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Impaired T-wave amplitude adaptation to heart-rate induced by cardiac deconditioning after 5-days of head-down bed-rest ☆

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ABSTRACT

The study of QT/RR relationship is important for the clinical evaluation of possible risk of acquired or congenital ventricular tachyarrhythmias. In the hypothesis that microgravity exposure could induce changes in the repolarization mechanisms, our aim was to test if a short 5-days strict 6° head-down bed-rest (HDBR) could induce alterations in the QT/RR relationship and spatial repolarization heterogeneity. Twenty-two healthy men (mean age 31 ± 6) were enrolled as part of the European Space Agency HDBR studies. High fidelity (1000 Hz) 24 h Holter ECG (12-leads, Mortara Instrument) was acquired before (PRE), the last day of HDBR (HDT5), and four days after its conclusion (POST). The night period (23:00–06:30) was selected for analysis. *X*, *Y*, *Z* leads were derived and the vectorcardiogram computed. Selective beat averaging was used to obtain averages of P–QRS–T complexes preceded by the same RR (10 ms bin amplitude, in the range 900–1200 ms). For each averaged waveform (i.e., one for each bin), T-wave maximum amplitude (Tmax), T-wave area (Tarea), RTapex, RTend, ventricular gradient (VG) magnitude and spatial QRS-T angle were computed. Non-parametric Friedman test was applied. Compared to PRE, at HDT5 both RTapex and RTend resulted shortened (−4%), with a decrease in T-wave amplitude (−8%) and area (−13%). VG was diminished by 10%, and QRS-T angle increased by 14°. At POST, QT duration and area parameters, as well as QRS-T angle were restored while Tmax resulted larger than PRE (+5%) and VG was still decreased by 3%. Also, a marked loss in strength of the linear regression with RR was found at HDT5 in Tmax and Tarea, that could represent a new dynamic marker of increased risk for life-threatening arrhythmias. Despite the short-term HDBR, ventricular repolarization during the night period was affected. This should be taken into account in astronauts for risk assessment during space flight.

1. Introduction

The study of QT/RR relationship is important for the clinical evaluation of possible risk of acquired or congenital ventricular tachyarrhythmia, predisposing to life-threatening arrhythmias.

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Microgravity is known to lead to cardiovascular deconditioning, with post-spaceflight orthostatic intolerance and decreased exercise capacity. Indeed, there are known and well-defined changes in the cardiovascular system with space flight, such as a reduction in plasma volume, decrease in left ventricular mass, and adaptation of the autonomic nervous system to the new environment. The combination of these physiologic adaptations suggests that modifications in the cardiac structure due to the weightlessness condition, together with adrenalin/neurohormonal changes and stress related to space flight, could also alter electrical conduction, although the evidence supporting this hypothesis consists mostly of minor changes in QT interval in a small number of astronauts after long-duration space flight.

In particular, the following findings were found during the years:

–Gemini and Apollo missions: occasional premature ventricular contractions [1,2];
–Apollo 15: prolonged run (22 beats) of nodal bige miny, followed by a series of premature ventricular and atrial beats, experienced by the lunar module pilot [3,4];
–Skylab: ectopic beats of both ventricular and supra ventricular origin reported in all crew members, with one individual experiencing a five-beat run of ventri cular tachycardia [1,5];
–Shuttle flights: premature ventricular contractions in one crew member, with rates as high as 16 ectopic beats per minute during reentry [1,6];
–US–Russian Shuttle-Mir program: 14-beat run of ventricular tachycardia [7];
–Mir program: over the last 10 years, 31 abnormal electrocardiograms, 75 dysrhythmias, and 23 conduc tion disorders were observed [8].

Other studies were performed by retrospectively analyzing ECG data obtained in previous space missions, thus concluding that extravehicular activity does not precipitate deleterious cardiac events during space flights [9–11], and that long duration space flight, compared to short missions, was found to lengthen QT interval, thus increasing the arrhythmia susceptibility [12].

