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Autonomic responses to exercise: Deconditioning/inactivity

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ABSTRACT

Experimental models of physical inactivity associated with a sedentary lifestyle or extreme forms of inactivity with bed rest or spaceflight affect the balance between parasympathetic and sympathetic nervous system regulation of the cardiovascular system. Deconditioning effects are rapidly seen in the regulation of heart rate to compensate for physical modifications in blood volume and cardiac function. Reflex regulation of cardiovascular control during exercise by metaboreflex and baroreflex is altered by bed rest and spaceflight. These models of extreme inactivity provide a reference to guide physical activity requirements for optimal cardiovascular health.

1. Introduction

Regular physical activity induces many positive adaptations in the regulation of cardiovascular function by the autonomic nervous system (*ref to chapter in this edition*). However, these adaptations can be quickly lost with adoption of a sedentary lifestyle or by experimentally or environmentally induced deconditioning. Extreme forms of physical inactivity during human spaceflight or head down bed rest have provided critical insight into the rate of change of cardiovascular fitness. These models have also provided opportunities to understand the necessary quantities of physical activity during the imposed periods of inactivity to maintain cardiovascular health.

2. Inactivity, bed rest and autonomic deconditioning

A key overall indicator of cardiovascular health and optimal balance between the parasympathetic and sympathetic nervous systems is provided by the measurement of heart rate during an incremental exercise test to assess maximal oxygen uptake. Early research indicated that inactivity is associated with a reduction in total blood volume that in turn affects cardiac stroke volume requiring an increase in submaximal heart rate with increased sympathetic and reduced parasympathetic activity to the sinoatrial node (Coyle et al., 1984) to maintain oxygen transport. Chronic physical inactivity associated with autonomic imbalance can increase the risk of developing cardiovascular disease (Thayer et al., 2010).

Bed rest studies using either horizontal (Saltin et al., 1968) or head down tilt (Lee et al., 2010; Pavy-Le Traon et al., 2007) have been used extensively to induce cardiovascular deconditioning in healthy young participants. Unavoidable bed rest during recovery from surgery or illness also has profound deconditioning effects (Killewich, 2006). Initially with bed rest, a reduction in total blood volume reduces cardiac stroke volume, maximum cardiac output and peak oxygen uptake. Cardiac atrophy is detected with as little as 2 weeks bed rest and is progressive with bed rest (Arbeille et al., 2001; Perhonen et al., 2001), ventricular relaxation is slowed (Dorfman et al., 2008), and cardiac chamber compliance is reduced (Hastings et al., 2012). These mechanical changes can be prevented by appropriate exercise countermeasures (Hastings et al., 2012) and their functional consequences appear to be limited (Convertino and Cooke, 2005). Interestingly in many (Engelke and Convertino, 1996) but not all (Hastings et al., 2012) bed rest studies the peak exercise heart rate is increased. One possible mechanism for the elevated heart rate is an increased concentration of norepinephrine, but not epinephrine, at peak exercise (Engelke and Convertino, 1996). However, it is also recognized that the intrinsic heart rate is reduced with exercise training (D'Souza et al., 2014; Hughson et al., 1977), this effect is reversed by detraining (D'Souza et al., 2014), and the in vitro equivalent of the maximum heart rate in response to norepinephrine is correlated with the intrinsic heart rate (Hughson et al., 1977). Intrinsic heart rate might also play a role in setting resting or submaximal heart rate after training or detraining (D'Souza et al., 2014) but the altered autonomic balance is probably determined in part by the duration and intensity of the training or the detraining (Deley et al., 2009). Recent evidence from a 24-hour head down bed rest demonstrated modifications of central neural response to an orthostatic challenge (Shoemaker et al., 2012). Future research can be directed at partitioning intrinsic and neural factors affecting cardiovascular control during exercise following physical inactivity.

