Potential myocardial injuries to normal heart with prolonged space missions: The hypothetical key role of magnesium

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Zusammenfassung

Russische tierexperimentelle Studien haben bei längeren Weltraumflügen Schädigungen des Herzmuskels aufgezeigt, die mit gestörter Mikrozirkulation und hohen myokardialen Katecholamin-Konzentrationen einhergingen. Anstieg der Katecholamine und signifikante Magnesiumverluste sind auch bei bemannten Weltraumflügen gezeigt worden. Beide Veränderungen könnten verstärkt werden durch die unablässige Belastung mit einem Defizit an Magnesium-Ionen, das durch Bindung von Magnesium-Ionen an Freie Fettsäuren entsteht, wobei letztere durch die Katecholamine freigesetzt werden. Ein Circulus vitiosus kann potentiell aus vier Mechanismen resultieren: 1. über die inverse Beziehung zwischen hohen Katecholaminspiegeln und niedrigen Konzentrationen an Magnesium-Ionen, 2. über hierdurch induzierte Koronarspasmen, welche das Endothel schädigen und so die Produktion von EDRF (endothelium-derived relaxing factor), d.h. von Stickoxid, vermindern, 3. über eine Verschlechterung der myokardialen Sauerstoffversorgung als Folge der Koronarspasmen und lokaler Thrombenbildung bei erhöhtem Sauerstoffbedarf und entsprechender Ischämie-induzierter weiterer Katecholamin-Liberation sowie 4. über eine verstärkte Angiotensin II-Wirkung aufgrund des Defizits an Magnesium-Ionen, wodurch Aldosteron freigesetzt wird, das wiederum die Magnesiumausscheidung erhöht. Magnesiummangel als auch hohe Katecholaminspiegel können das Herz durch erhöhte Bildung freier Radikale schädigen, die wieder die durch Strahlung bedingte Anhäufung ähnlicher Faktoren verstärken können. Aufgrund der durch Schwerelosigkeit bedingten, denkbaren Malabsorption ist es naheliegend zu spekulieren, dass eines Tages den Astronauten Magnesium über ein subkutanes Mikrochip-gesteuertes System zugeführt wird.

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Summary

The Russian experimental animal studies have demonstrated, with prolonged space flights, cardiac muscsle injuries with impaired microcirculation, and high cardiac concentrations of catecholamines. Elevation of the latter and significant losses of body magnesium, have been shown with manned orbital space flights. Both of these alterations could be aggravated by the necessity of unremitting endurance exercise with magnesium ion deficiency partly due to the removal of free magnesium ions from the circulation by chelation with catecholamine-induced free fatty acids. There is the potential for 4 vicious cycles; 1. The inverse relationship between high catecholamines and low magnesium ions. 2. Coronary vasospasm induced by both the latter with the potential for injury to the endothelium and reduction in endothelium-derived relaxing factors (nitric oxide). 3. Reduction in myocardial oxygen supply secondary to coronary vasospasm and local and systemic thrombogenesis and with increased oxygen demand with the potential for severe ischemia conducive to further catecholamine release. 4. Magnesium ion deficiency enhancing angiotensin 2 action, resulting in increased aldosterone and in turn increased magnesium excretion. Both magnesium deficiency and high catecholamines may injure the heart through increased free radical formation, which in turn may aggravate radiation-induced injury by similar mechanisms. Because of space-related potential malabsorption, it is tempting to speculate, that some day astronauts might receive magnesium by a subcutaneous microchip drug delivery device.

Introduction

About a decade ago, I developed an hypothesis, that extraordinary unremitting endurance exercise could injure permanently the normal heart, based upon my study of *Sy Mah*, who at that time was the holder of the Guinness Book of Records for having completed the most marathons [1, 2]. Several years later, I postulated that the normal heart could be injured as well, when subjected to particularly long space missions, by somewhat similar but more complex mechanisms [3, 4]. The space-related mechanisms stem from hypokinesia and microgravity, resulting in invariable dehydration as a result of both [5].

In the mid-ninties, at a Workshop on Microgravity Research, it was postulated that on space missions, the endothelium was at risk of becoming injured secondary to both mechanical and biomedical insults [6]. The presence of insulin resistance by astronauts during space flight [7], which could be secondary to a reduction of microvascular vasodilator capacity [8], and the significant reduction in cyclic-GMP (a second messenger of nitric oxide) [9] support the hypothesis suggested at this microgravity workshop, with the postulated mechanisms recently published [4].

Experimental animals in space

Studies by the Russians, of experimental animals in space, demonstrated pronounced impaired microcirculation and serious myocardial pathology, even on space flights of only a few weeks. Edema of the endothelium was demonstrated, with altered endothelial permeability, and some of the coronary vessels were completely occluded. There was also noted atrophy of the cardiac muscle. Other studies

suggested the possibility that some of these changes were stress-related, since there was significant increase in the concentration of norepinephrine in cardiac tissue. Finally, in addition to decreased activity of enzymes with injury of the mitochondria, there was evidence of impairment in the repair mechanism [5]. These animal studies suggest that even relatively brief space missions, may predispose to a myocardial infarction in the absence of coronary artery disease prior to the space flight.

