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A NUMERICAL MODEL TO ASSESS DECONDITIONING OF THE CARDIOVASCULAR SYSTEM IN LONG-TERM EXPOSURE TO MICROGRAVITY. VERIFICATION AND SIMULATION OF MARS MISSION SCENARIOS

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Abstract

Numerical simulations of the cardiovascular system are particularly important in scenarios where it is difficult to experiment different weightlessness exposure conditions. Technological advances in terms of computational power in the last years, and improvement of algorithms have recently made these techniques more reliable. We report in this paper results from extensive simulations undertaken in a computing facility in our University (UPC BarcelonaTech) aimed at evaluate the risks involved in a long-term exposure to reduced gravity loads for a very extensive range of possible mission scenarios. The simulation allows to introduce different levels of exposure to hypo or hypergravity, and analyze the consequences on relevant figures of cardiovascular deconditioning, such as heart rate, mean stroke volume or vascular resistance. Neurological or thermic stress or aerobic exercise can also be applied in order to better emulate a realistic long-term space mission comprising, for example, Extra Vehicular Activities (EVA) or physical exercise as countermeasures. Gender differences have also been studied, with significant different recommendations given as outcomes of the simulation, for both men and female astronauts. Our model is based on the previous works form Melchier et al. or Heldt et al. who described in analytical terms the process of orthostatic intolerance due to gravity alterations being applied on a human subject. We incorporated these Runge-Kutta equations by using Matlab® and Simulink® software. Results from these models were validated in parabolic flight. We later developed this model to take into account all control system parts involved in the human cardiovascular system, and we finally achieved an electrical-like control model in which we could easily measure the output of the system (vascular resistance, blood volume etc.) as a means to assess the level of cardiovascular deconditioning. Step-by-step changes of gravity and thermal stress were later applied, as well as other real-like mission inputs. Different scenarios of Moon and Mars exploration missions are considered, and their associated risks are quantified. The more relevant results are provided, including the finding that the vascular resistance deconditioning appears to be alike in both microgravity and the reduced gravity at the level of the Moon; which raises concerns for a successful manned Mars mission scenario. This work may contribute to a better understanding of the underlying processes involved for both women in man adaptation to long-term microgravity, and shows the potential of such numerical simulations for designing manned mission scenarios.

Keywords: microgravity, numerical simulation, cardiovascular system, vascular resistance, Mars, human exploration.

Acronyms/Abbreviations

International Space Station (ISS)
Red Blood Cell (RBC)
Artificial Gravity (AG)
Extra Vehicular Activity (EVA)
Orthostatic Tolerance Limit (OTL)
Permission Exposure Limits (PEL)

1. Introduction

Numerical simulations of the cardiovascular and other physiological systems are particularly important in scenarios where it is difficult to experiment weightlessness exposure conditions, and long-term spaceflight is an area where it may apply. Technological advances in terms of computational power and improvement of algorithms have improved in the last years, becoming these techniques more feasible.

One of the major concerns for both sort- and long-term spaceflight is the phenomenon of cardio-vascular deconditioning. The cardio-vascular system has as a primary function to circulate blood through the body.

Although responses of the cardio-vascular system to microgravity seem to have been relatively free of major threats to wellbeing and performance during flight, problems as orthostatic hypotension and diminished exercise capacity are commonly observed after return to Earth.

Regarding long-term effects, the expose to microgravity beyond nine months on the cardio-vascular system are entirely unknown. This is of great concern, because they may involve the emergence of irreversible alterations in cardio-pulmonary function. There is also concern that there may be a loss of cardiac mass during prolonged microgravity exposure. The worst-case of a major incapacitating event for International Space Station (ISS) crews over a one-year period is estimated to be 1% per person per year [1].

Research studies have focused on understanding the effects of spaceflight on the cardio-vascular system by studying heart rate, blood vessel performance, blood pressure, and blood volume during spaceflight and upon return to Earth. One goal of these studies have been to determine precisely when fluid shifts occur, because they are believed to be the precursor of other physiologic changes which take place in a microgravity environment.

Some studies performed on six astronauts before and after long-duration (129-190 days) spaceflights revealed that orthostatic intolerance in even more severe after long-duration than after short-duration flights. Five in six astronauts became pre- syncopal during tilt testing after long-duration flights, whereas just one had become pre-syncopal during stand testing after short-duration flights [2].

Diminished vascular function, for example, is a primary cardiovascular risk of spaceflight. Astronauts have experienced presyncopal episodes on landing day as a result of lower peripheral vascular resistance [3].

