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Article · August 2016

DOI: 10.3389/fspas.2016.00027

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MINI REVIEW
published: 23 August 2016
doi: 10.3389/fspas.2016.00027

Weightlessness and Cardiac Rhythm Disorders: Current Knowledge from Space Flight and Bed-Rest Studies

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Isolated episodes of heart rhythm disorders have been reported during 40 years of space flight, triggering research to evaluate the risk of developing life-threatening arrhythmias induced by prolonged exposure to weightlessness. In fact, these events could compromise astronaut performance during exploratory missions, as well as pose at risk the astronaut health, due to limited options of care on board the International Space Station. Starting from original observations, this mini review will explore the latest research in this field, considering results obtained both during space flight and on Earth, the latter by simulating long-term exposure to microgravity by head-down bed rest maneuver in order to elicit cardiovascular deconditioning on normal volunteers.

Keywords: cardiac arrhythmias, ventricular repolarization, signal processing, cardiac remodeling, head-down bed rest

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Specialty section:
This article was submitted to Cosmology, a section of the journal Frontiers in Astronomy and Space Sciences

Received: *23 May 2016*
Accepted: *09 August 2016*
Published: *23 August 2016*

Citation:
Caiani EG, Martin-Yebra A, Landreani F, Bolea J, Laguna P and Vaïda P (2016) Weightlessness and Cardiac Rhythm Disorders: Current Knowledge from Space Flight and Bed-Rest Studies. Front. Astron. Space Sci. 3:27. doi: 10.3389/fspas.2016.00027

INTRODUCTION

Human spaceflight represents a highly risky activity, depending on both engineering and human elements that could fail during the different steps of the mission. As regards the human factor, quantified probabilistic risk assessment and matching risk mitigation resources are at the basis of efficient preventive approaches to minimize medical disorders that could prevent mission success and put in danger the crew health (Gillis and Hamilton, 2012).

Among the possible risks, the occurrence of serious cardiac rhythm disorders (Sides et al., 2005) and related diminished cardiac and vascular function have been identified as primary cardiovascular risks of spaceflight in the NASA Bioastronautics Critical Path Roadmap in 2004, currently under revaluation process.

Indeed, cardiac electrical rhythm disturbances have been observed among astronauts and cosmonauts since the Apollo 15 mission (Johnson et al., 1975; Anzai et al., 2014), including one documented episode of non-sustained ventricular tachycardia (Fritsch-Yelle et al., 1992). As electrocardiographic (ECG) evaluation was not systematic, and performed only during extravehicular activities (EVA) and periodic exercise testing with elevated metabolic workload, it is not clear whether these potentially critical events, as anecdotal reports, were due to pre-existing conditions or as derived effects induced by weightlessness.

Fatal arrhythmias during space flight, such as ventricular tachycardia (VT) or ventricular fibrillation (VF), could lead to sudden cardiac arrest (SCA). During space flights up to 6 months, the possibility of SCA is about 1% per year (Russomano et al., 2013), so that the likelihood of a

need for cardiopulmonary resuscitation (CPR) in spaceflight is very low, but still exists. Survival is highly dependent upon the most rapid defibrillation with decreasing likelihood if first shock is delayed beyond 3 min, where survival rates in urban environment for patients with VT/VF initial rhythms, witnessed by out of hospital emergency medical services and shocked rapidly, were 36.7% (De Maio et al., 2003). This scenario is complicated by the fact that space missions lack the skill and medical manning levels, and facility resources of urban hospitals, together with the fact that in microgravity there is no collapsing fall with SCA to alert nearby potential responders (Gillis and Hamilton, 2012).