Ground-based studies represent an invaluable perspective to investigate human physiology during simulated microgravity conditions. Among them, the model of 6° Head-Down Bed Rest (HDBR) represents a unique opportunity for inducing and studying the effects of simulated prolonged exposure to microgravity on the cardiovascular system and for testing potential countermeasures. In the past years, several bed rest studies were performed; however, the attention of the investigators was more focused on the assessment of changes in cardiac autonomic control [13–21] than on ventricular repolarization. Only few studies were focused on the investigation of ventricular repolarization under different aspects:

Grenon et al. [22] aimed at the evaluation of microvolt T-wave alternans induced by 9–16 days of 4° HDBR; the reported results, based on ECG recordings performed before and after HDBR during bicycle exercise stress in 24 male subjects, suggested that HDBR alters cardiac repolarization processes in a manner that may increase susceptibility to the development of sustained alternance. Sakowski et al. [23] studied the effects of 90 days of 6° HDBR on repolarization heterogeneity by beat-to-beat QT interval variability, T-wave complexity, and 3-dimensional ECG. Reported results showed increased T-wave variability and complexity, enlarged spatial QRS-T angle and reduced spatial ventricular gradient, thus supporting the hypothesis that sedentary long-duration HDBR at least transiently increases susceptibility to ventricular dysrhythmias by increasing both temporal instability [24,25] and spatial heterogeneity [26–28] of action potential duration or morphology [29].

Based on these observations, we hypothesized that microgravity exposure could induce changes in the repolarization mechanisms, with potential effects on increasing the risk of arrhythmia susceptibility. Accordingly, our aim was to test if even a short 5-days strict 6° HDBR maneuver could induce alterations on the QT/RR relationship and spatial repolarization heterogeneity.

2. Methods

2.1. Study design and population

As part of the European Space Agency HDBR strategy, subjects were enrolled in a cross-over design with a wash out period of about 1.5 months between two consecutive campaigns, with one control and two countermeasure groups. Strict bed rest was performed at 6° head-down tilt position for a total of 5 days. Subjects were housed in the Institut de Médecine et de Physiologie Spatiales (MEDES) facility at the University hospital CHU Rangueil, Toulouse, France, or at the German Aerospace Center (DLR), Koln, Germany. Before the beginning and after the end of each 5-days HDBR, subjects were evaluated during 5 days of ambulatory period, during which lying in bed during the day was prohibited.

Twenty-two healthy men aged 31 ± 6 (range, 21–44 years) were recruited for this study. Each subject provided their voluntary written, informed consent to participate in protocols approved by the corresponding Institutional Review Boards

In this paper, our attention will be focused on the subjects in the control group only.

2.2. ECG data acquisition

The ECG signals were acquired using a 12-lead Holter 24-h high fidelity (1000 Hz) digital recorder (H12+, Mortara Instrument Inc., Milwaukee, WI) with beginning of the acquisition 6 days before the start of the HDBR (PRE), the fifth day of HDBR (HDT5) and 5 days after the end of HDBR (POST) (Fig. 1).

Fig. 1. Schematization of the different phases of the bed rest (BR) campaign. Arrows indicate the epochs in which Holter 24-h acquisitions were performed.

2.3. ECG signal processing

Only the RR values classified as in sinusal rhythm (H-scribe and SuperECG software, Mortara Instrument Inc.) were included in the following analysis. First, the RR intervals were classified as day-time (from 6:30 to 23:00) and night-time (from 23:00 to 06:30), to apply the next steps to the analysis of the night period only, to avoid misinterpretation due to daily movements or subject's involvement.

From the 12-leads, inverse Dower matrix transformation [30] was applied to obtain the orthogonal leads *X*, *Y*, *Z*, from which the vectorcardiogram was computed.