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The initial removal of upright posture causes a reduction in plasma norepinephrine concentration (Hughson et al., 1995) that is sustained during longer term bed rest (Christensen et al., 2005; Convertino et al., 1997; Edgell et al., 2007). Direct measurements of muscle sympathetic nerve activity following bed rest have generally shown reduced burst frequency (Kamiya et al., 2004; Pawelczyk et al., 2001; Shoemaker et al., 1998) but unchanged activity has been observed (Shoemaker et al., 1999). Lower circulating levels of catecholamines might result in adrenergic receptor hypersensitivity. This hypothesis was tested by infusion of sympathomimetic drugs in men following a 14-day strict head down bed rest (Convertino et al., 1997), and in women who completed a 56-day head down bed rest in two groups: one with strict bed rest (control) while the other performed regular aerobic and resistance exercises (Edgell et al., 2007). Heart rate response to isoproterenol was elevated after bed rest, and was initially attributed to increased beta-adrenergic receptor sensitivity (Convertino et al., 1997). However, in the study of women, heart rate was elevated only in the control subjects suggesting that the increased heart rate might have been a consequence of the reduced stroke volume in these women rather than altered sensitivity (Edgell et al., 2007). Post-bed rest leg vascular resistance responses investigated under alpha-adrenergic stimulation revealed no change in sensitivity (Convertino et al., 1997; Edgell et al., 2007). The role of these changes in cardiovascular responses on post-bed rest cardiac output and muscle blood flow during exercise has not been studied.

The cardiovascular responses to upright cycling exercise after head down bed rest have consistently shown an increase in heart rate at any submaximal work rate (Lee et al., 2010; Spaak et al., 2005; Trappe et al., 2006). Spaak et al. (2005) investigated the effects of up to 120-days of head down bed rest with no countermeasures on the cardiovascular responses during rest and light intensity exercise (50 W) in both supine and upright postures. Mean arterial blood pressure was not changed at rest or during exercise, but stroke volume was reduced at rest in both body positions and in supine exercise at 50 W by day 60. At the end of 120-day bed rest, stroke volume was reduced at rest and in exercise both supine and upright. Resting cardiac output was reduced and a reduction in total peripheral conductance was required for the maintenance of blood pressure. During exercise, cardiac output was not reduced at day 60, but it was by day 120. Taken together, the results from the study of Spaak and colleagues suggest that after 60-days of bed rest arterial vasoconstriction was important for regulation of resting arterial blood pressure in supine and upright postures, while heart rate had a greater contribution during upright exercise. In contrast to other studies that tested subjects to the point of syncope to reveal inadequate peripheral vascular responses (Arbeille et al., 2008), short-duration exposure to upright posture was not associated with impaired peripheral vasoconstriction.

The arterial baroreflex responses were assessed at rest and during exercise in these same subjects by acute posture changes (Linnarsson et al., 2006). At rest, baroreflex sensitivity was not altered until the end of the 120-day bed rest. These results contrast with observations from other bed rest studies measured at rest (Convertino et al., 1990; Eckberg et al., 2010; Fritsch et al., 1992) or with lower body negative pressure and orthostatic tolerance testing (Hughson et al., 1994a, 1994b). Baroreflex response was also reduced following 2-weeks of ambulatory deconditioning after a 10-week physical training program (Convertino and Fritsch, 1992). When measured during exercise, baroreflex sensitivity was reduced with brief head up tilt during and up to 15 days after head down bed rest when assessed by RR-interval: systolic blood pressure, and clear trends ($p \leq 0.08$) when assessed by heart rate: mean arterial pressure. There was a greater fall in arterial pressure (60–70%) during tilting up at 60- and 113-days of bed rest compared to pre-bed rest while the chronotropic response was only slightly enhanced (8–14%) suggesting impaired cardiac acceleration during exercise. In contrast, when baroreflex sensitivity was assessed with a hypertensive stimulus induced by rapidly tilting down during cycling, it was not affected by bed rest even though there was a greater rise in mean arterial pressure with tilt down during bed rest. These results suggest that during exercise the vagal response appeared to be intact and able to respond to the hypertensive stimulus with tilt down, but vagal and sympathetic responses were inadequate to increase heart rate to a hypotensive stimulus with tilt up (Linnarsson et al., 2006). These variant findings might have been related to the absolute heart rates required to elicit the full baroreflex responses.