In order to minimize these potential hazards, a number of potential countermeasures have been studied and put into practice. Physical exercise is well-known for its capacity to reduce these adaptations. A number of protocols have been carried out on board to improve physical health of cosmonauts and astronauts [4].

On the other hand, it has been reported a significant reduction in the percent of the whole blood that is comprised of red blood cells (hematocrit) in some astronauts. This reduction is what is often referred as space anemia. Overabundance of fluids in the upper part of the body causes the kidneys to remove this excess fluid, part of which is plasma. Then, the reduction in plasma volume causes an over-abundance of oxygen-carrying capability. That would reduce the production of erythropoietin and consequently decrease red blood cell production. As muscles lose mass in space they will require less oxygen and the process is reinforced. It is also possible that too much oxygen-carrying capacity in the blood may cause an increase in the destruction rate of red blood cells. Finally, as astronauts lose calcium in their bones, the structure and function of the bone and its marrow may change and may result in a decrease in red blood cell production.

Space anemia can be characterized by decreased Red Blood Cell (RBC) mass and has been reported from the early days of spaceflight. Comprehensive experiments by Alfrey et al. conducted aboard missions SLS-1 and SLS-2 provided an understanding of the mechanisms underlying spaceflight anemia [5, 6]. Therefore anemia appears to be a self-limiting and adaptive response to fluid shifts associated with microgravity.

Although a number of studies provide a well-stablished model of hematological changes in short-term spaceflights, more research is needed in terms of long-term behaviour of the entire cardiovascular system. As human and rodent model individuals have few opportunities to provide refinement into previous short-term models, numerical simulations arise as a new line of research. Long-term simulations may also preview any possible outcomes which are difficult to forecast in real models.

Studies of Artificial Gravity as a countermeasure to the cardiovascular deconditioning [7] have led to experimental results that have validated numerical cardiovascular models [8], showing the potential of this computational approach.

Overall, there are a number of current efforts [9, 10] which take into account the advantages of digital simulations, this paper being one more contribution to them.

2. Numerical Model

A number of numerical models have proposed in order to understand the response of the cardiovascular system to microgravity and return to Earth. A review of the early models that account for orthostatic intolerance can be found in the work of Melchier et al [11]. Modeling the response to gravity can be illustrated with the work of Heldt et al. [12]. A single cardiovascular model is used to simulate the steady-state and transient response to ground-based tests. The hemodynamic model is mathematically formulated in terms of an electrical-analog model in which inertial effects are neglected. Their entire model was described by 12 first-order differential equations. An adaptive step-size fourth-order Runge-Kutta integration routine was used to solve the system of differential equations numerically.

Based on these previous models, a parametric study was extended in order to see how different degrees of gravity exposure may affect the output parameters of the cardiovascular system.

A standard physiological control system was simulated with standard simulation tools (Matlab®, Simulink®. Then their parametric dependence with gravity was studied with a number of different trials and scenarios. A number of electrical-like modules were added to the previous model in order to assess the behaviour of spleen and bone marrow, and other organs as well.

We applied different acute inputs in order to simulate external perturbations to a steady-state scenario in low gravity. Countermeasures were taken in account as patterns applied along long duration terms. Further accounts of extreme external temperatures and exhaustion were applied to simulate Extra Vehicular Activities (EVA) in different conditions.

3. Numerical analysis and Results

3.1 Protocols and Results

The model was developed and validated comparing results with available published data as we found out in our previous communication [10]. Therefore, a first series of trials were conducted in standard gravity to assess the reliability of the model. Heart rate, stroke volume and main arterial pressure were assessed with no deviation with clinical standard data on ground.

Then a further analysis was undertaken in order to see the influence of the g parameter on the output results. We conducted a number of simulations with different gravity factors including 1/3, 1/6, 1/100, 1/1000, 1 µg and zero-g, in order to get a wide range of results. A transient acute response was found when applying the new steady gravity input. No significant differences within the steady-state compared to one g simulations were found if the simulated exposure time was less than four days. However, we found that when gravity is less than 23% of ground and time and exposure time longer than four days, significant differences were found.

We applied a number of different simulations with a pulmonary system module attached to the original control model, which is mainly a capacitor-resistance coupling. Gravity was applied from zero-g to one-g in 0.01 steps. Significant differences ($p<0.05$) in vascular resistance measured in the appropiate electrical model were found for gravity less than 0.43 in sixteen days. A full series of simulation was induced up to 2-years extended time. When taken into account risk probability, it was clearly above 1% of major malfunction probability in the physiological system at above 69 days, with g being less than 0.01. This risk was slightly raised when the simulated mission was extended up to two years.