Selective beat averaging [31] was used to obtain averages of P–QRS–T complexes preceded by the same stable heart rate in the range from 900 to 1200 ms: (1) a RR duration histogram with 10 ms bin amplitude was computed; and (2) for each bin *n*, the beats with the corresponding RR duration were located on the vectorcardiogram, and the following beat was extracted and assigned to the C(n) class. After beats realignment according to the R wave peak, filtering with a low pass FIR filter (15 Hz), a simple averaging operation was applied, thus obtaining a mean template M(n), representative of all the beats owing to the class C(n), from which the isoelectric line (defined by a stationary point between S- and T-waves and by a relative minimum after 800 ms) was subtracted.

For each template M(n), a procedure for the automated detection of some fiducial points, such as Tapex (defined as the maximum of the parabolic interpolation between up-slope and down-slope points [32]), Tend (defined as the point with maximum distance from the line that joints the Tapex and an adjusted point, dependent on beat length, after the T-wave), Tstart (defined as the point where the product of the first and second derivative falls below the 10% of a threshold defined as the product of the last maximum first and second derivatives) has been applied (Fig. 2).

Basing on these points, RTapex and RTend interval durations, T wave maximum and T wave area have been computed for each M(n) derived from the vectorcardiogram.

2.4. Spatial QRS-T angle and ventricular gradient

For each M(n) computed on the vectorcardiogram, the ventricular gradient (VG) magnitude (mV* ms) and its spatial orientation (azimuth, orientation in the transversal plane, and elevation, deviation from the transversal plane) were then calculated.

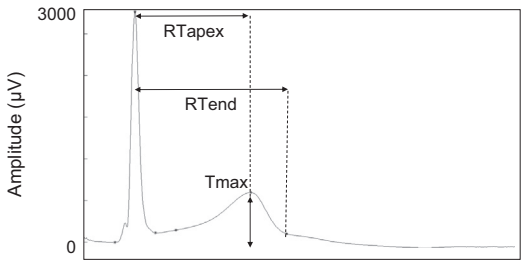

Fig. 2. Example of averaged beat M(n) computed from all beats on the vectorcardiogram preceded by an heart cycle with duration in the range 1200–1209 ms. Maximum amplitude, Tend and Tstart are evidenced.

The VG is defined as:

$$\mathrm{VG} = \int \vec{H}(t) \cdot dt \tag{1}$$

in which $\vec{H}(t)$ is the heart vector, as represented in the *X*, *Y*, and *Z* leads of the vectorcardiogram [33]. This integral, taken over the QRS–T interval, is nonzero due to action potential morphologic differences in the ventricles, most often thought of as action potential duration differences [29]. Orientation of the axes is in accordance with the American Heart Association recommendations: *x*-axis positive from right to left, *y*-axis positive in craniocaudal direction, and *z*-axis positive in anteroposterior direction [34]. Accordingly, the magnitude of the VG is computed as:

$$|\mathrm{VG}| = \sqrt{\begin{array}{l}(\int T\,dt_x + \int \mathrm{QRS}\,dt_x)^2 \\ +(\int T\,dt_y + \int \mathrm{QRS}\,dt_y)^2 \\ +(\int T\,dt_z + \int \mathrm{QRS}\,dt_z)^2\end{array}} \tag{2}$$

The spatial QRS-T angle, reflecting the difference in directions of propagation of depolarization and repolarization, was computed as follows: first, the mean spatial axes are obtained by vectorially adding the instantaneous heart vectors during the QRS complex and the T-wave. Then, the spatial QRS-T angle is computed as the angle between the mean spatial QRS axis and the mean spatial T axis [35].

2.5. Statistical analysis

Data are expressed as median (25th-percentile;75th-percentile), unless otherwise specified. Non-parametric Friedman test, and Wilcoxon signed rank post-hoc test, have been applied to evaluate the effect of HDBR on the computed ventricular repolarization parameters among timepoints (PRE, HDT5 and POST).

