PERSPECTIVES

## Big concepts, small N

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Kudos to *The Journal of Physiology*! Access to space is rare and difficult, and data derived from spaceflight deserve wide dissemination despite the inherent challenges to interpretation that result from limited sample size and abbreviated experimental techniques. Never are mechanistically orientated field experiments easy to undertake, and the study by Ferdinando Iellamo and colleagues featured in this issue of *The Journal* confronts these obstacles, serving as a superb case study that informs our understanding of the changes in cardiovascular regulation associated with spaceflight.

In November 1983 NASA began flying the European Space Agency developed Spacelab module, ushering a new era of internationally sponsored scientific research into low-earth orbit. With two modules flying 16 times over the next 15 years, many Spacelab missions were conceived with a predominant, if not exclusive, life sciences focus. The Spacelab Life Sciences (SLS-1, SLS-2) missions (STS-40 and STS-58) emphasized the study of cardiorespiratory, vestibular, and musculoskeletal adaptations to microgravity. Subsequently the Federal German Aerospace Research Establishment (DLR) sponsored the D-1 and D-2 missions (STS-61A and STS-68), perfecting a model of multidisciplinary investigation that was emulated by the Life and Microgravity Sciences Spacelab mission (STS-78), which centred on neuromuscular adaptation. The 1998 Neurolab mission (STS-90), with a neuroscience theme, concluded flights of the Spacelab module.

As commercial spaceflight activities grew, the privately managed SPACEHAB module commenced operations in 1993 in a variety of configurations to support shuttle flights and resupply missions to *Mir* and the International Space Station. By 2003 the debut of SPACEHAB's Double Research Module (DRM) offered a new laboratory similar in size and capability to the retired Spacelab. Flown in the space shuttle's cargo bay only once as the primary payload of the ill-fated STS-107 mission, the DRM provided the laboratory capability that enabled the study presented by Iellamo *et al.*

Iellamo *et al.* (2006) investigate several issues fundamental to our understanding of cardiovascular regulation in microgravity. First, building on the seminal work of Eckberg and colleagues, they test baroreflex regulation of vagally mediated R-R interval responses during spaceflight. Extending the topic further, they ask whether these potential changes might alter baroreflex function and cardiovascular regulation during dynamic exercise. Finally, they consider the possibility that metaboreflex function or stimulation changes during spaceflight. Despite the unavoidable fact that the sample size is small, the general finding that the four subjects appeared hyper-reflexive in-flight is novel and somewhat unexpected.

Some considerations regarding the interpretation of reflex responses deserve restatement here. The implicit assumption underlying studies that employ a systems-level of physiological inquiry is that mechanisms will interact; thus, the extent to which one can quantify and/or control competing/interacting influences determines the validity of the conclusions one might reach about the particular reflex under study. In this context, documented non-neuronal effects of spaceflight, such as hypovolaemia and its effect on cardiac filling and stroke volume, hyponutrition, and end-organ (i.e. vascular) remodelling, could affect the interpretation of these data. Moreover, the arousal level of the subjects (both psychological and physiological) could constitute a mitigating influence. Might such factors have contributed to the genesis of the Subject no. 1's pronounced hypertension recorded during the in-flight portion of the experiment?

In contrast to previous reports (Fritsch *et al.* 1992; Fritsch-Yelle *et al.* 1994), the study by Iellamo *et al.* (2006) presents individual cases where baroreflex-mediated regulation of heart rate *increased* during spaceflight. How such a change might have occurred is not immediately apparent. Whereas similar findings have been produced in a terrestrial environment by applying leg congesting cuffs to reduce venous return (Gisolf *et al.* 2005), blood volume distribution in free-fall, when hydrostatic gradients are nullified, is likely to differ profoundly from the terrestrial condition. Thus, it is probably best to avoid the temptation to extrapolate such ground-based findings to the in-flight trials reported by Iellamo *et al.*

Then there is the issue of the exercise trial itself. Since $\dot{V}_{O_2,max}$ declines during spaceflight (Levine *et al.* 1996; Stegemann *et al.* 1997; Trappe *et al.* 2006), did the greater cardiovascular and muscle metaboreflex-mediated responses result from the likely possibility that astronauts exercised at the same absolute, and thus greater relative, intensity during flight? Put another way, do the exaggerated blood pressure responses during exercise and post-exercise occlusion reported by Iellamo *et al.* represent an increase in the sensitivity of the muscle metaboreflex, or simply greater engagement of this reflex as a consequence of muscle and cardiovascular atrophy and deconditioning?

Like all field research, the utility of the findings from Iellamo *et al.* (2006) should be considered from an ergonomic perspective. Will these results aid the new NASA Vision for Space Exploration to return humans to the Moon and Mars? The answer to this question remains uncertain at this time. Limited data and numerous anecdotes imply that aerobic fitness of astronauts and cosmonauts wanes in the first few weeks of spaceflight while crews are adapting to the routine of living in free-fall (Popov *et al.* 2004). Yet changes in maximal aerobic power or other aspects of human physiology may be less likely to limit demanding activities such as extra-vehicular activity (EVA) than the physical capabilities (e.g. heat rejection, $CO_2$ scrubbing, mass) of the EVA suit itself. Awareness of this point may help explain NASA's recent unprecedented reduction in funding for physiological research. Nevertheless, it remains an inescapable conclusion that exercise will be a critical (and at this point, poorly understood) component of the suite of countermeasures required to maintain cardiorespiratory and musculoskeletal integrity during these future extended-duration (up to 30-month) space missions.

Two concluding points are implied in this fine study: First, our comprehension

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of cardiovascular regulation under microgravity conditions remains far from complete. Second, systems-level inquiry offers extraordinary opportunities to ponder how human physiology adapts to a chronic free-fall environment. Sadly, we will never be able to answer all of the questions that arise from this unique study of a dedicated crew of astronaut–researchers. The tragic loss of Rick Husband, Willie McCool, Mike Anderson, Dave Brown, 'KC' Chawla, Laurel Clark and Ilan Ramon in their final minutes of flight is a sobering reminder that the most dedicated members of field studies are often the subjects themselves.

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