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REVIEW

Space exploration — Surgical insights and future perspectives

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Abstract NASA's space exploration initiative envisions a return to the moon by 2020, the construction of inhabited lunar bases and manned missions to Mars. Such an ambitious program harbours increased risks, both logistical and physical (particularly that of trauma) within the context of a microgravity environment. This paper also discusses the cellular response to microgravity and the potential scientific and technological benefits of Space exploration.

On the 12 April 1961, aboard the spacecraft *Vostok 1*, Soviet cosmonaut Yuri Gagarin became the first human being to travel into space, spending 108 min orbiting the earth. The USA followed with a manned flight in May 1961 as part of ''Project Mercury''. Since then, the USA and Russia (the former USSR) have dominated space exploration, with several manned missions to the moon between 1968 and 1972, the construction of the Russian Mir Station and more recently the construction of the International Space Station as well as countless scientific experiments with the goal of determining the effects of space travel on the human body.

On 20 July 1989, President George H. W. Bush announced plans for the Space Exploration Initiative (SEI)[1] which envisions inhabited lunar bases being used as a launch pad for manned missions to Mars. On 14 January 2004, President George W. Bush reaffirmed this initiative with his ''Vision for Space Exploration''[2] where he laid out the following steps:

1. *The completion of the International Space Station (ISS) by 2010* — with the future focus of the station being the research of the long-term effects of space travel on human biology. This will allow the development of skills and technology needed to sustain further space exploration.
2. *To develop and test the new spacecraft, the ''Crew Exploration Vehicle'' (CEV) by 2008 with the first manned mission by 2014* — this spacecraft will be capable of carrying 6 astronauts to Mars.
3. *A return to the moon by 2020* — with robotic missions starting in 2008. This will lead to the

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construction of lunar bases which could be used as the launching point for missions to Mars. The lunar soil could be converted to rocket fuel or breathable air for subsequent missions to Mars.

4. *Human missions to mars and beyond* — with robotic landers serving as ''trailblazers''

''*Today I announce a new plan to explore space and extend a human presence across our solar system…We choose to explore space, because doing so improves our lives and lifts our national spirit.*''

President George W. Bush (January 2004)

Even by NASA's standards, this is an ambitious plan but evidence of progress is tangible, with the landing of the Mars Rover in January 2004 (Figs. 1 and 2), the launching of Mars Reconnaissance Orbiters, the construction and testing of the CEV and robotic landers well under way, and NASA Director Dr Michael Griffin's recent announcement that four astronauts will be sent to the Moon by 2020 at a cost of $104 billion.[3] This is a significant cost considering NASA's budget proposals of around $17 billion per annum for the next 5 years.[3]

The ambitious objectives of the SEI harbour increased risks relative to previous missions, especially that of traumatic injury. NASA experts have concluded that trauma is rated at the highest level for long term mission critical risk after studying a graph depicting the ''probable incidence versus impact on mission and health''.[4] Anticipated hazards for crewmembers in future long-term space flights may result in a variety of injuries including fractures, deep puncture wounds or lacerations. Billions of dollars are poured annually into advancing NASA's long-term agenda and the evaluation of prospective mission risks is paramount. It is within the context of this paradigm that the surgical knowledge base is playing an increasingly important role.

Logistical risks

The increased numbers of person hours spent in space, particularly in extravehicular activity as well as the requirement for greater movement, construction of high mass hardware, vehicle docking and refuelling, as well as the advancing age of the astronaut population will all add to overall risk of sustaining injury during space exploration.[5–7]

However, the time to definitive medical care on earth is estimated to be 24 h for the International Space Station, 7 days for a lunar base and 9–12 months for an expedition to Mars. This is further complicated by situational parameters, such as the potential lack of an immediate opportunity to

