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COMMENTARY

Potential renovascular hypertension, space missions, and the role of magnesium

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Abstract: Space flight (SF) and dust inhalation in habitats cause hypertension whereas in SF (alone) there is no consistent hypertension but reduced diurnal blood pressure (BP) variation instead. Current pharmaceutical subcutaneous delivery systems are inadequate and there is impairment in the absorption, metabolism, excretion, and deterioration of some pharmaceuticals. Data obtained from the National Aeronautics and Space Administration through the Freedom of Information Act shows that Irwin returned from his 12-day Apollo 15 mission in 1971 and was administered a bicycle stress test. With just three minutes of exercise, his BP was >275/125 mm Hg (heart rate of only 130 beats per minute). There was no acute renal insult. Irwin's apparent spontaneous remission is suggested to be related to the increase of a protective vasodilator, and his atrial natriuretic peptide (ANP) reduced with SF because of reduced plasma volume. With invariable malabsorption and loss of bone/muscle storage sites, there are significant ($P < 0.0001$) reductions of magnesium (Mg) required for ANP synthesis and release. Reductions of Mg and ANP can trigger pronounced angiotensin (200%), endothelin, and catecholamine elevations (clearly shown in recent years) and vicious cycles between the latter and Mg deficits. There is proteinuria, elevated creatinine, and reduced renal concentrating ability with the potential for progressive inflammatory and oxidative stress-induced renal disease and hypertension with vicious cycles. After SF, animals show myocardial endothelial injuries and increased vascular resistance of extremities in humans. Even without dust, hypertension might eventually develop from renovascular hypertension during very long missions. Without sufficient endothelial protection from pharmaceuticals, a comprehensive gene research program should begin now.

Keywords: magnesium, atrial natriuretic peptide, dust, renovascular hypertension, microgravity

"The farther backward you can look, the farther forward you are likely to see."

—Winston Churchill

Introduction

Even without radiation the endothelium is vulnerable to dysfunction/injuries with space flight (SF) because of oxidative stress involving both the cardiovascular system as well as the systemic circulation in the "Apollo 15 space syndrome."[1] This syndrome, which I described, was experienced by both Irwin and Scott on the first of three excursions to the lunar surface, even prior to dust inhalation in that habitat. My syndrome was characterized by very painful, apparently swollen, fingertips possibly secondary to peripheral vasospasm and compression by fluid trapped distally. Therefore it can be a warning that coronary vasospasm with ischemia (possibly silent) might also exist, predisposing the person to a myocardial infarction.

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51

Similarly vasoconstriction of systemic blood vessels could be the underlying mechanism of a decrease of calf blood flow of 40%. Measurements taken between 4–12 SF-days showed calf vascular resistance doubling. The blood pressure (BP) increased during SF.[2] With SF, vicious cycles can occur between magnesium (Mg) ion deficits and catecholamine elevations and also between catecholamine elevations and ischemia. Furthermore vicious cycles can also develop between reduced nitric oxide (NO), coronary vasospasm with turbulence, and endothelial injuries.[3]

Through information obtained by the Freedom of Information Act (FOIA), I acquired bicycle stress test data regarding Irwin on Apollo 15 showing extraordinary hypertension. The stress test data indicated a BP > 275/125 mm Hg with a heart rate of only 132 per minute after just three minutes of exercise. This test was probably performed on the day after his return from the 12-day mission. The resting BP was not shown, but at one minute the BP was 250/125, with the same heart rate. There was no evidence of an acute renal insult. On the other hand it is noteworthy that Shepard's bicycle stress test data, on the day after his return from the Apollo 14 mission, revealed a relatively normal response, with a BP of 200/75 at the same heart rate as Irwin's, but not reaching this level (132 per minute) until 13 minutes of exercise.

One mechanism for this discrepancy could be related to the variation in the chemical composition of the dust inhaled at various lunar landing site habitats.[4] Conrad's stress test data – the only other deceased moon walker (Apollo 12) – is not available, after a "careful search" by National Aeronautics and Space Administration (NASA) in response to my FOIA request in 2008.

