

The limits of medicine

The next small step

Kevin Fong

The microgravity experienced in space missions has serious effects on human physiology. How to get a crew to Mars in an optimal state for landing and exploration remains a matter of some debate

Astrodynamic considerations and existing propulsion technology limit the speed with which a crew can be delivered to and returned from the surface of Mars. A typical, energy efficient mission profile might involve six months of outward bound journey, up to a year and a half of exploration on the planet surface, and a return flight lasting another six months.¹ All told this comes to nearly one thousand days, more than twice the length of any single mission in the history of human space flight and an order of magnitude longer than routine International Space Station operations.

Several hazards await the crews of Mars missions, including radiation exposure and the psychological stress of spending 30 months in a confined habitat, further from Earth than any human in history, with death no more than a hull's thickness away. This article focuses on the effects of prolonged weightlessness on the human body and our current understanding of the effects of microgravity on physiology.

Physiology of microgravity

Prolonged exposure to microgravity seems to affect almost all physiological systems. Disturbances of haemopoiesis, immunosuppression, and endocrine changes have all been observed.²⁻⁴ The effects of microgravity that are of key importance to human space operations are those on the musculoskeletal, neurovestibular, and cardiovascular systems.

Effects on the musculoskeletal system

That demineralisation of bone should occur in the face of the unloading associated with weightlessness is predictable from Wolff's law. The rate and extent of this process is considerable, with losses of 1-2% of bone mass per month in flight.⁵ If unabated over the duration of a mission to Mars, this bone demineralisation, with its resultant hypercalcaemia and hypercalcuria, would leave crews at substantially increased risk of pathological fractures and renal calculus formation.

The osteoporosis associated with space flight has been well documented.⁶ The bone loss seems to be site specific, predominantly in the load bearing regions of the legs and lumbar spine.⁵ Study data variously implicate reduced bone formation resulting from osteoblastic dysfunction and excessive osteoclastic resorption.^{7, 8} Both processes are probably involved, but their relative



The biomedical problems associated with long duration space flight must be solved before a human exploration mission to Mars will be feasible

importance and how they are orchestrated remain unclear.

In the absence of gravitational load, skeletal muscle also atrophies. Reductions in muscle volume and in peak force and velocity of contraction have been observed. The quality and quantity of muscle also change, with phenotypic shifts in muscle fibre type evident from biopsy samples.⁹ These changes seem to occur in muscle groups associated with load bearing functions. In these groups the intrinsic mechanical and metabolic properties of slow twitch muscle fibres, associated with high oxidative capacity and low fatigueability, seem to alter to resemble those of fast twitch fibres responsible for developing explosive force in activities such as running and jumping.⁹

The current regimen of countermeasures, which relies on resistive exercise and dietary supplementation, provides some protection but is not uniformly effective in preventing musculoskeletal atrophy.³ However, oral bisphosphonates have recently been found effective in reducing bone losses in healthy subjects deconditioned by 17 weeks of bed rest and will soon be evaluated in spaceflight crews (personal communication, W H Paloski, NASA Human Adaptation and Countermeasures Office).

Effects on the cardiovascular system

Prolonged exposure to microgravity seems to be associated with a prolonged QTc interval on electrocardio-

Centre for Aviation,
Space and Extreme
Environments,
Middlesex Hospital,
London W1T 3AA

Kevin Fong
research fellow

kfong@ucl.ac.uk

BMJ 2004;329:1441-4

CEB/CBBC WORLDWIDE LTD 2004



The weightlessness experienced during space travel has profound effects on the human cardiovascular, musculoskeletal, and neurovestibular systems

grams,¹⁰ while limited data from studies with Holter monitors suggest an enhanced potential for arrhythmogenesis.¹¹ On returning to Earth, many astronauts have orthostatic intolerance: even after short flights, of nine to 14 days, up to 60-70% of returning crew members are unable to complete a 10 minute stand test without experiencing syncope or pre-syncope.¹² Longer flights are associated with a higher incidence of orthostatic intolerance.

The mechanisms underlying this phenomenon have been well investigated. The cephalad fluid shifts that result from loss of gravitational loading seem to be misinterpreted by the body as evidence of hypervolaemia and thus lead to endocrine changes that encourage intercompartmental fluid shifts and deplete the intravascular space. Although the resultant hypovolaemia plays a key role, other cardiovascular elements also seem to contribute to the post-flight orthostatic hypotension. This is shown by the inability of either fluid loading or mineralocorticoid administration to fully ameliorate this post-flight phenomenon.^{13 14}

Weightlessness and microgravity

The weightlessness experienced by astronauts in low Earth orbit is not due to an absence of a gravitational field. At an altitude of a few hundred kilometres the force of gravity due to the Earth's mass is diminished by less than 10%. The weightlessness occurs as a consequence of freefall. Consider the following: if you were unfortunate enough to be standing in a lift when the supporting cable snapped you would experience weightlessness from the moment of release until the moment of impact. In the same way astronauts in low Earth orbit or on their way to Mars "float" because they are in a vehicle that is in freefall around the Earth (with the added benefit of having no floor immediately in the way to spoil the experience).