To study the relationship with RR of the computed QT parameters, median values for each bin among all subjects were linearly correlated, and the Pearson coefficient computed.

3. Results

For technical reasons, the analysis was possible on 19/22 subjects.

Results (see Table 1), are presented as median values, computed over each bin, for each data epoch (i.e., PRE,

Table 1
Changes in the computed QT parameters induced by 5-days head-down-bed-rest. Results are reported as median (25th;75th percentiles) in the range 900–1200 ms.

	PRE	HDT5	POST
RTapex (ms)	286 (279;292)	272[a] (269;278)	285[a,b] (281;287)
RTend (ms)	380 (374;385)	365[a] (359;372)	377[b] (369;380)
Tapex (μV)	732 (710;749)	663[a] (651;683)	768[a,b] (757;788)
Tarea[a] (mV* ms)	88 (84;94)	76[a] (75;78)	87[b] (94;92)
VG[a] (mV* ms)	133 (131;136)	120[a] (115;123)	130[a,b] (126;132)
QRS-T angle (deg)	49 (47;51)	63[a] (60;65)	49[b] (49;50)

[a] $p < 05$ vs. PRE.
[b] $p < 05$ HDT5 vs POST.

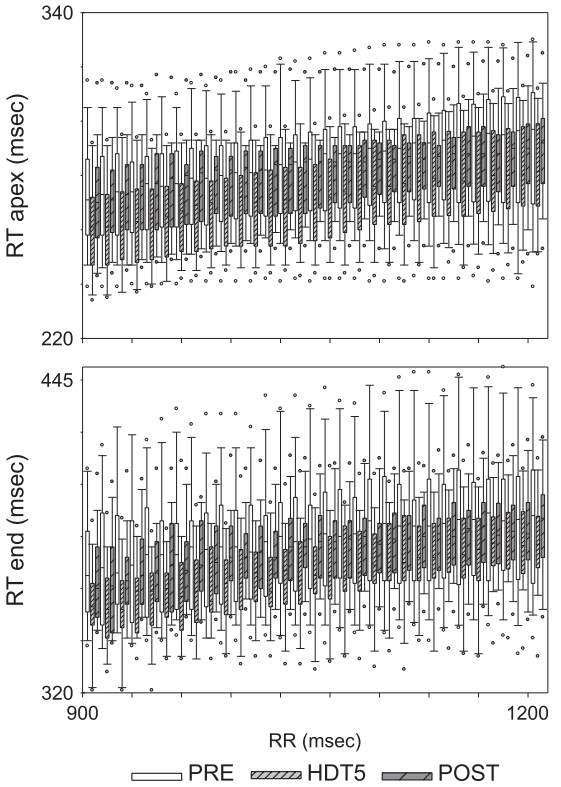

Fig. 3. Relationship between RR duration and RTapex (top) and RT-end (bottom). Wisker-plot represents median and 25–75th percentiles for each RR in the three considered conditions (PRE: white; HDT5: light gray; POST: dark gray).

