraceutical regimes and appropriate radiation shielding to keep astronauts' cardiovascular systems healthy.

Future studies answering these questions will provide important new insights into how cardiac function changes with inactivity, exercise, ageing and spaceflight, and enhance our understanding of the factors influencing cardiac plasticity.

References

- Anderson, J. L., Adams, C. D., Antman, E. M., Bridges, C. R., Califf, R. M., Casey, D. E., Chavey, W. E., Fesmire, F. M., Hochman, J. S., Levin, T. N., Lincoff, A. M., Peterson, E. D., Theroux, P., Wenger, N. K., & Wright, R. S. (2013). 2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology*, **61**(23), e179–e347.
- Arbab-Zadeh, A., Dijk, E., Prasad, A., Fu, Q., Torres, P., Zhang, R., Thomas, J. D., Palmer, D., & Levine, B. D. (2004). Effect of aging and physical activity on left ventricular compliance. *Circulation*, **110**(13), 1799–1805.
- Arbab-Zadeh, A., Perhonen, M., Howden, E., Peshock, R. M., Zhang, R., Adams-Huet, B., Haykowsky, M. J., & Levine, B. D. (2014). Cardiac remodeling in response to 1 year of intensive endurance training. *Circulation*, **130**(24), 2152–2161.
- Arbeille, P., Fomina, G., Roumy, J., Alferova, I., Tobal, N., & Herault, S. (2001). Adaptation of the left heart, cerebral and femoral arteries, and jugular and femoral veins during short- and long-term head-down tilt and spaceflights. *European Journal of Applied Physiology*, **86**(2), 157–168.
- Baevsky, R. M., Baranov, V. M., Funtova, I. I., Diedrich, A., Pashenko, A. V., Chernikova, A. G., Drescher, J., Jordan, J., & Tank, J. (2007). Autonomic cardiovascular and respiratory control during prolonged spaceflights aboard the International Space Station. *Journal of Applied Physiology*, **103**(1), 156–161.
- Baggish, A. L., Wang, F., Weiner, R. B., Elinoff, J. M., Tournoux, F., Boland, A., Picard, M. H., Hutter, A. M., & Wood, M. J. (2008). Training-specific changes in cardiac structure and function: A prospective and longitudinal assessment of competitive athletes. *Journal of Applied Physiology*, **104**(4), 1121–1128.

