Doctoral Dissertation
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# Impact of posture and gravity on the cardiovascular system: a validated multiscale modeling approach for ground-based and spaceflight applications

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# Summary

The present thesis is aimed at exploring the response of the human cardiovascular system to a number of ground-based clinical and spaceflight-related applications, by resorting to a mathematical model calibrated and validated *in vivo*. The numerical framework developed for the purpose of this work encompasses a 1D representation of the arterial circulation linked to a 0D circuital analog of the remaining systemic (peripheral and venous return) and cardiopulmonary circulations. In addition, lumped parameter models of the cerebrovascular and ocular circulations, as well as specific models of short-term homeostatic control, are considered to inquire into the specific response of such compartments to different gravity conditions and postures. The model is then applied to several cases of interest to inquire into hidden or unknown mechanisms shaping the overall hemodynamic response. The computational model was used to characterize the global cardiovascular and hemodynamic response to numerically simulated varying posture under normal Earth gravity (1g), to varying gravity experienced during a numerically simulated parabolic flight trajectory, and to numerically simulated acute exposure to head-down tilt position assumed as ground-based analogue of human spaceflight. Additionally, from a clinical point of view, we employed the model also to explore a clinical problem related to the detrimental implications of atrial fibrillation onto perfusion of the myocardium, showing the validity of the presented numerical tool to conduct medical investigations.

To the purpose of validating our computational framework, the present work includes also two distinct experimental campaigns whose goal was to investigate the human physiological response to different scenarios. A first series of head-up tilt experiments was conducted, aimed at evaluating the impact of orthostatic stress onto the overall cardiovascular response; then, a second experimental study was carried out to the end of exploring the acute (up to one hour) effects of head-down tilt position onto the ocular and cardiovascular parameters.

The main findings presented in the following highlight that gravity - either through posture variation or due to actual modification of the gravity vector magnitude - induces marked responses of the human cardiovascular system that can be related, at first, to blood migration across the different body pools. Secondly, a series of control regulation mechanisms activates such to preserve the system's

homeostasis, by promoting cardiac chronotropic and inotropic control, regulation of vascular tone, and autoregulation of specific dependent vasculature (e.g., cerebrovascular bed). As observed in our studies, the extent of the autonomic response elicited by posture or gravity changes and of the overall cardiovascular response is strictly related to the extent of the corresponding posture/gravity magnitude change, as shown, for instance, in the investigation of the different cardiovascular parameters changes with respect to each simulated tilt angle or to the different phases of a parabolic flight. In addition, the implications of such gravity-driven hemodynamics changes elicited at different levels of the cardiovascular system are responsible for a number of additional observed behaviors, ranging from wave dynamics phenomena, to the insurgence of possible cerebrovascular and ocular consequences. Furthermore, the application of the model to the clinical scenario of atrial fibrillation shows how this conditions affects to gradually worse extents the different layers of the myocardium, at increasingly higher ventricular frequency.

The present work, thus, not only highlights the importance and noticeable usefulness of novel, *in vivo* calibrated and validated computational frameworks in the context of clinical diagnostics and prognostics strategies, but shows also promising insights into a number of so far poorly explored topics strictly related to the fields of bioastronautics and space medicine. In particular, our results help shed light onto the functioning principles of autonomic responses in combination with posture changes on Earth, contributing to the overall understanding of dysautonomias and orthostatic tolerance under normal Earth gravity. Furthermore, altered-gravity environments and ground-based analogues of spaceflight provides information regarding the human cardiovascular, cerebrovascular and ocular systems coping to hyper- and microgravity, leading to a better comprehension of microgravity-induced cardiovascular deconditioning, of potentially dangerous ocular diseases, and to the design of future, successful countermeasures to enable long-term human spaceflight.