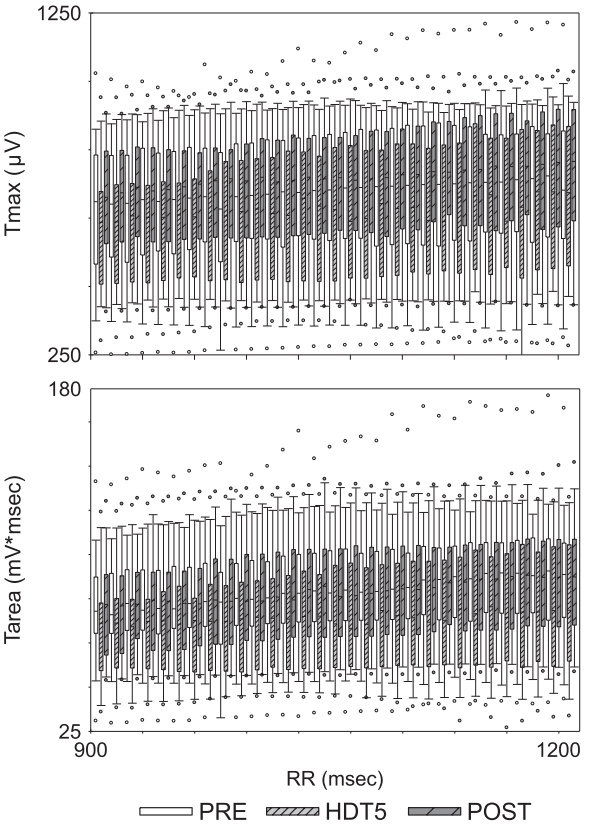

Fig. 4. Relationship between RR duration and Tmax (top) and Tarea (bottom). Wisker-plot represents median and 25–75th percentiles for each RR in the three considered conditions (PRE: white; HDT5: light gray; POST: dark gray).

HDT5, POST), together with the relevant boxplot computed over the considered RR duration range.

As regards temporal parameters, compared to PRE, at HDT5 both RTapex and RTend were shortened (−4.5% and −3.7%, respectively), while at POST they were restored compared to control values (Fig. 3).

As regards amplitude parameters, compared to PRE, at HDT5 a decrease in Tapex (−8%) and Tarea (−13%) was found. At POST, while Tarea was restored, Tapex resulted augmented than PRE (+5%) (Fig. 4).

As regards ventricular spatial heterogeneity parameters (Fig. 5), the magnitude of the VG was reduced by 10% at HDT5, together with an increase of 28% in QRS-T angle, while at POST QRS-T angle was back to its control values, and VG resulted still diminished by 2.8%.

Results of linear correlation with RR are presented in Table 2. At PRE, all the duration and amplitude parameters showed a good linear correlation ($r^2 > 0.70$) with the RR duration. Conversely, at HDT5 a worsening of this relationship was observed in both Tarea and Tmax, associated with a slope reduction, while for RTapex and RTend the strength of the relation was maintained. At POST, the strength of the relation of Tmax and Tarea with RR appeared trending towards being restored to PRE values.

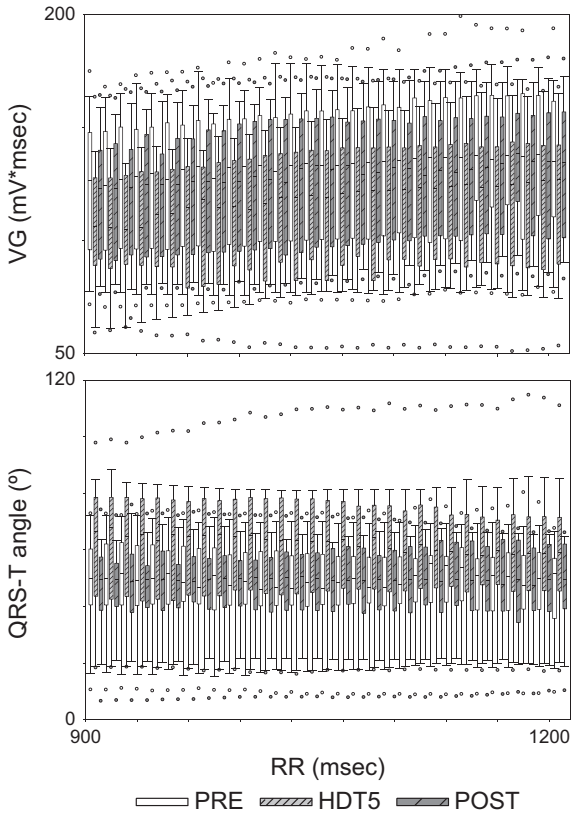

Fig. 5. Relationship between RR duration and magnitude of the ventricular gradient (top), and QRS-T angle (bottom). Wisker-plot represents median and 25–75th percentiles for each RR in the three considered conditions (PRE: white; HDT5: light gray; POST: dark gray).