- Baldwin, C., van Kessel, G., Phillips, A., & Johnston, K. (2017). Accelerometry shows inpatients with acute medical or surgical conditions spend little time upright and are highly sedentary: Systematic review. *Physical Therapy*, **97**(11), 1044–1065.
- Bhella, P. S., Hastings, J. L., Fujimoto, N., Shibata, S., Carrick-Ranson, G., Palmer, M. D., Boyd, K. N., Adams-Huet, B., & Levine, B. D. (2014). Impact of life-long exercise “dose” on left ventricular compliance and distensibility. *Journal of the American College of Cardiology*, **64**(12), 1257–1266.
- Bozkurt, B., Fonarow, G. C., Goldberg, L. R., Guglin, M., Josephson, R. A., Forman, D. E., Lin, G., Lindenfeld, J. A., O'Connor, C., Panjath, G., Piña, I. L., Shah, T., Sinha, S. S., & Wolfel, E. (2021). Cardiac rehabilitation for patients with heart failure: JACC expert panel. *Journal of the American College of Cardiology*, **77**(11), 1454–1469.
- Braunwald, E. (2012). The treatment of acute myocardial infarction: The past, the present, and the future. *European Heart Journal-Acute Cardiovascular Care*, **1**(1), 9–12.
- Buckey, J. C., Gaffney, F. A., Lane, L. D., Levine, B. D., Watenpugh, D. E., Wright, S. J., Yancy, C. W., Meyer, D. M., & Blomqvist, C. G. (1996). Central venous pressure in space. *Journal of Applied Physiology*, **81**(1), 19–25.
- Bungo, M. W., Goldwater, D. J., Popp, R. L., & Sandler, H. (1987). Echocardiographic evaluation of space shuttle crewmembers. *Journal of Applied Physiology*, **62**(1), 278–283.
- Carrick-Ranson, G., Howden, E. J., Brazile, T. L., Levine, B. D., & Reading, S. A. (2023). Effects of aging and endurance exercise training on cardiorespiratory fitness and cardiac structure and function in healthy midlife and older women. *Journal of Applied Physiology*, **135**(6), 1215–1235.
- Carrick-Ranson, G., Sloane, N. M., Howden, E. J., Bhella, P. S., Sarma, S., Shibata, S., Fujimoto, N., Hastings, J. L., & Levine, B. D. (2020). The effect of lifelong endurance exercise on cardiovascular structure and exercise function in women. *The Journal of Physiology*, **598**(13), 2589–2605.
- Cheng, S., Fernandes, V. R. S., Bluemke, D. A., McClelland, R. L., Kronmal, R. A., & Lima, J. A. C. (2009). Age-related left ventricular remodeling and associated risk for cardiovascular outcomes: The Multi-Ethnic Study of Atherosclerosis. *Circulation: Cardiovascular Imaging*, **2**(3), 191–198.
- Clifford, P. S., Hanel, B., & Secher, N. H. (1994). Arterial blood pressure response to rowing. *Medicine and Science in Sports and Exercise*, **26**(6), 715–719.
- de Groot, P. C., van Dijk, A., Dijk, E., & Hopman, M. T. (2006). Preserved cardiac function after chronic spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, **87**(9), 1195–1200.
- Diedrich, A., Paranjape, S. Y., & Robertson, D. (2007). Plasma and blood volume in space. *American Journal of the Medical Sciences*, **334**(1), 80–86.
- Dorfman, T. A., Levine, B. D., Tillery, T., Peshock, R. M., Hastings, J. L., Schneider, S. M., Macias, B. R., Biolo, G., & Hargens, A. R. (2007). Cardiac atrophy in women following bed rest. *Journal of Applied Physiology*, **103**(1), 8–16.