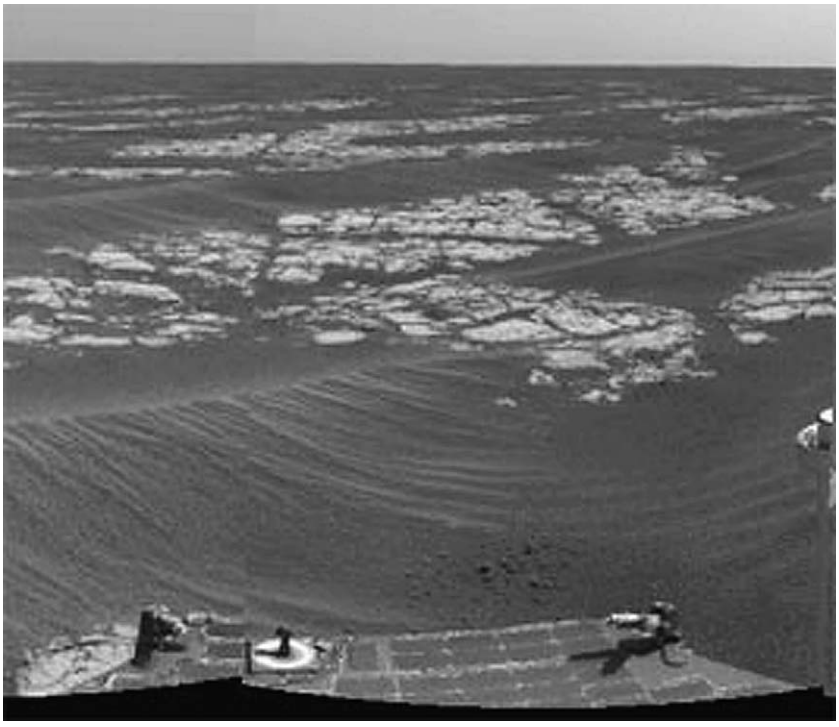

Figure 1 Mosaic produced from frames taken by rovers navigation camera on 13th September 2005 — it shows fractured blocks of ancient sedimentary rock separated by recent sand dunes (picture courtesy of NASA.gov).

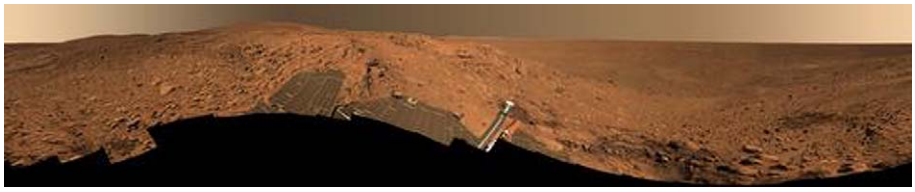

Figure 2 A panoramic image taken from the Mars Rover in September 2005 (picture courtesy of NASA.gov).

return to earth, together with the patient being non-transportable, or unable to withstand the shock of landing. The ability to correctly diagnose and manage injuries in space will not only minimize the cost in terms of morbidity and mortality, but also financially, with an unscheduled medical evacuation to earth estimated to cost $250 million in 1987.[8]

Current technological limitations have the corollary of strict limitations on mass, volume, power and the level of onboard medical expertise for space flights. In space, operating is inherently difficult; parabolic flight experiments done on NASA's KC-135 aircraft,[9] demonstrate the impact of limited volume, weight, water and other supplies, adjusting to new aseptic techniques, safe removal of hazardous material, disinfection of equipment, stability—mobility issues as well as the risk of contamination.[10,11]

The exploration of the next frontier will thus necessitate a higher standard of on-site medical care than is currently available. More extensive medical training and autonomy for astronauts will be required as well as greater freedom from the aforementioned technical constraints. In part, these can be delivered through access to remote medical expertise, such as telemedicine, as well as the ability to manage wounds more effectively in a microgravity environment.