Among non-fatal arrhythmias observed during space flight, premature ventricular contractions (PVC) maybe clinically important when frequent (>2 on resting ECG, or >1% of total beats or >5/min on 24 h Holter ECG), as they could underlie serious conditions (ischemia, myocarditis, cardiomyopathy, electrolyte disturbances, thyroid problems, effects of medications or chemicals, cardiac structural problems) (Jennings et al., 2010). Also, it is estimated that 10% of patients presenting with ventricular arrhythmias are idiopathic, without obvious structural heart disease (Klein et al., 1992), where the most common forms are the right ventricular outflow tract (RVOT) monomorphic PVC and the RVOT VT (Miles, 2001). Additional factors induced by space flight, such as sudden pressure changes (Ptak et al., 2013) or rapid onset and offset of +Gx or +Gz acceleration (Torphy et al., 1966; Rogge et al., 1969; Zawadzka-Bartczak and Kopka, 2011) could also increase arrhythmia susceptibility.

Since 1959, 11 cases of atrial fibrillation (AF), atrial flutter, or supraventricular tachycardia have been recorded among active corps crewmembers, and six additional cases have been identified among retired astronauts, but no episode was observed during space flight. Since 2001, five active astronauts out of ∼100 underwent radiofrequency ablation treatment for atrial arrhythmias (mostly AF), demonstrating complete recovery and absence of any symptom during preflight training and the actual mission (Gray et al., 2010). While total prevalence has been found in line with that (5%) of the normal population, even if appearing at much younger age (mid-40s) among the astronaut cohort, it has been concluded that at this time there is no evidence that space flight increases the likelihood of developing atrial arrhythmias during space flight (Barr, 2010).

Beyond these terrestrial heart risks, some concern exists that prolonged exposure to microgravity might lead to cardiac rhythm disturbances: bradycardia related to long-duration spaceflights that could result in prolongation of the QT interval (D'Aunno et al., 2003), use of medications, changes in the autonomic nervous system (Fritsch et al., 1992; Fritsch-Yelle et al., 1996; Meck et al., 2001; Rossum et al., 2001; Liu et al., 2015), development of apoptosis in response to pathological, physiologic, and/or genetic signals (Mallat et al., 1996; James, 1998) resulting in cardiac atrophy (Platts et al., 2010), radiation exposure inducing structural changes (Cucinotta et al., 2005), psychological stress (Kanas et al., 2001), potassium deficiency (Smith and Zwart, 2008). The combination of these adaptations suggests that modifications in the cardiac structure, together with adrenalin/neurohormonal changes and stress related to space flight, could also alter electrical conduction increasing the inhomogeneity of electrical repolarization, and thus potentially increasing the risk of inducing cardiac rhythm disturbances.

As regards medications, they can be used as a countermeasure in the context of long term space flight. Biphosphonates, for example, used on Earth and associated with increased bone mineral density and reduced fracture incidence in patients with osteoporosis, previous fracture, or both, may prove useful for astronauts, too. However, in two large, randomized, placebo-controlled trials, yearly 5-mg infusions of the bisphosphonate zoledronic acid were associated with significantly increased arrhythmia propensity than in the placebo group (Camm, 2010). Other drugs (i.e., Modafinil) that help ISS crew members optimize their performances in case of need have side effects that could impact heart rhythm. As an example, a 1.8-fold increase in risk of sudden death or ventricular arrhythmia was found in adult patients who initiated methylphenidate therapy (Schelleman et al., 2012).

In order to fulfill a risk mitigation strategy for cardiac rhythm disturbances during space flight, in absence of a high number of recorded events, a mitigation strategy to establish space normal values needs to be defined. To this purpose, head-down (−6°) bed rest (HDBR), as a ground-based analog representing a model of chronic circulatory unloading simulating sustained exposure to microgravity, offers a unique opportunity for studying the effects of prolonged space flight on the cardiovascular system as well as testing the efficacy of possible countermeasures (CM). In fact, HDBR allows recruiting several normal subjects and study them using a cross-over (for short- and mid-duration campaigns) or multi-group (for longer 60 days HDBR campaigns) designs in relatively shorter time than performing research in astronauts. Recent findings related to research on ventricular repolarization (VR) changes induced by the HDBR analog will be presented in the following paragraphs.