Table 2
Correlation coefficient (r^2) and slope (in parenthesis, see units of measure) of the linear correlation between the computed QT parameter and RR.

	PRE	HDT5	POST
RTapex	0.99 (0.085)	0.95 (0.067)	0.87 (0.056)
RTend	0.93 (0.072)	0.93 (0.081)	0.92 (0.075)
Tmax (μV/ms)	0.96 (0.29)	0.25(0.125)	0.90 (0.29)
Tarea (mV)	0.96 (64)	0.49 (19)	0.91 (48)
VG (μV)	0.83 (0.038)	0.89 (0.067)	0.81 (0.04)
QRS-T (deg/ms)	0.05 (0.006)	0.85 (−0.03)	0.12 (−0.002)

As regards ventricular spatial heterogeneity parameters, the QRST angle showed low correlation with RR and horizontal fitting line, while the VG magnitude presented an increase in r^2 and slope from PRE to HDT5, and subsequent reduction in POST.

4. Discussion

By eliminating the head-to-foot hydrostatic gradient, the HDBR position leads to an initial increase in diastolic filling and forward stroke volume. Short-term activation of volume regulatory mechanisms by this central fluid shift results in loss of plasma volume and establishment of a new hemodynamic steady state within 24–48 h [36] that could affect not only the cardiac mechanics, but also its electrical counterpart. Automated analysis of QT interval from Holter recordings allows for the evaluation of such electrical changes in the ventricular repolarization phase.

The proposed procedure of selected beat averaging appeared able to overcome some of the limitations connected with previous averaging methods, revealing to be effective in the improvement of the signal-to-noise ratio, due to the high number of beats included in each of the 10 msec duration classes, while not affecting the T wave original morphology. This allowed the automatic detection of fiducial points (T wave start, apex and end) for the calculation of repolarization parameters from each template to be fast and reliable.

In our study focused on detecting stationary changes in the QT/RR relationship and ventricular spatial heterogeneity over the night period, we detected changes both in QT temporal, amplitude, ventricular gradient and QRS-T angle parameters showing that, despite the short duration HDBR, it introduces alterations in the cardiac electrophysiology.

In particular, the decrease in VG together with the increase in QRS-T angle found at HDT5 underlines augmented repolarization heterogeneity that has been associated with risk of life-threatening arrhythmias, as it is functionally linked to dispersion of refractoriness, which facilitates ventricular tachycardia [29]. This finding confirms that found by Sakowski et al. [23] after 30 days of HDBR, suggesting that this phenomenon is visible even after few days of HDBR, and disappears soon after the conclusion of the study. However, none of the subjects actually developed spatial QRS-T angles $> 130^{\circ}$ that is considered a limit of normality in males when inverse Dower matrix transformation is used [35].

Also, at HDT5 a shortening in RTapex and -end, together with a reduction in Tmax and Tarea have been observed. These results are comparable with that observed in [23], and they could be related to the loss of fluids and hypovolemia, resulting in diminished plasma volume and shrinking of the heart cavities, measured in the same subjects after 5 days of HDBR [37], as well as to modifications in autonomic nervous system [38,39], secondary to cardiac deconditioning.

As regards linear regression with RR in the range 900–1200 ms, we chose this among the possible applicable models for its simplicity, also supported by previous results in wide populations [40]. At HDT5, Tmax and Tarea showed a marked loss in strength of the linear regression with RR, and a reduced slope, evidencing and impaired T-wave amplitude adaptation to heart-rate compared with PRE. While healthy subjects are characterized by RR dependency of the T-amplitude [41], other studies have shown less pronounced dependency in patients with acute myocardial infarction [42], thus supporting the hypothesis that impairment of T-amplitude adaptation to RR could represent a new dynamic marker of increased risk for life-threatening arrhythmias. Also, a reduction in slope was found at POST in RTapex, but not in RTend. This is in agreement with the loss of adaptation of QTapex, but not QTend, to abrupt RR changes elicited by the tilt-test maneuver after HDBR that we found in the same

subjects [43]. This could be explained by modifications in the L-type calcium and potassium currents that regulates the initial phase of fast adaptation of action potential duration [44], that are reflected also in the RTapex/RR relation during the night period.