- Dorfman, T. A., Rosen, B. D., Perhonen, M. A., Tillery, T., McColl, R., Peshock, R. M., & Levine, B. D. (2008). Diastolic suction is impaired by bed rest: MRI tagging studies of diastolic untwisting. *Journal of Applied Physiology*, **104**(4), 1037–1044.
- Ehsani, A. A., Hagberg, J. M., & Hickson, R. C. (1978). Rapid changes in left ventricular dimensions and mass in response to physical conditioning and deconditioning. *American Journal of Cardiology*, **42**(1), 52–56.
- Fleg, J. L., Morrell, C. H., Bos, A. G., Brant, L. J., Talbot, L. A., Wright, J. G., & Lakatta, E. G. (2005). Accelerated longitudinal decline of aerobic capacity in healthy older adults. *Circulation*, **112**(5), 674–682.
- Fraser, K. S., Greaves, D. K., Shoemaker, J. K., Blaber, A. P., & Hughson, R. L. (2012). Heart rate and daily physical activity with long-duration habitation of the International Space Station. *Aviation Space and Environmental Medicine*, **83**(6), 577–584.
- Fu, Q., Shibata, S., Hastings, J. L., Platts, S. H., Hamilton, D. M., Bungo, M. W., Stenger, M. B., Ribeiro, C., Adams-Huet, B., & Levine, B. D. (2019). Impact of prolonged spaceflight on orthostatic tolerance during ambulation and blood pressure profiles in astronauts. *Circulation*, **140**(9), 729–738.
- Fujimoto, N., Hastings, J. L., Bhella, P. S., Shibata, S., Gandhi, N. K., Carrick-Ranson, G., Palmer, D., & Levine, B. D. (2012). Effect of ageing on left ventricular compliance and distensibility in healthy sedentary humans. *The Journal of Physiology*, **590**(8), 1871–1880.
- Fujimoto, N., Prasad, A., Hastings, J. L., Arbab-Zadeh, A., Bhella, P. S., Shibata, S., Palmer, D., & Levine, B. D. (2010). Cardiovascular effects of 1 year of progressive and vigorous exercise training in previously sedentary individuals older than 65 years of age. *Circulation*, **122**(18), 1797–1805.
- Fujimoto, N., Prasad, A., Hastings, J. L., Bhella, P. S., Shibata, S., Palmer, D., & Levine, B. D. (2012). Cardiovascular effects of 1 year of progressive endurance exercise training in patients with heart failure with preserved ejection fraction. *American Heart Journal*, **164**(6), 869–877.
- Gao, W., Sanna, M., Chen, Y.-H., Tsai, M.-K., & Wen, C.-P. (2024). Occupational sitting time, leisure physical activity, and all-cause and cardiovascular disease mortality. *Journal of The American Medical Association Network Open*, **7**(1), e2350680.
- Hajj-Boutros, G., Sonjak, V., Hedge, E. T., Mastrandrea, C., Lagacé, J.-C., St-Martin, P., Divsalar, D. N., Sadeghian, F., Chevalier, S., Liu-Ambrose, T., Blaber, A. P., Dionne, I. J., Duchesne, S., Hughson, R., Kontulainen, S., Theou, O., & Morais, J. A. (2023). Impact of 14 days of bed rest in older adults and an exercise countermeasure on body composition, muscle strength, and cardiovascular function: Canadian Space Agency standard measures. *Gerontology*, **69**(11), 1284–1294.
- Hargens, A. R., & Vico, L. (2016). Long-duration bed rest as an analog to microgravity. *Journal of Applied Physiology*, **120**(8), 891–903.