On the stress test, on the day of his return, Irwin showed "cyanosis of the finger tips" from the 18th–20th minutes with a BP of 200/90, consistent with venous blood trapped distally, which supports my syndrome on the likelihood of space syndrome. I postulated that the severe hypertension was a complication of dust inhalation. The inhalation had occurred for a total of almost seven days; about 40 hours in the lunar habitat, two days orbiting the moon, making the survey, dust brought into the command module and the three-day journey home.[4] The vulnerability to endothelial injuries is far greater in males and in addition the endothelium does not heal adequately after the age of 30 years.[3] Furthermore, assuming that some day the problems of hypertension related to dust, brought from the habitats on the moon, will be resolved with removal of even ultrafine dust,[4] there are the problems stemming from depletion of the reservoirs for water ie, primarily in skeletal muscle and Mg reservoirs in muscle and bone (about 60% in the latter). This loss stems from hypokinesia (decreased movement) compounded by decreased thirst and is conducive to oxidative stress-induced renovascular hypertension.[5] To prevent this, gene therapy may be necessary[6,7] since there are multiple problems with pharmaceuticals; there is invariable SF-malabsorption,[8] deterioration of some medications no longer meeting United States Pharmacopeia (USP) standards[9] and impairment in pharmaceutical metabolism and excretion because of potential SF injuries to the liver[10] and kidneys.[11]

Whereas Fritsch-Yelle and colleagues[12] found reduced BP on shuttle missions of 5–10 days; Shiraishi and colleagues[13] found that the waking BP was not different from preflight levels. On the other hand Watenpaugh and colleagues[2] found that SF BP increased in comparison to postflight supine levels and they suggested that premission differences in baseline conditions could account for these discrepancies. However the absence of a significant drop (<10%) in nocturnal BP[12,13] indicates that those during SF are "nondippers," which portends to renal disease as discussed below.

Potential renovascular hypertension

There is a predisposition for progressive oxidative stress-induced renal disease[5] intensified by atrial natriuretic peptide (ANP) deficiencies[6,14–16] with a >40% reduction on Spacelab 2 and excessive levels of catecholamines[1,3,4,17,18] and the combination of endothelin[19] and significant angiotensin I elevations ($P < 0.0001$)[17] conducive to sustained renal vasoconstriction.[20,21]

There is a potential synergism regarding endothelin and angiotensin II blockade which has been shown to improve endothelial function. Blockade of both has also been shown to increase renal blood flow in healthy subjects,[21] but, as emphasized above, pharmaceuticals can not be utilized. Proteinuria, considered an expression of endothelial dysfunction[22] and a strong predictor of renal disease progression,[23–25] with stimulation of endothelin expression in renal cells,[19] was shown after space missions.[17,18] Proteinuria was more pronounced after prolonged missions but disappeared during the recovery period[17] possibly related to reductions back to premission catecholamine levels.[23] SF reductions of vascular endothelial growth factor (VEGF) from thrombocytopenia with platelet aggregation from endothelial dysfunction[26] and impaired VEGF expression as a result of SF insulin resistance[27] would impair capillary repair in damaged glomeruli and contribute to proteinuria.[28,29]

Furthermore the reduced diurnal variabilities in blood pressures ("nondipper") as noted previously increases the risk of renal dysfunction. The mechanisms may be related to increased sympathetic nervous system activity and possibly insulin resistance, both of which have been shown with SF.[1,3,4,17,30] Many cosmonauts have shown higher levels of blood creatinine during and after SF in comparison to their preflight levels, and there is decreased concentrating ability after SF.[17] It was also found that urine osmolarity in response to fluid deprivation was consistently lower after flight than before, but only if the flight lasted more than 30 days.[17]

Studies after short missions and hypokinesia of rat heart tissue showed narrowing of the small vessels, some occlusions, and endothelial projections conducive to increased permeability.[18,31] Leach Huntoon and colleagues[17] postulated that increased permeability of capillary membranes may be the most important mechanism for SF-induced plasma volume reduction of >10% conducive to endothelial injuries with vicious cycles and angiotensin elevations and reduced secretion of ANP.