Microgravity and the operational environment

Much of the risk of traumatic injury and poor wound healing are due to the microgravity environment itself (where the effects of gravity are greatly reduced). In microgravity, people, objects and structures, once accelerated in weightlessness, could deliver unexpected and potentially lacerating or crushing blows.[11] This is because objects in weightlessness retain their mass (which is independent of gravitational changes). Forces are thus developed by any acceleration imparted to an object (from Newton's First Law Force = Mass × Acceleration).

Such risks are magnified by the decreased perception of the threat posed by unintended acceleration because of the lack of apparent weight, as well as the loss of the pivotal role gravity plays in weight discrimination.[12] As a consequence, humans operating under such conditions are not as sensitive to inertial mass judgements[12] and show a marked decrease in proprioceptive ability[13] (Fig. 3).

Microgravity and the astronaut

Microgravity also induces an array of physiological and pathological changes amongst the mission crew, which can affect the natural history of any trauma sustained in space.[14] An astronaut injured in space has intrinsically poor wound healing,[15—17] faces high growth rates of antibiotic resistant bacteria[18,19] and may be immune-compromised.[20—23] In addition, prolonged exposure to a microgravity environment leads to muscle loss and decreased bone density.

Microgravity has been shown to increase head oedema, a 10—20% reduction in cardiac stroke volume, enlargement of the liver and pancreas, reduced red blood cell mass.[24] In addition, studies of operative procedures in a microgravity environment have shown subjective increases in the force and volume of venous bleeding compared with that at 1*g*.[25]

How cells sense microgravity

The shape of adherent cells, such as those comprising skin and soft tissue, is determined by the properties of the surrounding extracellular matrix (ECM) and adjacent cells.[26] Cells are malleable and respond to micromechanical forces (MMFs) by converting such mechanical stimuli into intracellular chemical signals that upregulate and remodel structural proteins and angiogenic growth factors.[27—30] Cytoskeletal elements and signaling proteins are concentrated around clusters of ECM bound integrins, called focal adhesions, ready to relay signals from external mechanical forces.[31] Along with stretch activated ion channels and

Figure 3 A man experiencing weightlessness.

geometric cytoskeletal distortion, they regulate cellular growth and differentiation in response to mechanical stimuli.[32]

Changing the molecular architecture and mechanics within the cytoskeleton or interconnected nuclear scaffolds results in local alterations in thermodynamics or kinetic parameters, the corollary of which can be major effects on cellular biochemistry.[33] Studies have shown that tension applied to the ECM has not only induced angiogenesis, but has also controlled directional capillary sprouting and network formation.[34,35]

Endogenously, tension is generated within the cytoskeleton by cellular non-muscular actin—myosin filaments and resisted by the cell's ECM anchors. The level of tension within the cytoskeleton increases with either increasing ECM rigidity or stretch (generated by the actin—myosin filaments). The balance between the forces exerted on the cell either stimulates cell growth and proliferation or results in cell apoptosis. Using integrin coated microfabricated surfaces, Ingber et al. showed that flattened cells have a survival advantage over their rounded counterparts.[36]

Cells use a tension-dependent form of architecture, known as tensegrity, with the level of pre-existing tension or 'tone' in the cytoskeleton known as pre-stress.[37] Gravity acting on the whole organism is a major contributor to pre-stress within individual tissues and cells, due to their hierarchical organization. When an individual is placed in a microgravity environment, they experience an acute decrease in pre-stress, not only at the whole body level but also at the cellular and molecular level.[37] As tensegrity is the architectural basis for mechanostransduction, a microgravity environment may render a cell which is not only less likely to divide and grow but also less capable of mechanotransuction.

Perspectives on future space exploration

Space exploration has resulted in countless scientific and technological advancements. For more than 40 years, NASA has run a Commercial Technology Program that has facilitated the transfer of NASA technology to the private sector. The resulting commercialization has contributed to the development of commercial products and services in the fields of health and medicine, industry, consumer goods, computer technology and the environment. With established technological benefits for those willing to invest, not least national pride and international prestige, other countries are eager to develop their own programs. In 2003, China's Shenzhou V mission saw the first Chinese man in space and India has a well established space program that will likely lead to a manned mission in the future.