Physical exercise was applied as a pattern of aerobic exercise, thirty minutes every day for every mission. We saw how the estimated overall risk was slightly reduced only for missions longer than 134+/- 12 days ($p<0.05$). When a final step of one-g was applied to simulate transition to normal gravity at the end of the mission, risk of a distress due to hypovolemia was indeed reduced up to 19+/-4 % showing better results as elapsed time in simulation was higher.

Thermal distress was applied as well as strong exercise to simulate EVAs for a time not longer than 8 hours, three times a week. The risk of an acute physiological disfunction was increased but in terms of a healthy subject scenario, was not a major concern as it not added more than 1.5% risk to the initial values. A series of tests were conducted for longer missions showing that this pattern was not jeopardizing an entire mission.

3.2 Gender differences

All Physiological differences are a matter of concern regarding long-term microgravity effects on the cardiovascular system. Women seem to have greater sensitivity to orthostatic intolerance than men [13].

Some countermeasures have been proposed for both men and women, such as Artificial Gravity (AG). Goswami et al. [14] found that after an individualized centrifugation training was applied, both men and women showed an increase in Orthostatic Tolerance Limit (OTL) after AG was applied.

We studied from our model which was the response of men vs female in terms of aerobic exercise response according to the patterns presented before. Differences in the physiological of men vs women were parametrized according to current findings accepted in the literature. Muscular mass formation was specially taken into account.

It was found (Fig. 1) that after more than 6 months in microgravity ($g<0.1$) exposure and an aerobic exercise pattern applied, the overall risk reduction of a major cardiovascular disfunction was reinforced in women vs men for every g applied from 0.1 to 10^{-6} g.

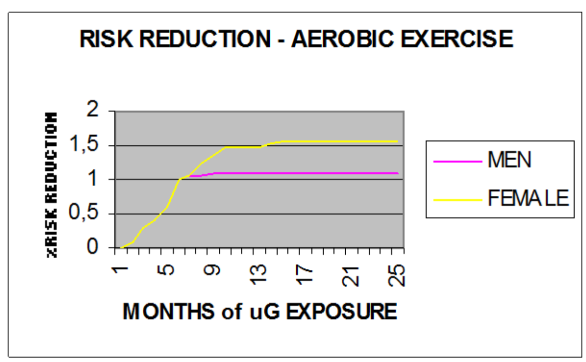

Fig. 1. Gender differences in risk reduction after an applied aerobic exercise pattern.

The difference was statistical significant in the simulation when exposure to microgravity was simulated for more than 210 days, resulting in a total 1.5+/- 0.2 risk reduction for female, and 1.1+/- 0.1 in men. This result was found to be nearly constant for 9 months of exposure or more, in concordance with previous results.

4. Moon and Mars missions analysis

Space radiation is the most limiting factor for manned spaceflight. Current estimations establish between 3 and 5% as Permission Exposure Limits (PEL) of added risk of putting a mission in jeopardy, as an acceptable one [15]. Space radiation is not considered in this model, therefore we can estimate only weightlessness effects on the total risks. Although these particular effects are not the primary concern, it is also worth considering to evaluate these risks. By using the model, we can consider steady conditions, with no EVAs, a pattern of aerobatic exercise during the Mars mission, and no additional considerations regarding other health hazards.

After a standard Moon and Mars missions were considered, additional risks were estimated as following:

Moon Mission (+/- 0.01%)
7 days stay --- 0.04%
15 days stay – 0.045%-
30 days stay – 0.060%
60 days stay 0.071%
75 days stay 0.083%
100 days stay 0.10%
300 days stay 0.18%
500 days stay 0.43%
1000 days stay 0.74%
5000 days stay 2.45%

Mars Mission (+/- 0.05%)

Elapsed time on Mars:
3 months 0.40%
6 months 0.60%
9 months – 0.80%
15 months - 1.20%
18 months 1.45%
27 months 1.65%
54 months 3.15%

The results from the model suggest that added risks are within safety limits, but not negligible.

5. Conclusions

A system to simulate the physiological response of the body to the long-term influence of microgravity has been developed. The system is capable to focus on the behaviour of a concrete organ in the body as well as to assess the risks of a major physiological malfunction. Different inputs and input patterns along elapsed mission time can be applied to simulate countermeasures such as physical exercise.

Numerical modelling has proven to be a valuable tool to predict possible risks of developing organ and systems malfunctions in spaceflight.

The system has been validated with the available published data and has been used to assess risks coming from the blood-forming organs, or reduced vascular function when coming back to Earth after spaceflight.