Mechanisms for endothelial injury

Too much or too little exercise may damage the endothelium through similar mechanisms [4]. Therefore, the intensity, duration, and frequency of exercise would have to be individualized on longer missions, rather than utilizing a rigid exercise schedule for all crew members.

High shear stress and turbulence, precipitated by catecholamine-induced coronary vasospasm may injure the endothelium and in turn lead to further vasospasm by a vicious cycle. High catecholamines, with release of high levels of free fatty acids, which bind magnesium ions, may persist by ongoing vicious cycles as well. A third vicious cycle can be precipitated by elevations of catecholamines related to ischemia. These mechanisms can injure the normal heart from extraordinary unremitting endurance exercise [2, 3].

On space flights, because of skeletal muscle and bone loss, thereby depleting the magnesium reservoir, the potential for a magnesium deficit [5, 10-13] is far greater than the potential deficit of magnesium from unremitting exercise alone.

There are in addition, invariable angiotensin elevations complicating hypokinesia [13, 14], microgravity [5] and specifically secondary to impairment in the thirst mechanism [14, 15]. *Zorbas* has shown in experimental animals [14] and humans [16] subjected to hypokinesia, that even relatively brief periods of hypokinesia (as little as 7 days of strict bedrest) with partial loss of the water reservoir in skeletal muscle primarily [15], can cause pronounced dehydration, stemming from a marked increase in the rate of fluid excretion [16].

With the additional insult of microgravity, resulting in a shift of fluid to the upper part of the body, the volume regulating Henry-Gauer reflex, causes excess renal loss of extracellular fluids in short-term flights, and during long space missions, greater loss of intracellular fluids [5].

A water deficit [17] is clearly a two-edged sword with the potential of injuring ultimately the endothelium [4, 10], because not only is there a compensatory potentially damaging elevation of the renin-angiotensin system [5], but a devastating effect upon the endothelilum from loss of the protective effect of water counteracting increased free radicals (superoxide anions) [18]; these superoxide anions inactivate nitric oxide [19].

It is conceivable that on the Apollo-15 mission in 1971, a malfunction of the in-suit water device of *James Irwin*, resulting in no access to water for up to 7 hours on 3 excursions on the lunar surface, contributed to *Irwin's* myocardial infarction 21 months after that mission, by injuring the endothelium [4, 10].

In addition to catecholamine elevations produced by high angiotensin levels and exercise as well as magnesium deficiencies [4], sleep deprivation can contribute to these catecholamine elevations. *Monk* et al. [20] have shown that in a study of astronauts on a space mission, the mean number of hours of sleep was reduced to 6.

Catecholamines [17] can undergo autoxidation with the electrons produced, captured by molecular oxygen, producing superoxide anions and other activated oxygen species [21]. Magnesium ion deficiency, aggravated by excessive catecholamines with in turn a vicious cycle, would contribute to this oxidative stress [4, 22].

Whereas nitric oxide [4, 10] is a vasodilator and is antithrombotic, as well as an antioxidant, angiotensin-II is a vasoconstrictor, prothrombotic and a pro-oxidant. An imbalance between angiotensin-II and nitric oxide may alter the adhesive properties of the endothelial lining and ultimately lead to atherogenesis [19].

Insulin resistance

In addition to the potential for endothelial injuries from microgravity and hypokinesia, resulting in 3 vicious cycles [4], there is the potential for a fourth vicious cycle. Magnesium deficiency, by enhancing the activity of angiotensin-II, and thereby increasing aldosterone release, would in turn increase the renal loss of magnesium resulting in a vicious cycle [23, 24].

Since insulin resistance may be precipitated by a magnesium deficiency [23] and high sympathetic tone [25, 26], it is not surprising that insulin resistance has been demonstrated during space flights [7, 17]. Using C-peptide as a marker for insulin secretion (C-peptide is released by the processing of proinsulin into mature insulin [27] *Stein* et al. [7] demonstrated during a space flight as well as bedrest that C-peptide excretion increased with time, while energy intake remained constant, indicative of insulin resistance. A reduced capillary surface area, with impairment in microvascular endothelial function, may contribute to insulin resistance [8]. This may be because the diffusion distance from capillary to muscle cells, where glucose is taken up, would be increased [28].

Since insulin sensitivity relates to microvascular function, the presence of insulin resistance during space flights supports the hypothesis that space missions may predispose to endothelial dysfunction [29, 30], which may ultimately lead to coronary heart disease [10, 31].

This hypothesis is further supported by the finding of a significant reduction in plasma cyclic GMP (a second

messenger of nitric oxide) during a long-term space flight and after 5 days of simulated microgravity (6° head-down tilt) [9].