Analysis of the same subjects when undergoing artificial gravity countermeasure could further elucidate about its effectiveness in preventing changes in ventricular repolarization, and HDBR studies conducted on longer periods (21 days and 90 days) could confirm that observed in this short-term HDBR.

4.1. Limitations

Environmental conditions of HDBR at MEDES and DLR were not perfectly identical: DLR facility is underground and each subject is in its own room, while at the MEDES facility the subjects are exposed to natural light and grouped two per room. As regards QRS-T angle computation, the applied inverse Dower transformation has been shown to not accurately represent the true angle computed by Frank leads, overestimating it by about 20° [45–46]. However, as the same transformation was applied to all the different ECG acquisitions, the same bias has affected similarly the QRS-T angle computation before, during, and after HDBR.

5. Conclusions

In conclusion, despite the short-term HDBR, ventricular repolarization during the night period was affected, and selective beat averaging allowed quantification of these changes. This should be taken into account in astronauts for risk assessment during space flight. Further studies are needed to find out whether these changes could indeed mediate an increased arrhythmogenic risk during space flight, and eventually to develop a simple test able to monitor this risk.

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References

[1] J.B. Charles, M.W. Bungo, W. Fortner, Cardiopulmonary function, in: A. Nicogossian, C. Huntoon, S. Pool (Eds.), Space Physiology and Medicine, 3rd edition, Lea & Febiger, Philadelphia, 1994, pp. 286–304.
[2] W.R. Hawkins, J.F. Zieglschmid, Clinical aspects of crew health, in: R. Johnston, L.D. Dietlein, C.A. Berry (Eds.), Biomedical results of Apollo (NASA SP-368), Government Printing Office, Washington DC, 1975.
[3] L.D. Dietlein, Summary and conclusions, in: R. Johnston, L.D. Dietlein, C.A. Berry (Eds.), Biomedical Results of APOLLO (NASA SP-368), Government Printing Office, Washington DC, 1975.
[4] W.R. Douglas, Current status of space medicine and exobiology, Aviat. Space Environ. Med. 49 (1978) 902–904.
[5] R. Smith, K. Stanton, D. Stoop, et al., Vectorcardiographic changes during extended space flight (M093): Observations at rest and during exercise, in: R.S. Johnson, L.F. Dietlein (Eds.), Biomedical results of Skylab (NASA SP-377), 1977.
[6] M.W. Bungo, P.C. Johnson, Cardiovascular examinations and observations of deconditioning during the space-shuttle orbital flight test program, Aviat. Space Environ. Med. 54 (1983) 1001–1004.
[7] J.M. Fritsch-Yelle, U.A. Leuenberger, D.S. D'Aunno, et al., An episode of ventricular tachycardia during long-duration spaceflight, Am. J. Cardiol. 81 (1998) 1391–1392.
[8] M.R Barratt, D.R Hamilton, ABIM, FRCPC, personal communications, 2003.
[9] J.M. Fritsch-Yelle, J.B. Charles, M.M. Jones, et al., Microgravity decreases heart rate and arterial pressure in humans, J. Appl. Physiol. 80 (1996) 910–914.
[10] D.L. Baisden, M.M. Jones. Cardiac Dysrhythmia Analysis on Flights STS-1–STS-61C, NASA, Houston, 1988.