CHANGES IN VENTRICULAR REPOLARIZATION DURING HDBR

Potential changes in repolarization heterogeneity has been investigated during HDBR over the last decade using conventional temporal and amplitude parameters, as well as several advanced measures (Laguna et al., 2016), such as beat-to-beat QT variability (QTV) (Atiga et al., 1998), T-wave complexity (Schlegel et al., 2010), and parameters of 3-dimensional ECG, including the spatial ventricular gradient (SVG) and spatial mean QRS-T angle (Cortez and Schlegel, 2010).

Spatial Ventricular Gradient and QRS-T Angle

In 19 male subjects undergoing 5-days HDBR while in control (CTRL) with no CM applied, computerized analysis of 24 h Holter ECG based on selective beat averaging applied to the night period showed a 10% decrease in SPV and a 28% increase in

QRS-T angle parameters (Caiani et al., 2013a) compared to pre-HDBR values. As concerns SPV and QRS-T angle, the nature of the observed changes could underline augmented repolarization heterogeneity that has been associated with risk of life-threatening arrhythmias, as functionally linked to dispersion of refractoriness, thus potentially facilitating ventricular tachycardia (Draisma et al., 2006). When a 25 min/day standing exercise CM was applied in a sub-group of 10 subjects during the 5-days HDBR, the pro-arrhythmic effects induced by bed rest appeared slightly reduced (SPV −9%, QRS-T angle +21%) compared to pre-HDBR, but not canceled (Caiani et al., 2013b). The directionality of these changes were confirmed also in other 8 subjects studied during a 21-days HDBR, where SPV was reduced by 13%, and QRS-T angle increased by 6% (Caiani et al., 2014b). These findings were in agreement with the changes observed after 30 days in SPV (−28%) and QRS-T angle (+6%) by Sakowski et al. (2011) in 20 subjects (14 men and 6 women) during a 90-days HDBR, where at day 90 the QRS-T angle was found increased by 18%, while SPV decreased by 35%, compared to pre-HDBR values. While after 5-days HDBR no subject reached a QRS-T angle considered outside the normal range (Scherptong et al., 2008), after 90-days HDBR few subjects developed angles > 100°, commonly associated to three-to-fivefold increased hazard ratio for cardiovascular mortality or sudden death (Kardys et al., 2001; Yamazaki et al., 2005). Interestingly, in all studies the considered parameters recovered to pre-HDBR values soon after conclusion of HDBR.

Both after short- or long-term space flight, the transition from weightlessness in space to Earth gravity causes a decrease in blood and stroke volume and a cardiac and vascular remodeling to maintain blood pressure, resulting in a reduction in cardiac output and vasoconstrictor reserve, with neural mechanisms of heart rate regulation disturbed, thus contributing to orthostatic intolerance lasting from 5 to 25 days (Vandeput et al., 2013). A recent study showed that these changes could be different between European and Chinese astronauts, with a significant increase in sympathetic activity and a decrease in vagal modulation in the European astronauts when standing whereas post-spaceflight orthostatic tachycardia was significantly reduced in Chinese astronauts (Liu et al., 2015). However, no specific increased risk of arrhythmia has been reported during the recovery period after space flight, in agreement with recovery of parameters observed after HDBR.

Amplitude and Temporal Parameters

Using the same selective beat averaging applied to the night period, compared to pre-HDBR, a significant reduction in T wave peak amplitude, was visible both in short- (−8%)(Caiani et al., 2013a), where standing exercise CM seemed able to partially reduce this decrease (−4%) (Caiani et al., 2013b), and mid-HDBR (−13%) (Caiani et al., 2014a). Also, dipolar T-wave voltage over the 12-leads was reduced (−6%) with 90-days HDBR (−6%) (Sakowski et al., 2011).