The exploration of space carries great risks but also great rewards. It is not simply about colonising the rest of the solar system or searching for little

green men on Mars. Space exploration unlocks our scientific potential. By providing a unique set of conditions in which we can study human physiology, we gain unique insights into how cells react to their environment through mechanotransduction as well as a deeper understanding of complex physiological processes like wound healing, bone and muscle physiology. Such insights can be exploited within conventional laboratories in greater detail and spin-off technologies from the space program enhance everyday aspects of our lives. Greater research within simulated microgravity environments and the support of the wider medical community for the space program will lead yet further cycles of discovery and innovation.

References

1. Dick S. Summary of space exploration initiative. NASA. <http://history.nasa.gov/seisummary.htm>.
2. Bush GW. The vision for space exploration. Available from: http://www.nasa.gov; January 2004.
3. The vision for space exploration. NASA. Available from: http://www.nasa.gov/missions/solarsystem/explore_main.html.
4. Billica R. Medical management of U.S. astronauts. *J Clin Pharmacol* 1994;**34**:510–2.
5. Houtchens BA. Medical-care systems for long-duration space missions. *Clin Chem* 1993;**39**(1):13–21.
6. Campbell MR, Billica RD. A review of microgravity surgical investigations. *Aviat Space Environ Med* 1992;**63**(6):524–8.
7. Dons RF, Fohlmeister U. Combined injury syndrome in space-related radiation environments. *Adv Space Res* 1992;**12**(2–3):157–63.
8. Stazhadze LL, Goncharov IB, Neumyvakin IP, Bogomolov VV, Vladimirov IV. Problems of anesthesia, surgical care and resuscitation during manned space flights. *Kosm Biol Aviakosm Med* 1982;**16**(4):9–12.
9. Markham SM, Rock JA. Microgravity testing a surgical isolation containment system for space station use. *Aviat Space Environ Med* 1991;**62**(7):691–3.
10. McCuaig K. Surgical problems in space: an overview. *J Clin Pharmacol* 1994;**34**(5):513–7.
11. McCuaig KE, Houtchens BA. Management of trauma and emergency surgery in space. *J Trauma* 1992;**33**(4):610–25.
12. Ross H, Brodie E, Benson A. Mass discrimination during prolonged weightlessness. *Science* 1984;**225**(4658):219–21.
13. Money KE, Cheung BS. Alterations of proprioceptive function in the weightless environment. *J Clin Pharmacol* 1991;**31**(10):1007–9.
14. Kirkpatrick AW, Campbell MR, Novinkov OL, Goncharov IB, Kovachevich IV. Blunt trauma and operative care in microgravity: a review of microgravity physiology and surgical investigations with implications for critical care and operative treatment in space. *J Am Coll Surg* 1997;**184**(5):441–53.
15. Tairbekov MG, Margolis LB, Baibakov BA, Gabova AV, Dergacheva GB. Cell growth and motility in culture (in vitro) under microgravity conditions. The fibroblast experiment. *Izv Akad Nauk Ser Biol* 1994;(5):745–50.
16. Shaw SR, Vailas AC, Grindeland RE, Zernicke RF. Effects of a 1-week spaceflight on morphological and mechanical properties of growing bone. *Am J Physiol* 1988;**254**:R78–83.
17. Buravkova LB, Romanov YA. The role of cytoskeleton in cell changes under condition of simulated microgravity. *Acta Astronaut* 2001 Mar–Jun;**48**(5–12):647–50.