- Hastings, J. L., Krainski, F., Snell, P. G., Pacini, E. L., Jain, M., Bhella, P. S., Shibata, S., Fu, Q., Palmer, M. D., & Levine, B. D. (2012). Effect of rowing ergometry and oral volume loading on cardiovascular structure and function during bed rest. *Journal of Applied Physiology*, **112**(10), 1735–1743.
- Hearon, C. M., Dias, K. A., MacNamara, J. P., Hieda, M., Mantha, Y., Harada, R., Samels, M., Morris, M., Szczepaniak, L. S., Levine, B. D., & Sarma, S. (2022). 1 Year HIIT and omega-3 fatty acids to improve cardio-metabolic risk in stage-A heart failure. *Journal of the American College of Cardiology: Heart Failure*, **10**(4), 238–249.
- Hedge, E. T., Mastrandrea, C. J., & Hughson, R. L. (2023). Loss of cardiorespiratory fitness and its recovery following two weeks of head-down bed rest and the protective effects of exercise in 55- to 65-yr-old adults. *Journal of Applied Physiology*, **134**(4), 1022–1031.
- Hedge, E. T., Patterson, C. A., Mastrandrea, C. J., Sonjak, V., Hajj-Boutros, G., Faust, A., Morais, J. A., & Hughson, R. L. (2022). Implementation of exercise countermeasures during spaceflight and microgravity analogue studies: Developing countermeasure protocols for bedrest in older adults (BROA). *Frontiers in Physiology*, **13**, 928313.
- Hieda, M., Sarma, S., Hearon, C. M., Dias, K. A., Martinez, J., Samels, M., Everding, B., Palmer, D., Livingston, S., Morris, M., Howden, E., & Levine, B. D. (2020). Increased myocardial stiffness in patients with high-risk left ventricular hypertrophy: The hallmark of stage-B heart failure with preserved ejection fraction. *Circulation*, **141**(2), 115–123.
- Hieda, M., Sarma, S., Hearon, C. M., MacNamara, J. P., Dias, K. A., Samels, M., Palmer, D., Livingston, S., Morris, M., & Levine, B. D. (2021). One-year committed exercise training reverses abnormal left ventricular myocardial stiffness in patients with stage B heart failure with preserved ejection fraction. *Circulation*, **144**(12), 934–946.
- Hill, J. A., & Olson, E. N. (2008). Cardiac plasticity. *New England Journal of Medicine*, **358**(13), 1370–1380.
- Howden, E. J., Sarma, S., Lawley, J. S., Opondo, M., Cornwell, W., Stoller, D., Urey, M. A., Adams-Huet, B., & Levine, B. D. (2018). Reversing the cardiac effects of sedentary aging in middle age—a randomized controlled trial: Implications for heart failure prevention. *Circulation*, **137**(15), 1549–1560.
- Hughson, R. L., Helm, A., & Durante, M. (2018). Heart in space: Effect of the extraterrestrial environment on the cardiovascular system. *Nature Reviews Cardiology*, **15**(3), 167–180.
- Hughson, R. L., Peterson, S. D., Yee, N. J., & Greaves, D. K. (2017). Cardiac output by pulse contour analysis does not match the increase measured by rebreathing during human spaceflight. *Journal of Applied Physiology*, **123**(5), 1145–1149.
- Hughson, R. L., Robertson, A. D., Arbeille, P., Shoemaker, J. K., Rush, J. W. E., Fraser, K. S., & Greaves, D. K. (2016). Increased postflight carotid artery stiffness and in-flight insulin resistance resulting from 6-mo spaceflight in male and female astronauts. *American Journal of Physiology-Heart and Circulatory Physiology*, **310**(5), H628–H638.
- Jensen, M. B., Houborg, K. B., Nørager, C. B., Henriksen, M. G., & Laurberg, S. (2011). Postoperative changes in fatigue, physical function and body composition: An analysis of the amalgamated data from five randomized trials on patients undergoing colorectal surgery. *Colorectal Disease: The Official Journal of the Association of Coloproctology of Great Britain and Ireland*, **13**(5), 588–593.
- Johansen, L. B., Gharib, C., Allevard, A. M., Sigauco, D., Christensen, N. J., Drummer, C., & Norsk, P. (1997). Haematocrit, plasma volume and noradrenaline in humans during simulated weightlessness for 42 days. *Clinical Physiology*, **17**(2), 203–210.
- Khine, H. W., Steding-Ehrenborg, K., Hastings, J. L., Kowal, J., Daniels, J. D., Page, R. L., Goldberger, J. J., Ng, J., Adams-Huet, B., Bungo, M. W., & Levine, B. D. (2018). Effects of prolonged spaceflight on atrial size, atrial electrophysiology, and risk of atrial fibrillation. *Circulation: Arrhythmia and Electrophysiology*, **11**(5), e005959.
- Kortebein, P., Symons, T. B., Ferrando, A., Paddon-Jones, D., Ronsen, O., Protas, E., Conger, S., Lombeida, J., Wolfe, R., & Evans, W. J. (2008). Functional impact of 10 days of bed rest in healthy older adults. *The Journals of Gerontology-Series A, Biological Sciences and Medical Sciences*, **63**(10), 1076–1081.
- Kozáková, M., Malshi, E., Morizzo, C., Pedri, S., Santini, F., Biolo, G., Pagani, M., & Palombo, C. (2011). Impact of prolonged cardiac unloading on left ventricular mass and longitudinal myocardial performance: An experimental bed rest study in humans. *Journal of Hypertension*, **29**(1), 137–143.
- Kumaresan, A., Pannu, A., Mueller, A., De Lima, A., Naseem, H., O'Connor, S. P., Valencia, J., Garcia, D., Gosling, A. F., Talmor, D., & Shaefi, S. (2022). Echocardiographic evidence of cardiac atrophy in the critically ill. *Critical Care Explorations*, **4**(11), e0804.
- Lakatta, E. G., & Levy, D. (2003). Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part II: the aging heart in health: links to heart disease. *Circulation*, **107**(2), 346–354.
- Lee, S. M. C., Ribeiro, L. C., Martin, D. S., Zwart, S. R., Feiveson, A. H., Laurie, S. S., Macias, B. R., Crucian, B. E., Krieger, S., Weber, D., Grune, T., Platts, S. H., Smith, S. M., & Stenger, M. B. (2020). Arterial structure and function during and after long-duration spaceflight. *Journal of Applied Physiology*, **129**(1), 108–123.
- Levine, B. D. (2008). VO₂max: What do we know, and what do we still need to know? *The Journal of Physiology*, **586**(1), 25–34.
- Levine, B. D., Lane, L. D., Buckey, J. C., Friedman, D. B., & Blomqvist, C. G. (1991). Left ventricular pressure-volume and Frank-Starling relations in endurance athletes: Implications for orthostatic tolerance and exercise performance. *Circulation*, **84**(3), 1016–1023.
- Levine, B. D., Zuckerman, J. H., & Pawelczyk, J. A. (1997). Cardiac atrophy after bed-rest deconditioning: A non-neural mechanism for orthostatic intolerance. *Circulation*, **96**(2), 517–525.