Healthy subjects have been found characterized by a RR dependency of the T-wave amplitude (Haarmark et al., 2010), while a less pronounced dependency was present in patients with acute myocardial infarction (Johannesen et al., 2010), thus supporting the hypothesis that impairment of T-wave amplitude adaptation to RR could represent a new dynamic marker of increased risk for life-threatening arrhythmias. After 5-days HDBR, a marked loss in strength of the linear regression of T-wave amplitude (and area) with RR was observed, thus evidencing possible impaired T-wave amplitude adaptation to heart-rate induced by this condition (Caiani et al., 2013a).

As regards temporal indices, while the RTend interval (Caiani et al., 2013a,b, 2014a) was found reduced during 5- and 21-days HDBR, Bazett corrected QT interval (QTc) did not change during 90-days HDBR, accompanied by a significant reduction in beat-to-beat duration (RR), but resulted significantly increased compared to pre-HDBR during recovery (Sakowski et al., 2011). These changes in the QTc interval significantly correlated with changes in serum potassium, and were partially explained by potassium loss despite the controlled potassium dietary intake, consistent with results from long-duration spaceflight (D'Aunno et al., 2003).

QT Variability and QT/RR Dependence

The VR as assessed by the QT interval, measured from QRS onset to T end, and its dependency with the RR interval (or heart rate), have been proposed as a pro-arrhythmic risk indices (Pueyo et al., 2004). In general, QTV was found increased with HDBR. When QTV was decomposed to estimate the variability fraction driven by heart rate variability (HRV) and the unexplained component (Porta et al., 1998), both 5-days (Bolea et al., 2013a) and 21-days (Bolea et al., 2013b) HDBR were found to increase the amount of HRV-dependent QTV, accompanied by a reduced power component at high frequency (HF, 0.15–0.4 Hz) in HRV, suggesting a shift in the sympatho-vagal balance, with prolonged exposition to simulated microgravity associated to a stronger linear dependency and to a slower ability to restore the pre-HDBR linear dependency values at termination, in particular for transmural dispersion variability. Similar results were also observed after 90-days HDBR, where different indices were used to compute these parameters (Sakowski et al., 2011).

QT interval represents the time period where depolarization and repolarization of all ventricular cells occurs, whereas QTpeak is an incomplete measure of this time period. In particular, the difference between QT and QTpeak, measured by the Tpe (Tpeak to Tend) interval, has been proposed as an index for evaluation of VR and restitution dispersion (Mincholé et al., 2011). While exploring the QT-RR hysteretic dynamics following abrupt changes in RR induced by tilt-test in the same 22 males in control group, before and after 5-days HDBR, a shortening in the memory lag of the QT/RR dependency was found, with a QTpeak lag shorter than QT, thus highlight variations in the Tpe interval with HDBR (Bolea et al., 2012). In particular, VR dispersion is related to heterogeneities in the action potential duration (APD) of the ventricular tissue. Pueyo et al. (2010) reported that APD adapts to abrupt RR changes in two phases: a fast initial phase <30 s related with L-type calcium and potassium currents, followed by a slow phase >2 min produced mainly

by intracellular sodium concentration dynamics among others. These two phases are observed in different magnitude in the QT and QTpeak series before HDBR, and consequently in Tpe, at the beginning of the tilt-test. However, after 5-days HDBR, the initial fast phase of adaptation seems to disappear, or at least is less pronounced, in Tpe, as evidenced by the similarity between QT and QTpeak series. A possible explanation of this phenomenon was related to the sympathovagal response, impaired by HDBR (Xiao et al., 2003), where deconditioning could affect autonomic modulation of L-type calcium and potassium currents, thus leading to a decrease in the initial phase of APD adaptation to an abrupt HR acceleration (Bolea et al., 2012).