It is therefore wrong to refer to astronauts as existing in a "zero G" environment. However, because of small perturbations arising from sources such as vibration within the vehicle and local gravitational effects, astronauts do not experience perfect weightlessness while in space. As a result the term microgravity has come to be used to describe the state of near weightlessness associated with freefall and space flight.

Investigations have revealed alterations in total peripheral resistance, vascular reactivity, and sympathetic drive.^{15 16} Volume repletion and use of extrinsic vasopressor agents have reduced some but not all of the symptoms associated with post-flight orthostatic intolerance.

Effects on the neurovestibular system

Space flight is associated with disorientation, space motion sickness, and impaired ability to acquire and track visual targets.¹⁷⁻¹⁹ The early phases of low earth orbit missions are associated with space motion sickness, and a study of 24 shuttle missions found that this was experienced by nearly 70% of astronauts flying for the first time.²⁰ The symptoms tend to subside after acclimatisation of 24-72 hours, after which the dominant neurovestibular effects are disorientation and impaired visuomotor tracking. On return to Earth, these symptoms resolve but only after a period of re-adaptation during which performance is markedly impaired.

The absence of gravitational stimulation of the otolith organ seems to be heavily implicated in the observed neurovestibular effects. This is thought to contribute to sensory conflict and may interfere with central processing tasks associated with visuomotor skills. Over time, the central nervous system is apparently able to adapt by re-weighting sensory inputs—relying more heavily on visual cues than proprioceptive and otolithic inputs—but this adaptation is not complete, as shown by the deficits observed.^{21 22}

Postflight decrements in sensorimotor control have been well characterised from both basic science and occupational health perspectives. Early in a flight all crew members experience disrupted postural stability, locomotor coordination, and gaze control. The underlying cause seems to be adaptation of the vestibular system to microgravity. As missions get longer, adaptation of the somatosensory and motor control systems starts to be important. The mechanisms of this slower phase of in-flight adaptation are not yet well understood, but such understanding may be critical for the success of extended duration missions beyond low Earth orbit. In longer missions the incidence of postflight autonomic dysfunction increases. For example, orthostatic hypotension, which can exacerbate the balance control deficits, may result in part from vestibular autonomic system alterations.

Discussion

Microgravity clearly exerts a profound and widespread effect on human physiology. Some of these changes represent appropriate physiological adaptations and can be thought of as an attempt to achieve new "space normal" homeostatic set points. However this "space normal" state is clearly not appropriate for Earth's gravity and is likely not appropriate for the reduced gravity on Mars, roughly a third that of Earth's.

It is said that the two most difficult feats in all of rocket science are starting and stopping. Having survived the violence of takeoff and a marathon six month flight, the crews of the first expeditions to Mars will be faced with a dangerous landing several hundred million kilometres from Earth. A sensible

precaution would be to try to deliver the crew to Mars in an optimal state for the landing and for the ensuing programme of planetary exploration. How this might best be achieved remains a matter of some debate.

Artificial gravity—the next small step?

For short duration missions, lasting up to 16 days, most clinically important problems associated with space flight occur on landing during the re-adaptation to Earth's gravity. Returning crews are supported and monitored within the first few hours of touchdown, and close surveillance continues for the following week. For missions to Mars, however, this re-adaptation will take place on the surface of Mars in the absence of a medical support team or a definitive healthcare facility.

Although study of human physiology in microgravity has provided unique insight into physiological processes, our efforts in designing targeted, effective, single system countermeasures have been met with limited success. This has led to resurgence in the popularity of artificial gravity as a potential multisystem countermeasure. First mooted as early as 1911 by Konstantin Tsiolkovsky,²³ artificial gravity relies on the Einstein equivalence principle to mimic the effect of gravitational loading using the centrifugal forces associated with circular motion.²⁴

For an object, or in this case a person, in a vehicle rotating around some central point, the centrifugal force, and hence the perceived loading, is proportional to the square of the angular velocity and the radius of rotation. This implies that the shorter the radius the more rapid the rate of rotation required for the same effective gravitational load. In simple terms this demands the construction either of large, slowly rotating vehicles or small, rapidly spinning human centrifuges that can be contained within more conventional spacecraft. Several obstacles must be overcome before such vehicles might be realised. Astronauts already take their light, heat, atmosphere, water, and food with them, and space farers of the future could be taking their own gravity too. At the time of writing a large scale study of the efficacy and practicality of such a countermeasure is in progress at NASA's Johnson Space Center in the United States (personal communi-