With the limitations exposed of this model, we conclude that risks of a major physiological malfunction are increased in scenarios such as an EVA, but totally controlled and not a major concern when conducted in long-term missions. This is in accordance to previous in-flight experiences with available data.

We also conclude that, when a pattern of physical exercise is applied as a countermeasure the risk is decreased as the physiological system responds better as decondition is diminished, according to well-known previous experiences.

Estimations from different scenarios of manned missions to the Moon and Mars have been considered, suggesting that microgravity exposure is a secondary health factor risk, after space radiation.

This is but one more numerical simulation that adds itself to the endeavour for a total understanding of what may happen to our human body in long-term spaceflight missions.

References

[1] Hamilton D. "Cardiovascular disorders. Principles of Clinical Medicine for Spaceflight." Barrat M. Pool SL (Eds.) Chapter 18, 2004.

[2] Meck JV, Reyes CJ, Perez SA, Goldgerger AL, Ziegler MG "Marked exacerbation of orthostatic intolerance after long- vs. short duration spaceflight in veteran astronauts." *Psychosomatic Medicine* (2001) 63:865-873.

[3] Convertino V.A., Crooke W.H. "Vascular functions in humans following cardiovascular adaptations to spaceflight." *Acta Astronautica* 60 (2007) 259-266.

[4] Bogomolov V.V., Grigoriev A.I., Kozlovskaya I.B. "The Russian experience in medical care and health

maintenance of the International Space Station." *Acta Astronautica* 60 (2007) 237-246.

[5] Udden, M.M., Driscoll, T.B., Piickett, M.H., Leach-Huntoon C.S., and Alfrey C.P. "Decreased production of red blood cells in human subjects exposed to microgravity." *J. Lab. Clin. Med*. 125: 442-449 (1995).

[6] Alfrey C.P. Udden M.M. Leach-Huntoon C.S., Driscoll T. and Pickett M.H. "Control of red blood cell mass in spaceflight." *J. App. Physiol*. 81: 98-104 (1996).

[7] Díaz-Artiles A. "Exercise under Artificial Gravity. Experimental and computational approaches". PhD dissertation (2015). Accessed online on 10.08.2016: http://dspace.mit.edu/handle/1721.1/98799

[8] Heldt T., Mukkamala R., Moody G.B., and Mark R.G., "CVSim: An Open-Source Cardiovascular Simulator for Teaching and Research," *Open Pacing. Electrophysiol. Ther*. J, vol. 3, pp. *45-54*, (2010).

[9] White R.J., McPhee J.C. "The Digital Astronaut: An integrated modelling and database system for space biomedical research and operations." *Acta Astronautica* 60 (2007) 273-280.

[10] Perez-Poch A. "Simulation of microgravity long-term effects on blood-forming organs." *57th International Astronautical Conference* 2007, Valencia (Spain). Conference Paper # IAC-06-A1.7-A2.7.05.

[9] Melchior FM, Srinivasan RS, Charles JB "Mathematical modelling of human cardiovascular system to orthostatic stress." *Am. J. Physiol*. 262(6 Pt 2): H1920-1933. 1992.

[10] Heldt T., Shim EB, Kamm RD, Mark RG, "Computational modeling of cardiovascular response to orthostatic stress." *J. Appl. Physiol*. 92(3): 1239-1254. 2002.

[11] Prisk GK, Fine JM, Cooper TK, West JB. "Vital Capacity, Respiratory Muscle Strength and Pulmonary Gas Exchange during Long-Duration Exposure to Microgravity." *Journal of Applied Physiology*, 101:439-447 (2006).

[12] Prisk GK, Fine JM, Cooper TK, West JB. "Pulmonary gas exchange is not impaired 24 h after extravehicular activity." *Journal of Applied Physiology*, 99(6):2233-8 (2005).

[13] Blaber AP, Goswami N, Bondar RL, Kassam MS, "Impairment of cerebral blood flow regulation in astronauts with post flight orthostatic intolerance. *Stroke* 42: 1844–1850 (2011). doi:10.1161/STROKEAHA.110.610576

[14] Goswami, N.; Evans, J.; Schneider, Stefan; W., M.; Mulder, E.; Rössler, A.; Hinghofer-Szalkay, H.; and Blaber, A. P., "Effects of Individualized Centrifugation Training on Orthostatic Tolerance in Men and Women" Plos One (2015), doi:10.1371/journal.pone.0125780

[15] Cucinotta F. "Radiation risk acceptability and limitations." Accessed on-line at 10.8.2016: https://three.jsc.nasa.gov/articles/AstronautRadLimitsFC.pdf