T-Wave Alternans

T-wave alternans (TWA) is defined as a consistent beat-to-beat alternation in amplitude, duration or morphology of the ST-segment and/or the T wave. It reflects heterogeneity in time and space of VR and it has been proposed as a noninvasive risk marker for predicting sudden cardiac arrest and ventricular vulnerability (Verrier et al., 2011). Based on ECG recordings performed during bicycle exercise stress in 24 males before and after 9 to 16 days of $-4°$ bed rest, it was suggested that VR is altered with bed rest in a manner that may increase susceptibility to the developments of sustained alternans (Grenon et al., 2005). However, the heterogeneity of the observed subjects' response, and of the HDBR duration, did not allow drawing final conclusions about the potential negative effects of HDBR on cardiac electrical stability. More recent results obtained in 44 males studied showed that, despite the augmented VR heterogeneity induced by HDBR measured by the decrease in SPV and the increase in QRS-T angle, neither 5-days nor 21-days HDBR were able to alter ventricular repolarization heterogeneity under stress conditions. Indeed, the absence of any significant increase in normalized TWA indices between pre- and post-HDBR during orthostatic tolerance test and peak aerobic power test by bicycle exercise up to exhaustion showed that the augmented ventricular heterogeneity related to HDBR was not sufficient to increase TWA under stress conditions (Martín-Yebra et al., 2015).

Alterations in LV Mass

Alterations in left ventricular (LV) volumes and mass take place soon after entering into HDBR, due to activated short-term volume regulatory mechanisms resulting in loss of plasma volume (Charles and Bungo, 1991; Charles and Lathers, 1991). In particular, it has been recently shown by 2-D and 3-D echocardiography that after 5-days HDBR the LV mass and volume decreased by 16 and 14%, respectively, and artificial gravity CM was not effective in preventing these changes (Caiani et al., 2014a). Similar results were observed in 38 astronauts before and after 9–16 days of spaceflights, where a reduction of 10% in LV mass and LV end-diastolic volume measured immediately after landing was completely reversed after 3 days (Summers et al., 2005). Also, in multiple HDBR studies after 14-days (Levine et al., 1997), 21-days (Carrick-Ranson et al., 2013; Caiani et al., 2013c), and 5-weeks (Kozakova et al., 2011; Hastings et al., 2012), the LV mass was found reduced. As in humans the reductions in LV load require a minimum of 6 months to result in statistically significant changes in LV mass (Dunn et al., 1987), and as the observed changes were fully reversed few days after HDBR termination, modifications could be attributed to decreased physiological loading and dehydration, resulting in reduced plasma, and blood volume. In agreement with this explanation, a reduction in intracardiac interstitial fluid volume during the course of exposure to spaceflight was predicted by a computational model (Summers et al., 2007).

CONCLUSIONS

The risk of developing malignant arrhythmias during space flight represents an open problem, in particular if future commercial spaceflight would become more accessible to individuals with significant medical histories, even with implanted devices (Blue et al., 2015). Based on the existing literature, mainly focused on short-duration space flight and its analog HDBR up to 90 days duration, changes in VR mechanisms occur and can be quantified using several techniques and indices. Despite the fact that these changes underline augmented repolarization heterogeneity, potentially associated with the risk of life-threatening arrhythmias, clear responses in term of risk quantification, direct relation with specific eliciting factors and potential countermeasure effectiveness, are still lacking. These facts highlight the need for additional research specifically focused to address this risk, both during long-duration space flight and HDBR. Future results could contribute to provide additional physiological insight, as well as to address risk factor mitigation.

AUTHOR CONTRIBUTIONS

All authors equally contributed to the conception of the work, revising it critically for important intellectual content, final approval of the version to be published, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. In addition, EC was responsible for drafting the work.

FUNDING

This research has been performed thanks to the contribution of the Italian Space Agency (contracts no I/047/10/0 and 2013-033-R.0 - QTBed, and contracts no I/061/10/0 and 2013/032/R.0 - AEQUABED, recipient Dr. EC), and supported by CIBER-BBN through Instituto de Salud Carlos III and FEDER (Spain), project TEC2013-42140-R funded by MINECO and FEDER, and by Gobierno de Aragòn and European Social Fund (EU) through BSICoS Group (T96). PV research was funded by Centre National d'Études Spatiales (CNES) (contract CNES/4800000632).

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.