Summary points

Human exploration missions to Mars are being planned by international space agencies, but the biomedical problems associated with long duration space flight must be solved before these missions can take place

Exposure to weightlessness leads to changes in human physiology; most are appropriate adaptations but a few are maladaptive

The effects of extended periods of weightlessness on the cardiovascular, musculoskeletal, and neurovestibular systems may compromise the crews' operational effectiveness

Rotating vehicles or short arm centrifuges that generate artificial gravity may provide a countermeasure

cation, W H Paloski, NASA Human Adaptation and Countermeasures Office).

To still boldly go

One could be forgiven for wondering what the value of these expeditions to Mars might be and, in particular, why, with the considerable risk presented to human crews, robotic and automated missions should not be used to achieve the same goals. Mars holds the answers to many questions we have about the history of the Earth and our solar system. More importantly, the exploration of this planet could yield information about the origins of life itself—knowledge as fundamental to the life science community as the study of particle physics is to physical science.

Fossils of the earliest life forms so far found on Earth may be as old as 3.4 billion years.²⁵ However, these specimens were not, and could not have been, identified by parachuting a robotic vehicle into promising terrain. Rather, this discovery, and the debate surrounding it, relied on decades of careful geological fieldwork and patiently sifting through large quantities of carefully collected material with microscopes.^{26 27}

But the question of why missions to Mars should not be carried out by automated rovers with cameras instead of humans is perhaps simpler to explain than this. Just ask yourself why we do not practise medicine in the same way. Whether you are a physician or an astronaut, the same truth holds: there is simply no substitute for being there yourself.

Competing interests: KF is chair of the UK Space Biomedical Advisory Committee and a fellow of the National Endowment for Science Technology and the Arts.

Educational resources

- National Aeronautics and Space Administration (NASA)—www.nasa.gov
- European Space Agency (ESA)—www.esa.int/esaCP/index.html
- National Space Biomedical Research Institute—www.nsbri.org/
- National Endowment for Science Technology and the Arts—www.nesta.org/
- The University College London MSc in human performance under extreme conditions (with space medicine as one of the modules) starts in September 2005. For more details contact the Administrator, MSc School of Human Health and Performance, Archway Campus, University College London, London N19 3UA. Tel: 020 7288 3183

- 1 Turner MJL. *Expedition Mars*. Chichester: Springer-Praxis, 2003.
- 2 Smith SM. Red blood cell and iron metabolism during space flight. *Nutrition* 2002;18:864-6.
- 3 Sonnenfeld G, Shearer WT. Immune function during space flight. *Nutrition* 2002;18:899-903.
- 4 Macho L, Kvetnansky R, Fickova M, Popova IA, Grigoriev A. Effects of exposure to space flight on endocrine regulations in experimental animals. *Endocr Regul* 2001;35:101-14.