- Limper, U., Moestl, S., Tank, J., Prisk, G. K., Heusser, K., Hoffmann, F., Gofsmann, A., Migeotte, P.-F., Gauger, P., Beck, L. E. J., Schlegel, H. W., Levine, B. D., & Jordan, J. (2021). A 20-year evolution of cardiac performance in microgravity in a male astronaut. *Clinical Autonomic Research*, **31**(1), 139–141.
- Madden, K. M., Feldman, B., & Chase, J. (2021). Sedentary time and metabolic risk in extremely active older adults. *Diabetes Care*, **44**(1), 194–200.
- Marshall-Goebel, K., Laurie, S. S., Alferova, I. V., Arbeille, P., Auñón-Chancellor, S. M., Ebert, D. J., Lee, S. M. C., Macias, B. R., Martin, D. S., Pattarini, J. M., Ploutz-Snyder, R., Ribeiro, L. C., Tarver, W. J., Dulchavsky, S. A., Hargens, A. R., & Stenger, M. B. (2019). Assessment of jugular venous blood flow stasis and thrombosis during spaceflight. *Journal of The American Medical Association Network Open*, **2**(11), e1915011.
- Martin, D. S., South, D. A., Wood, M. L., Bungo, M. W., & Meck, J. V. (2002). Comparison of echocardiographic changes after short- and long-duration spaceflight. *Aviation Space and Environmental Medicine*, **73**(6), 532–536.
- Martinez, M. W., Kim, J. H., Shah, A. B., Phelan, D., Emery, M. S., Wasfy, M. M., Fernandez, A. B., Bunch, T. J., Dean, P., Danielian, A., Krishnan, S., Baggish, A. L., Eijsvogels, T. M. H., Chung, E. H., & Levine, B. D. (2021). Exercise-induced cardiovascular adaptations and approach to exercise and cardiovascular disease: JACC state-of-the-art review. *Journal of the American College of Cardiology*, **78**(14), 1453–1470.
- Martínez-Velilla, N., Casas-Herrero, A., Zambom-Ferraresi, F., Sáez De Asteasu, M. L., Lucia, A., Galbete, A., García-Baztán, A., Alonso-Renedo, J., González-Glaría, B., Gonzalo-Lázaro, M., Apezteguía Iráizoz, I., Gutiérrez-Valencia, M., Rodríguez-Mañas, L., & Izquierdo, M. (2019). Effect of exercise intervention on functional decline in very elderly patients during acute hospitalization: A randomized clinical trial. *Journal of The American Medical Association Internal Medicine*, **179**(1), 28–36.
- Mastrandrea, C. J., Hedge, E. T., Robertson, A. D., Heckman, G. A., Ho, J., Granados Unger, F., & Hughson, R. L. (2023). High-intensity exercise does not protect against orthostatic intolerance following bedrest in 55- to 65-yr-old men and women. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, **325**(2), R107–R119.
- Milliken, M. C., Stray-Gundersen, J., Peshock, R. M., Katz, J., & Mitchell, J. H. (1988). Left ventricular mass as determined by magnetic resonance imaging in male endurance athletes. *American Journal of Cardiology*, **62**(4), 301–305.
- Mitchell, J. H., Levine, B. D., & McGuire, D. K. (2019). The Dallas bed rest and training study: Revisted after 50 years. *Circulation*, **140**(16), 1293–1295.
- Montero, D., & Lundby, C. (2017). Refuting the myth of non-response to exercise training: ‘Non-responders’ do respond to higher dose of training. *The Journal of Physiology*, **595**(11), 3377–3387.