Radiation

Although the radiation exposure on orbital flights [5] and the Apollo missions [10], were not considered significant, the degree of radiation risk on a Mars mission is unknown, but is expected at times to be quite high [32]. Even with radiation shelters on board, the flights would have to be scheduled in such a way as to reduce exposure to high cosmic rays and solar flare activity [32]. The potential radiation risk to the coronary vessels [33], by impairment in endothelial function, with decreased nitric oxide production [34], would compound potential injuries induced by hypokinesia and microgravity.

Calcium overload

In addition to the previously described ischemic mechanisms which may lead to calcium overload [35] of the myocardium and the arterial wall, and potentially leading to a myocardial infarction, other conditions complicating space flights, can precipitate calcium overload with cell necrosis, i.e. catecholamine elevations [36], insulin resistance [37] and magnesium ion deficiency [38].

Still another contributing factor of possible significance in this regard, is the presence of elevated carbon dioxide levels, as noted in the Russian space station MIR (Euro MIR 94). Whereas the normal CO_2 conditions on Earth is .03%, during the Euro MIR 94 missions, readings of .5%-.7% CO_2 were obtained. Studies of chronically elevated CO_2 atmosphere by *Drummer* et al. [39] revealed reduced serum calcium levels, despite a reduction in fecal and urinary calcium losses. Since there was suppression of bone formation as well, these investigators suggested that there may be, with prolonged space missions, an intracellular shift of calcium, related to this high CO_2 environment.

A look into the future

If too much or too little exercise on space missions can injure the normal heart [1-4, 10, 11] and if no matter how much one exercises or how much water is ingested, the reservoir in muscle and bone of vital electrolytes such as potassium and magnesium and in addition water, remain depleted [11-14], what can be done to protect the myocardium? Certainly with the array of side effects complicating the usage of pharmaceuticals, it would be impractical to administer these to astronauts on space missions at least in the foreseeable future. Assuming that over the next few decades, methods will be developed to protect the space crews from high radiation, and potential risk from elevated CO_2 levels, what further measures appear imperative for a Mars mission?

Selection of crews

In addition to excluding astronaut candidates with obvious risk factors for cardiovascular disease, it appears prudent to avoid those candidates with the Ace DD genotype since this genotype may be conducive to angiotensin-II elevations particularly in the absence of other risk factors for coronary artery disease [3, 4].

In addition, it appears reasonable to avoid selecting astronauts who might experience deterioration of endothelial function with aging. After age 30 – unfortunately for all of us – the delicate endothelial cells are replaced by inadequate substitutes [4, 40]. Therefore, I believe, our best chance of avoiding endothelial injuries with the potential of irreversible vascular injury or death, is to ensure that the crew return from Mars before age 30 [40].

Finally, in selecting a crew for a Mars mission, it should be kept in mind, that being a male is an obvious risk factor for coronary disease; in the third and fourth decades the mortality rate from ischemic heart disease is 6 times greater than in females [41]. Therefore, I suggest, that for a Mars mission, our best chance of success is with an all female crew [4, 42]. It is noteworthy that on marginal magnesium intakes, young females retain magnesium better than young males. Estrogen's enhancement of magnesium utilization and uptake by soft tissues and bone, may explain the resistance of young women to heart disease [41]. Clearly this would be an advantage to astronauts with the potential for irreversible depletion of magnesium reservoirs [11, 13]. Even in the fifth decade, skeletal muscle magnesium is significantly higher in normotensive women, compared to normotensive men [43].

„Pharmacy on a Chip"

On a Mars mission, if magnesium stores are progressively depleted with in turn the impossibility of completely correcting potassium deficits [13, 44] what measures can be taken to resolve this potentially fatal problem? *Seelig* [44] has emphasized that in the presence of an aldosterone-induced chloride loss (as might occur from a magnesium deficit [23]) resulting in a metabolic alkalosis, and volume contraction, only with magnesium chloride can the potassium depletion be corrected.

But with the magnesium reservoir depleted, and in the presence of space-related potential malabsorption [45], what can be done to ensure adequate magnesium levels? A recently developed non-invasive method of measuring tissue magnesium levels, perhaps daily if necessary, coupled with recently patented control-release microchips might provide a solution.

Less than 1% of the total body magnesium is in the serum, and red blood cell levels do not always represent the true magnesium status of the body tissues. The availability of measuring the whole cell magnesium content in sublingual cells, might be utilized daily, to determine the proper dosage

of magnesium to be administered, for example on a Mars mission. Sublingual magnesium determinations have been shown to correlate closely with cardiac tissue levels [46, 47].

But if magnesium is not adequately absorbed under conditions of spaceflight [45] through the intestinal route and subcutaneous magnesium is not yet available, how can magnesium be delivered adequately to restore the vital reservoir? If a suitable subcutaneous magnesium product can be manufactured, there may be an innovative device to administer it to astronauts daily if needed. *Santini* et al. have just patented a microchip, which can be imbedded subcutaneously; this has the capability of providing the administration of over 1000 minidoses of a substance [48]. Perhaps other electrolytes can be administered on very long space missions by this method as well.

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