Too much or too little exercise will deplete Mg ions[3] that are antioxidants as well as calcium (Ca) blockers.[27] On spacecraft, it has been postulated that there may be a shift of Ca into the cells complicating high carbon dioxide levels.[4] This may contribute to Ca overload of the mitochondria as shown in rats after SF.[31] Contributing to SF oxidative stress[32] and in turn Ca overload is the necessity of 100% oxygen for 1–2 hours prior to a space walk to prevent decompression sickness.[4] Mg could reduce this oxidative stress,[27,33] but there is no suitable subcutaneous delivery device for Mg, since at this time a reliable subcutaneous microchip device can't be replenished.[27] Invariable SF malabsorption and reduced storage sites could be responsible for significant SF Mg deficits ($P < 0.0001$) after shuttle missions.[17] In addition to the 200% increase of plasma angiotensin after, for example, the Skylab flights of up to 84 days,[17] there could be the predisposition for an active intrarenal renin–angiotensin system. SF is conducive to increased angiotensin effects from both reduced plasma volume[17] and ANP deficits with reduced NO[15] and also from Mg ion deficits. Magnesium also affects the synthesis and release of ANP.[16] An intrarenal renin–angiotensin system resulting from SF-reduced NO could contribute to chronic kidney disease stemming from inflammation both directly and through interaction with oxidative stress mechanisms.[17,18,32,34,35] Elevated sympathetic nerve activity has been shown unequivocally in patients with renovascular hypertension,[36] but until a few years ago

the catecholamine levels were not thought to be elevated with SF. This concept has now been shown to have been incorrect. Christensen and colleagues,[37] for example, have shown that plasma norepinephrine (NE) and plasma renin activity[38] were increased even to levels above those of the seated ground-based position. Plasma NE was approximately twice the value of the supine position on the ground, predisposing those in SF to nondipping, as noted above.[30] Furthermore, it was stated that the reason for this was unclear. Certainly one mechanism may be the reductions of SF Mg ion levels with, in turn, elevations of catecholamines, along with elevations of angiotensin and aldosterone ($P = 0.0008$) with ongoing vicious cycles.[1,3,4,17,18,27,39] Magnesium may also provide protection against the renal damaging effects of aldosterone, predisposing the person to fibrosis.[39–41]

Gender selection

Pertaining to the predisposition for renovascular hypertension, young females have several clear advantages. The endothelium is not adequately repaired after the age of 30 years,[3] and the cardiovascular mortality rate is six times higher in males than females under the age of 35 years. This could be related not only to estrogen's vascular advantages[3] and probably to the fact that males have no physiological way of losing iron, predisposing them to oxidative stress, but also could be related to other clear advantages in females. The levels of ANP in females are approximately twice those of young men.[42] During the 438-day mission of Polyakov and after just five months in space, his cyclic guanosine monophosphate (cGMP) levels were undetectable, which supports my hypothesis.[3,43] cGMP is a second messenger of both NO and ANP, and Polyakov's cGMP did not return to premission levels until three months after this mission. The cGMP–signaling pathway has been postulated as an important regulator of renal physiology.[15] ANP receptors are expressed on the surface of renal endothelial cells,[15] and ANP inhibits renin release and can reduce renal damage from an ischemic insult.[38]

