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PERSPECTIVES

Orthostatic intolerance after space flight

Wouter Wieling*, John R. Halliwill† and John M. Karemaker‡

*Departments of *Internal Medicine and ‡Physiology, Room F4-221, Academic Medical Centre, Cardiovascular Research Institute, University of Amsterdam, PO BOX 22700, 1100 DE Amsterdam, The Netherlands and † Department of Anesthesiology and General Clinical Research Center, Mayo Clinic and Foundation, Rochester, MN, USA*

Email: w.wieling@amc.uva.nl

Physiologists have always been challenged by the adjustments of the human body to hostile environments. The set of papers in this issue of *The Journal of Physiology* (Cox *et al.* 2002; Ertl *et al.* 2002; Levine *et al.* 2002) fits into the tradition of the study of human responses to extreme physical circumstances. The Neurolab project represents a huge undertaking that required major contributions from many different collaborators, and the coordination of efforts at different institutions. The studies succeeded because of the dedication and years of work of the astronauts involved. The manuscripts present the fundamental findings from the first direct recordings of sympathetic vasoconstrictor nerves and noradrenaline kinetics in humans during microgravity. Despite the difficulties of performing such measurements on the space shuttle and the small numbers of astronauts involved, unique data are set forth that represent a major advance in our understanding of the physiology of space flight.

The main hypothesis tested in the present series of experiments was that a reduced function of the sympathetic system is responsible for the orthostatic intolerance exhibited by astronauts on return to earth. The investigators succeeded in obtaining direct recordings of muscle sympathetic nerve activity and measuring sympathetic neurotransmitter kinetics in space. In contrast to widely held expectations, baseline sympathetic activity was not found to be reduced in space. The astronauts showed normal sympathetic responses during simulated orthostatic stress induced by lower body negative pressure (LBNP) and were able to maintain their arterial pressure at normal levels. Accordingly, arterial pressure and sympathetic responses to Valsalva straining were augmented in space and not degraded as postulated. Sympathetic baroreflex gain was normal. Thus, the postulated reduction in sympathetic function could not be confirmed.

The investigators compared the cardiovascular physiology in space to the supine terrestrial values and concluded that microgravity induced a state of increased sympathetic activity. However, it should be noted that the augmentation observed is mild; the sympathetic activation at baseline and the blood pressure response to Valsalva straining are roughly comparable to operating characteristics in the seated upright position on earth (Saltin, 1992). In this light, it would have been of interest to document the cardiovascular changes induced by Valsalva straining in different body positions on earth (Van Lieshout *et al.* 1991; Saltin, 1992) prior to and after space flight in addition to the in-flight measurements on the space shuttle.

The habit of considering the circulation of supine man as the physiological baseline has probably developed because the doctor usually examines his patient in bed. However, since a healthy active human spends more than two-thirds of the day on his or her feet or haunches, it would be more reasonable to assume that, in human subjects, the predominant upright posture defines the normal operating characteristics of the cardiovascular system (Saltin, 1992). Taking the upright posture as a reference, one could argue that sympathetic activity is reduced during microgravity. Whatever the opinion about the benchmark for sympathetic activity, the adaptation of the cardiovascular system to microgravity is a handicap on return to earth. The additional vasoconstriction (i.e. vasoconstrictor reserve) that can ultimately be made available to adjust to orthostatic stress may be diminished (Schondorf & Wieling, 2000).

The data from the present and previous studies indicate that orthostatic intolerance after space flight can be attributed to decreases of cardiac filling pressure and stroke volume during orthostatic stress due to a decreased blood volume. It now appears that cardiovascular sympathetic regulatory responses are normal. Decreased pumping capacity due to cardiac atrophy and increased venous pooling that is secondary to impairment of the skeletal muscle pump most likely plays an important additional role (Saltin, 1992). it has been known for more than 5 decades that reduced leg muscle tone is associated with syncope and, vice versa, leg muscle tensing enhances cerebral perfusion (for review see Smit *et al.* 1999). The effects of rapid extracellular fluid expansion as a measure to combat orthostatic tolerance remains to be determined (Van Lieshout *et al.* 1991; Saltin, 1992).

Earlier studies indicating that astronauts with the most severe post-flight orthostatic intolerance appear to have less augmentation of plasma noradrenaline levels and smaller increases in systemic vascular resistance during standing than their orthostatically tolerant collegues are explained by impending vasovagal faints in these subjects. Alternatively, one must consider the fact that none of the Neurloab astronauts developed post-flight orthostatic intolerance. Would sympathetic function have been maintained had the subject cohort included individuals that developed severe orthostatic intolerance? These are the types of the interpretative caveats that have always accompanied the great endaveours characterising physiology under difficult circumstances.

The orthostatic impairment observed in astronauts on return from space travel closely resembles the clinical syndrome of orthostatic intolerance after ground-based simulation of microgravity by prolonged head-down bedrest (Saltin, 1992). Detailed studies in small numbers of otherwise normal humans after exposure to unusual circumstances (Saltin, 1992; Cox *et al.* 2002; Ertl *et al.* 2002; Levine *et al.* 2002) and in unique patients (Van Lieshout *et al.* 1991) provide a better understanding of the altered physiology that leads to post-flight and post-bedrest orthostatic symptoms and might help to elucidate pathophysiology and improve the management of the large number of patients with orthostatic intolerance.

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