- 5 Vico L, Collet P, Guignandon A, Lafage-Proust MH, Thomas T, Rehailla M, et al. Effects of long-term microgravity exposure on cancellous and cortical weight-bearing bones of cosmonauts. *Lancet* 2000;355:1607-11.
- 6 Turner RT. What do we know about the effects of space flight on bone? *J Appl Physiol* 2000;89:870-7.
- 7 Carmeliet G, Nys G, Bouillon R. Microgravity reduces the differentiation of human osteoblastic MG-63 cells. *J Bone Miner Res* 1997;12:786-94.
- 8 Carmeliet G, Vico L, Bouillon R. Space flight: a challenge for normal bone homeostasis. *Crit Rev Eukaryot Gene Expr* 2001;11:131-44.
- 9 Fitts RH, Riley DR, Widrick JJ. Functional and structural adaptations of skeletal muscle to microgravity. *J Exp Biol* 2001;204:3201-8.
- 10 D'Aunno DS, Dougherty AH, DeBlock HF, Meck JV. Effect of short- and long-duration spaceflight on QTc intervals in healthy astronauts. *Am J Cardiol* 2003;91:494-7.
- 11 Fritsch-Yelle JM, Leuenberger UA, D'Aunno DS, Rossum AC, Brown TE, Wood ML. An episode of ventricular tachycardia during long-duration spaceflight. *Am J Cardiol* 1998;81:1391-2.
- 12 Buckley JC Jr, Lane LD, Levine BD, Watenpaugh DE, Wright SJ, Moore WE, et al. Orthostatic intolerance after spaceflight. *J Appl Physiol* 1996; 81:7-18.
- 13 Watenpaugh DE. Fluid volume control during short-term space flight and implications for human performance. *J Exp Biol* 2001;204:3209-15.
- 14 Shi SJ, South DA, Meck JV. Fludrocortisone does not prevent orthostatic hypotension in astronauts after spaceflight. *Aviat Space Environ Med* 2004;75:235-9.
- 15 Waters WW, Ziegler MG, Meck JV. Postspaceflight orthostatic hypotension occurs mostly in women and is predicted by low vascular resistance. *J Appl Physiol* 2002;92:586-94.
- 16 Zhang LF. Vascular adaptation to microgravity: what have we learned? *J Appl Physiol* 2001;91:2415-30.
- 17 Lackner JR. Spatial orientation in weightless environments. *Perception* 1992;21:803-12.
- 18 Reschke MF, Kozlovskaya IB, Somers JT, Kornilova LN, Paloski WH, Berthoz A. Smooth pursuit deficits in space flights of variable length. *J Gravit Physiol* 2002;9:P133-6.
- 19 Harm DL, Parker DE. Preflight adaptation training for spatial orientation and space motion sickness. *J Clin Pharmacol* 1994;34:618-27.
- 20 Davis JR, Vanderploeg JM, Santy PA, Jennings RT, Stewart DF. Space motion sickness during 24 flights of the space shuttle. *Aviat Space Environ Med* 1988;59:1185-9.
- 21 Holstein GR, Kukielka E, Martinelli GP. Anatomical observations of the rat cerebellar nodulus after 24 hr of spaceflight. *J Gravit Physiol* 1999;6:P47-50.
- 22 Parker DE, Reschke MF, Arrott AP, Homick JL, Lichtenberg BK. Otolith tilt-translation reinterpretation following prolonged weightlessness: implications for preflight training. *Aviat Space Environ Med* 1985; 56:601-6.
- 23 Tsiolkovsky KE. Exploration of global space with jets. In: *Collected works*. Vol 2. Moscow: Nauka, 1953:100-39.
- 24 Clement G, Pavy-Le Traon A. Centrifugation as a countermeasure during actual and simulated microgravity: a review. *Eur J Appl Physiol* 2004; 92:235-48. (Epub 2004 May 20.)
- 25 Schopf JW. Microfossils of the early Archean apex chert: new evidence of the antiquity of life. *Science* 1993;260:640-6.
- 26 Crawford I. Human exploration of the moon and Mars: implications for Aurora. *Astronomy and Geophysics* 2004;45:228.
- 27 Brasier MD, Green OR, Jephcoat AP, Kleppe AK, Van Kranendonk MJ, Lindsay JE, et al. Questioning the evidence for Earth's oldest fossils. *Nature* 2002;416:28.

Retroactive prayer: lots of history, not much mystery, and no science

Jeffrey P Bishop, Victor J Stenger

Many claims are made for the power of prayer, but the idea that it could work retrospectively has caused considerable controversy. It is also beyond current scientific knowledge

Department of Internal Medicine, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-9030, USA

Jeffrey P Bishop
associate professor of medicine

Department of Physics, University of Colorado, Boulder Campus Box 232, Boulder, CO 80309-0232, USA

Victor J Stenger
adjunct professor of physics

Correspondence to: J P Bishop
jeffrey.bishop@utsouthwestern.edu

BMJ 2004;329:1444-6

Leibovici first raised the possibility of retroactive prayer in 2001. He reported a study that showed prayer done for patients well after they had left the hospital, had reduced the length of stay in hospital and duration of fever from blood stream infections.¹ In short, prayer somehow seemed to act backward in time to shorten patients' stay in the hospital. The study was intended lightheartedly to illustrate the importance of asking research questions that fit with the scientific model of the world.² Olshansky and Dossey subsequently argued that a logical explanation might be found for Leibovici's results.³ They point to numerous other randomised controlled trials to support their thesis that prayer could work at a distance of space and that it might be plausible that prayer could act retroactively in time. We argue that their claim is built on a confusion and lacks a deep physical model. There is considerable foginess about what science means in relation to the world of spirituality, and we wish to throw some light on the subject.

Examining the clinical science

The latest reported clinical trial of intercessory prayer is a three year study of 750 patients in nine hospitals and 12 prayer groups from around the world, including lay and monastic Christians, Sufi Muslims, and Buddhist monks.⁴ Prayers were even emailed to Jerusalem and placed in the Wailing Wall. Patients awaiting angioplasty for coronary artery obstruction were selected at random by computer and sent to the



Praying at the Wailing Wall

12 prayer groups. The prayer groups prayed for complete recovery of patients. The clinical trial was double blind; neither the hospital staff nor the patients knew who was being prayed for. The findings were reported at the American College of Cardiology's