Metabolic balance studies of young adults showed that with marginal intakes of Mg, males tended to be in negative Mg balance whereas females remained in equilibrium. Catecholamine levels in males, in turn, are therefore higher with vicious cycles between Mg ion deficits and catecholamine elevations[39] (Figure 1). After SF of only 18–22 days, rats showed an increased activity of the juxtaglomerular apparatus[18] and similarly, experimental Mg deficiency has been shown to cause hypertrophy of this structure, resulting
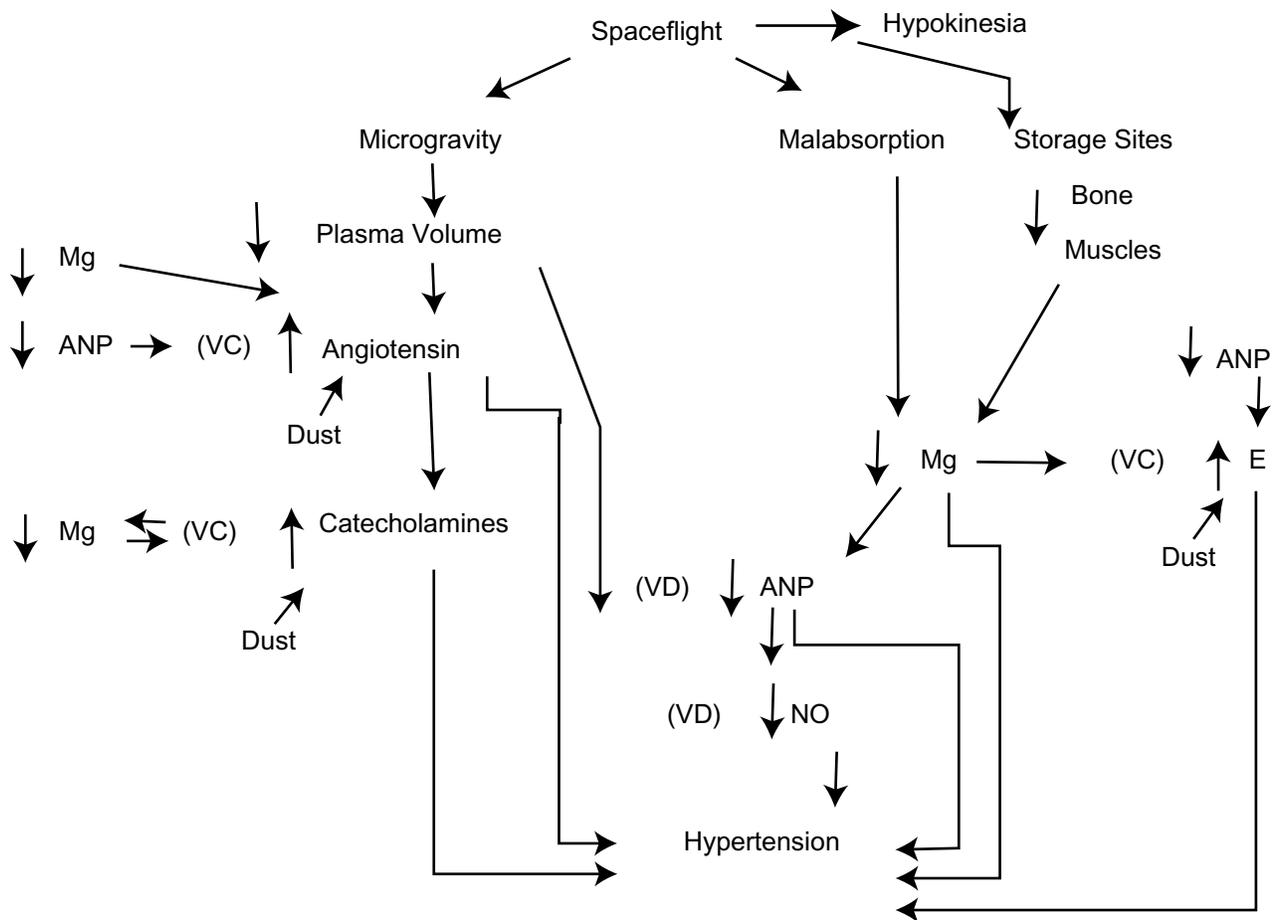
Figure 1 Proposed mechanisms showing how decreased atrial natriuretic peptide can cause severe hypertension secondary to dust inhalation, microgravity, and hypokinesia.
Abbreviations: Catecholamines, epinephrine, norepinephrine, increased by dust; VC, vessel constriction; VD, vessel dilatation; Mg, magnesium ions; ANP, atrial natriuretic peptide; hypokinesia, decreased movement; angiotensin, angiotensin effect, increased by dust; NO, nitric oxide (endothelial derived relaxing factor); E, endothelin, increased by dust.

in aldosterone secretion, and in turn, an increased Mg loss and another vicious cycle.[27,39] VEGF levels are significantly higher during the formative stage (early teens) in females, although not in adulthood,[44] which would enhance repair of the endothelium as well as increase the development of collateral circulation.[28,29]