3. Spaceflight and autonomic deconditioning

Cardiovascular deconditioning as a consequence of spaceflight is well documented (Watenpaugh and Hargens, 1996), but is also complicated by individual susceptibility to weightlessness, different durations of exposure, variable daily routines in terms of work tasks and exercise/countermeasure sessions. From the perspective of exercise deconditioning, the primary focus has been on peak exercise performance and measurement of oxygen uptake. Early spaceflight was conducted in small vehicles that precluded sufficient exercise countermeasures. The Skylab missions included extensive exercise countermeasures and the three astronauts on the 84-day Skylab 4 increased their peak oxygen uptake by ~10% late inflight compared to pre-flight (Michel et al., 1977; Rummel et al., 1975). Submaximal and maximal exercise performances were measured during and after space shuttle flights of 9–15 days (Spacelab Life Sciences, SLS, missions (Levine et al., 1996; Shykoff et al., 1996)) and 17 days (Life and Microgravity Spacelab, LMS, STS-78 (Trappe et al., 2006)). There were some differences in results between these studies. During SLS missions, inflight submaximal heart rate was not significantly changed with respect to pre-flight (Shykoff et al., 1996). Interestingly during the SLS missions, the peak oxygen uptake was not different from pre-flight while immediate post-flight peak oxygen uptake was reduced (Levine et al., 1996). Results from the LMS mission from 4 male astronauts were enhanced by a parallel 17-day bed rest study of 8 men that permitted contrasts in effects and time course (Trappe et al., 2006). In these experiments, an increase of ~10 beats/min in 4 astronauts exercising at 150 W was not statistically significant. In the parallel bed rest study, heart rate increased a similar ~10 beats/min after 8 days, which was significant. The peak oxygen uptake was not measured directly in the LMS mission. Rather, the researchers were restricted to a work rate corresponding to 85% of pre-spaceflight peak where heart rate was elevated suggesting a reduction in peak oxygen uptake. Taken together, these results suggest small changes in autonomic control of the cardiovascular system during exercise in spaceflight to account for a reduction in cardiac stroke volume by reduced total blood volume (Alfrey et al., 1996; Leach et al., 1996; Watenpaugh and Hargens, 1996) and cardiac atrophy (Bungo et al., 1987; Perhonen et al., 2001).

The impact of spaceflight on resting sympathetic neural activity is still uncertain. While resting heart rate and blood pressure are reduced over 24 h in space (Fritsch-Yelle et al., 1996a), this could simply be a response to changes in activity patterns (Fraser et al., 2012). Urinary excretion rate of norepinephrine was reduced during Skylab missions (Leach et al., 1996) but, plasma norepinephrine levels (Christensen et al., 2005; Norsk et al., 1995), muscle sympathetic nerve activity and norepinephrine spillover (Ertl et al., 2002) were elevated. Post-flight testing has focused on autonomic responses to post-flight orthostatic stress (Buckey et al., 1996; Eckberg et al., 2010; Fritsch-Yelle et al., 1996b; Hughson et al., 2012; Levine et al., 2002). Research has revealed populations of astronauts who had post-flight elevations in baseline norepinephrine and maintained orthostatic tolerance, while others had low baseline norepinephrine and poor orthostatic tolerance (Meck et al., 2004). Further, tyramine infusions increased norepinephrine release mostly in the astronauts showing the greatest reduction in orthostatic tolerance (Meck et al., 2004). These data suggest that, in some cases, the sympathetic nerves are producing norepinephrine but they fail to release it in satisfactory quantities for some astronauts.