- Morseth, B., Graff-Iversen, S., Jacobsen, B. K., Jørgensen, L., Nyrnes, A., Thelle, D. S., Vestergaard, P., & Løchen, M.-L. (2016). Physical activity, resting heart rate, and atrial fibrillation: The Tromsø Study. *European Heart Journal*, **37**(29), 2307–2313.
- Norsk, P. (2020). Adaptation of the cardiovascular system to weightlessness: Surprises, paradoxes and implications for deep space missions. *Acta Physiologica*, **228**(3), e13434.
- Norsk, P., Asmar, A., Damgaard, M., & Christensen, N. J. (2015). Fluid shifts, vasodilatation and ambulatory blood pressure reduction during long duration spaceflight. *The Journal of Physiology*, **593**(3), 573–584.
- Nybo, L., Schmidt, J. F., Fritzdorf, S., & Nordsborg, N. B. (2014). Physiological characteristics of an aging olympic athlete. *Medicine and Science in Sports and Exercise*, **46**(11), 2132–2138.
- O’Gara, P. T., Kushner, F. G., Ascheim, D. D., Casey, D. E., Jr., Chung, M. K., de Lemos, J. A., Ettinger, S. M., Fang, J. C., Fesmire, F. M., Franklin, B. A., Granger, C. B., Krumholz, H. M., Linderbaum, J. A., Morrow, D. A., Newby, L. K., Ornato, J. P., Ou, N., Radford, M. J., Tamis-Holland, J. E., ... Zhao, D. X. (2013). 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology*, **61**(4), e78–e140.
- Ohyama, Y., Ambale-Venkatesh, B., Noda, C., Chugh, A. R., Teixido-Tura, G., Kim, J.-Y., Donekal, S., Yoneyama, K., Gjesdal, O., Redheuil, A., Liu, C.-Y., Nakamura, T., Wu, C. O., Hundley, W. G., Bluemke, D. A., & Lima, J. A. C. (2016). Association of aortic stiffness with left ventricular remodeling and reduced left ventricular function measured by magnetic resonance imaging: The Multi-Ethnic Study of Atherosclerosis. *Circulation: Cardiovascular Imaging*, **9**(7), e004426.
- Pelliccia, A., Kinoshita, N., Pisicchio, C., Quattrini, F., DiPaolo, F. M., Ciardo, R., Di Giacinto, B., Guerra, E., De Blasiis, E., Casasco, M., Culasso, F., & Maron, B. J. (2010). Long-term clinical consequences of intense, uninterrupted endurance training in Olympic athletes. *Journal of the American College of Cardiology*, **55**(15), 1619–1625.
- Perhonen, M. A., Franco, F., Lane, L. D., Buckley, J. C., Blomqvist, C. G., Zerwekh, J. E., Peshock, R. M., Weatherall, P. T., & Levine, B. D. (2001). Cardiac atrophy after bed rest and spaceflight. *Journal of Applied Physiology*, **91**(2), 645–653.
- Perhonen, M. A., Zuckerman, J. H., & Levine, B. D. (2001). Deterioration of left ventricular chamber performance after bed rest: “Cardiovascular deconditioning” or “hypovolemia”. *Circulation*, **103**(14), 1851–1857.
- Pišot, R., Marusic, U., Biolo, G., Mazzucco, S., Lazzar, S., Grassi, B., Reggiani, C., Toniolo, L., Di Prampero, P. E., Passaro, A., Narici, M., Mohammed, S., Rittweger, J., Gasparini, M., Blenkuš, M. G., & Šimunič, B. (2016). Greater loss in muscle mass and function but smaller metabolic alterations in older compared with younger men following 2 wk of bed rest and recovery. *Journal of Applied Physiology*, **120**(8), 922–929.