Gene therapy

How can we offset the SF reductions in cGMP[43] to maintain endothelial function by utilizing novel pharmacological compounds to prevent renal disease and in turn hypertension? How can we break self-perpetuating vicious cycles? Oxidative stress involving the kidneys and blood vessels triggers hypertension, whereas conversely hypertension has been shown to cause oxidative stress and inflammation in the kidney and cardiovascular tissue of experimental animals.[45] With very long missions, gene therapy may be the only option even without consideration of renal complications.[46] Gene therapy has been proposed, for example,

to prevent invariable space anemia.[7] This, therefore, could be of vital importance in preventing ANP deficiencies.[6] There is a 10% red blood cell mass loss within one week of entering space.[17] Anemia may contribute to endothelial dysfunction by reducing oxygen delivery and intensifying oxidative stress since red blood cells have important antioxidant functions.[47] In addition there are SF reductions in platelets, the primary source of VEGF, which, in turn, play an important role in angiogenesis, function, and repair of the endothelium.[27] With SF there are reductions of water because of reduced thirst and loss of storage sites for water and Mg, and an impairment in red blood cell production. Therefore there is a reduction of three natural antioxidants conducive to endothelial dysfunction.[1,3,4,48,49] Furthermore, there is no subcutaneous device available to replenish Mg.[27]

Without the availability of pharmaceuticals for use in SF, there is no alternative but the use of gene therapy. In addition to its use to correct invariable SF anemia,[7] gene

therapy studies have been conducted to reduce BP.[6,50,51] NO is generated by NO synthase (NOS) enzymes and NOS gene transfer has been shown to reverse endothelial dysfunction in several diseases including hypertension and atherosclerosis. In addition NOS gene therapy has been shown to improve renal function and since NO is antifibrotic, this therapy may reduce the potential for renal fibrosis complicating aldosterone excess.[40,52] A major stumbling block, however, has been finding a suitable vector to deliver the gene to the site of action and this may require several years (possibly decades) of SF research involving vector studies with progressively wider applications.[53]

A number of viruses have been developed for gene transfer but the focus has been primarily on retroviruses, adenoviruses, adeno-associated viruses, and lentiviruses. The latter are currently of great interest; they are a type of retrovirus that can infect both dividing and nondividing cells because their virus "shelf" can get through the intact membrane of the nucleus of the target cell. However because of persistent serious immune reactions with viruses, some researchers are directing their investigations to nonviral gene delivery. For example liposomal gene transfer has been investigated but there is a relatively low level of gene expression compared with that achieved from viral vectors.[52]

It has been emphasized[52] that gene therapy has not proven to be nearly as successful as had been predicted, which may be due to only transient transfection efficiencies. In addition if the expression of NOS gene therapy is not tightly regulated to the target site, there is the potential complication of pronounced hypotension with impending shock. McCarthy and colleagues[52] conclude, by stating that although thousands of patients have been treated with gene transfer therapies, reproducibility of positive results has yet to be demonstrated conclusively.

I have stressed that one of the major concerns with SF is the vulnerability of the endothelium and, therefore, research must include the correction of ANP, NO, VEGF, and red blood cell deficiencies, the latter because of its antioxidant effect; this effect is shared by Mg administration,[33] which also has an anti-inflammatory and antifibrotic effect, and can prevent aldosterone-induced renal dysfunction (proteinuria).[40] Since transfection efficiency may be temporary,[52] gene therapy will have to be repeatedly reevaluated, depending upon the length of the mission. This will involve regularly scheduled diagnostic evaluation tests. How complex will these tests be and how much equipment and personnel will be required?

The gravity on the moon is 1/6 G whereas Mars is 0.38 G. Investigators have argued for decades as to how much <1 G is tolerable. Since we have Earth genes, I believe that any fraction <1 G may be ultimately intolerable. There is a solution, but we are only at the threshold of a process that may require many decades of gene therapy research before we are ready to embark on very long missions or colonize other planets. Is it "our destiny to colonize" before this research is complete? Some animals that spend all their lives in caves can't adapt to the outside. Are we spared the restrictions of Nature? We share at least 80% of the same genes as rats.

Conclusions

Even though with relatively short missions (six months), the mean 24-hour BP is not elevated unless there is hypertension from inhalation of dust in the habitats without adequate protection devices, it seems reasonable to speculate that ultimately, astronauts will develop renovascular hypertension unless gene therapy is utilized. Until a suitable replenishable subcutaneous device is developed, Mg, necessary for the synthesis as well as the release of ANP, cannot be administered. Space missions of considerable length are more likely to succeed with a female crew. In addition to ongoing pharmaceutical research, a comprehensive gene research program should begin now. Specifically gene therapy may be necessary to suppress activity of an upregulated intrarenal renin–angiotensin system.

Disclosure

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