18. Tixador R, Richoilley G, Gasset G, Templier J, Bes JC, Moatti N, et al. Study of minimal inhibitory concentration of antibiotics on bacteria cultivated in vitro in space (Cytos 2 experiment). *Aviat Space Environ Med* 1985;**56**(8):748–51.
19. Moatti N, Lapchine L, Gasset G, Richoilley G, Templier J, Tixador R. Preliminary results of the ''Antibio'' experiment. *Naturwissenschaften* 1986;**73**(7):413–4.
20. Hales NW, Yamauchi K, Alicea A, Sundaresan A, Pellis NR, Kulkarni AD. A countermeasure to ameliorate immune dysfunction in vitro simulated microgravity environment: role of cellular nucleotide nutrition. *In Vitro Cell Develop Biol Anim* 2002;**38**:213–7.
21. Durnova GN, Vorotnikova EV. Histological study of the lymphoid organs of rats after a 7-day space flight on the Kosmos 1667 biosatellite. *Kosm Biol Aviakosm Med* 1988 Mar–Apr;**22**(2):75–7.
22. Konstantinova IV, Rykova MP, Lesnyak AT, Antropova EA. Immune changes during long-duration missions. *J Leukoc Biol* 1993;**54**(3):189–201.
23. Taylor GR. Immune changes in humans concomitant with space flights of up to 10 days duration. *Physiologist* 1993;**36**(Suppl. 1):S71–4.
24. Grigoriev AI, Bugrov SA, Bogomotov VV, Egoriv AD, Kozlovskaya IB, Pestov ID, et al. Medical results of the Mir year-long mission. *Physiologist* 1991;**34**(Suppl.):S44–8.
25. Campbell MR, Billica RD, Johnston 3rd SL. Surgical bleeding in microgravity. *Surg Gynecol Obstet* 1993;**177**(2):121–5.
26. Ruoslahti E. Stretching is good for a cell. *Science* 1997;**276**:1345–6.
27. Saaristo A, Veikkola T, Enholm B, Hytonen M, Arola J, Pajusola K, et al. Adenoviral VEGF-C overexpression induces blood vessel enlargement, tortuosity, and leakiness but no sprouting angiogenesis in the skin or mucous membranes. *FASEB J* 2002;**16**(9):1041–9.
28. Quinn TP, Schlueter M, Soifer SJ, Gutierrez JA. Cyclic mechanical stretch induces VEGF and FGF-2 expression in pulmonary vascular smooth muscle cells. *Am J Physiol Lung Cell Mol Physiol* 2002;**282**(5):L897–903.
29. Takei T, Rivas-Gotz C, Delling CA, Koo JT, Mills I, McCarthy TL, et al. Effect of strain on human keratinocytes in vitro. *J Cell Physiol* 1997;**173**(1):64–72.
30. Zheng W, Seftor EA, Meininger CJ, Hendrix MJ, Tomanek RJ. Mechanisms of coronary angiogenesis in response to stretch: role of VEGF and TGF-beta. *Am J Physiol Heart Circ Physiol* 2001;**280**(2):H909–17.
31. Burridge K, Chrzanowska-Wodnicka M. Focal adhesions, contractility, and signaling. *Annu Rev Cell Dev Biol* 1996;**12**:463–518.
32. Lansman JB, Hallam TJ, Rink TJ. Single stretch-activated ion channels in vascular endothelial cells as mechanotransducers? *Nature* 1987;**325**(6107):811–3.
33. Ingber DE. Tensegrity: the architectural basis of cellular mechanotransduction. *Annu Rev Physiol* 1997;**59**:575–99.
34. Korff T, Augustin HG. Tensional forces in fibrillar extracellular matrices control directional capillary sprouting. *J Cell Sci* 1999;**112**(Pt 19):3249–58.
35. Baker AB, Sanders JE. Angiogenesis stimulated by mechanical loading. *Microvasc Res* 2000;**60**(2):177–81.
36. Chen C, Mrksich M, Huang S, Whitesides G, Ingber D. Geometric control of cell life and death. *Science* 1997;**276**.
37. Ingber D. How cells (might) sense microgravity. *FASEB J* 1999;**13**(Suppl.):S3–15.