- Psaty, B. M., Manolio, T. A., Kuller, L. H., Kronmal, R. A., Cushman, M., Fried, L. P., White, R., Furberg, C. D., & Rautaharju, P. M. (1997). Incidence of and risk factors for atrial fibrillation in older adults. *Circulation*, **96**(7), 2455–2461.
- Riley-Hagan, M., Peshock, R. M., Stray-Gundersen, J., Katz, J., Ryschon, T. W., & Mitchell, J. H. (1992). Left ventricular dimensions and mass using magnetic resonance imaging in female endurance athletes. *American Journal of Cardiology*, **69**(12), 1067–1074.
- Ross, R., Blair, S. N., Arena, R., Church, T. S., Despres, J.-P., Franklin, B. A., Haskell, W. L., Kaminsky, L. A., Levine, B. D., Lavie, C. J., Myers, J., Niebauer, J., Sallis, R., Sawada, S. S., Sui, X., & Wisloff, U. (2016). Importance of assessing cardiorespiratory fitness in clinical practice: A case for fitness as a clinical vital sign. *Circulation*, **134**(24), e653–e699.
- Saltin, B., Blomqvist, G., Mitchell, J. H., Johnson, R. L., Wildenthal, K., & Chapman, C. B. (1968). Response to exercise after bed rest and after training. *Circulation*, **38**, (5 Suppl), VII1–VII78.
- Sarzynski, M. A., Ghosh, S., & Bouchard, C. (2017). Genomic and transcriptomic predictors of response levels to endurance exercise training. *The Journal of Physiology*, **595**(9), 2931–2939.
- Shephard, R. J. (2009). Maximal oxygen intake and independence in old age. *British Journal of Sports Medicine*, **43**(5), 342–346.
- Shibata, S., Perhonen, M., & Levine, B. D. (2010). Supine cycling plus volume loading prevent cardiovascular deconditioning during bed rest. *Journal of Applied Physiology*, **108**(5), 1177–1186.
- Shibata, S., Wakeham, D. J., Thomas, J. D., Abdullah, S. M., Platts, S., Bungo, M. W., & Levine, B. D. (2023). Cardiac effects of long-duration space flight. *Journal of the American College of Cardiology*, **82**(8), 674–684.
- Sutton, J. R. (1992). Limitations to maximal oxygen uptake. *Sports Medicine*, **13**(2), 127–133.
- Venturelli, M., Schena, F., & Richardson, R. S. (2012). The role of exercise capacity in the health and longevity of centenarians. *Maturitas*, **73**(2), 115–120.
- Wang, E., Næss, M. S., Hoff, J., Albert, T. L., Pham, Q., Richardson, R. S., & Helgerud, J. (2014). Exercise-training-induced changes in metabolic capacity with age: The role of central cardiovascular plasticity. *Age (Omaha)*, **36**(2), 665–676.
- Weiner, R. B., Deluca, J. R., Wang, F., Lin, J., Wasfy, M. M., Berkstresser, B., Stöhr, E., Shave, R., Lewis, G. D., Hutter, A. M., Picard, M. H., & Baggish, A. L. (2015). Exercise-induced left ventricular remodeling among competitive athletes: A phasic phenomenon. *Circulation: Cardiovascular Imaging*, **8**(12), e003651.
- Westby, C. M., Martin, D. S., Lee, S. M. C., Stenger, M. B., & Platts, S. H. (2016). Left ventricular remodeling during and after 60 days of sedentary head-down bed rest. *Journal of Applied Physiology*, **120**(8), 956–964.
- Wood, K. N., Murray, K. R., Greaves, D. K., & Hughson, R. L. (2019). Inflight leg cuff test does not identify the risk for orthostatic hypotension after long-duration spaceflight. *Nature Partner Journals Microgravity*, **5**, 22.

Additional information

Competing interests

None declared.

Author contributions

E.T.H. drafted the initial version of the manuscript. All authors critically revised and approved the final version of the manuscript. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

Funding

E.T.H. was supported by a Canadian Institutes of Health Research Banting and Best Canada Graduate Scholarship (201911FBD-434513-72081). R.L.H. was supported by grants from Canadian Institutes of Health Research (UH1-161690) and Natural Sciences and Engineering Research Council of Canada (RGPIN-2023-03719). B.D.L. was supported by grants from National Aeronautics and Space Administration (80NSSC20K0987, NNJ04HH01A and 96-OLMSA-01B), National Institutes of Health (5R01AG017479) and National Space Biomedical Research Institute (CA00701).

Acknowledgements

R.L.H. is the Schlegel Research Chair in Vascular Aging and Brain Health.

Keywords

ageing, astronaut, bed rest, endurance exercise training, inactivity

Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the HTML view of the article. Supporting information files available:

Peer Review History

Link to a podcast