[11] A.C. Rossum, M.L. Wood, S.L. Bishop, et al., Evaluation of cardiac rhythm disturbances during extravehicular activity, Am. J. Cardiol. 79 (1997) 1153–1155.
[12] D.S. D'Aunno, A.H. Dougherty, H.F. DeBlock, et al., Effect of short- and long-duration spaceflight on QTc intervals in healthy astronauts, Am. J. Cardiol. 91 (2003) 494–497.
[13] B. Saltin, G. Blomqvist, J.H. Mitchell, et al., Response to exercise after bed rest and after training, Circulation 38 (1968). VII1-78.
[14] A.L. Goldberger, D. Goldwater, V. Bhargava, Atropine unmasks bed-rest effect: a spectral analysis of cardiac interbeat intervals, J. Appl. Physiol. 61 (1986) 1843–1848.
[15] J. Hartikainen, I. Tarkiainen, K. Tahvanainen, et al., Circadian variation of cardiac autonomic regulation during 24-h bed rest, Clin. Physiol. 13 (1993) 185–196.
[16] C.G. Crandall, K.A. Engelke, V.A. Convertino, et al., Aortic baroreflex control of heart rate after 15 days of simulated microgravity exposure, J. Appl. Physiol. 77 (1994) 2134–2139.
[17] C.G. Crandall, K.A. Engelke, J.A. Pawelczyk, et al., Power spectral and time based analysis of heart rate variability following 15 days head-down bed rest, Aviat. Space Environ. Med. 65 (1994) 1105–1109.
[18] K.I. Iwasaki, R. Zhang, J.H. Zuckerman, et al., Effect of head-down-tilt bed rest and hypovolemia on dynamic regulation of heart rate and blood pressure, Am. J. Physiol. Regul. Integr. Comp. Physiol. 279 (2000) R2189–R2199.
[19] K. Hirayanagi, S. Iwase, A. Kamiya, et al., Functional changes in autonomic nervous system and baroreceptor reflex induced by 14 days of 6 degrees head-down bed rest, Eur. J. Appl. Physiol. 92 (2004) 160–167.
[20] K. Iwasaki, R. Zhang, M.A. Perhonen, et al., Reduced baroreflex control of heart period after bed rest is normalized by acute plasma volume restoration, Am. J. Physiol. Regul. Integr. Comp. Physiol. 287 (2004) R1256–R1262.
[21] K. Iwasaki, T. Shiozawa, A. Kamiya, et al., Hypergravity exercise against bed rest induced changes in cardiac autonomic control, Eur. J. Appl. Physiol. 94 (2005) 285–291.
[22] S.M. Grenon, X. Xiao, S. Hurwitz, et al., Simulated microgravity induces microvolt T wave alternans, Ann. Noninvasive Electrocardiol. 10 (2005) 363–370.
[23] C. Sakowski, V. Starc, S.M. Smith, T.T. Schlegel, Sedentary long-duration head-down bed rest and ECG repolarization heterogeneity, Aviat. Space Environ. Med. 82 (2011) 416–423.
[24] W.L. Atiga, H. Calkins, J.H. Lawrence, G.F. Tomaselli, J.M. Smith, R.D. Berger, Beat-to-beat repolarization lability identifies patients at

risk for sudden cardiac death, J. Cardiovasc. Electrophysiol. 9 (1998) 899–908.
[25] G. Piccirillo, D. Magri, S. Matera, M. Magnanti, A. Torrini, et al., QT variability strongly predicts sudden cardiac death in asymptomatic subjects with mild or moderate left ventricular systolic dysfunction: a prospective study, Eur. Heart J. 28 (2007) 1344–1350.
[26] I. Kardys, J.A. Kors, I.M. van der Meer, A. Hofman, D.A. van der Kuip, J. C. Witteman, Spatial QRS-T angle predicts cardiac death in a general population, Eur. Heart J. 24 (2003) 1357–1364.
[27] P.M. Okin, M. Malik, K. Hnatkova, E.T. Lee, J.M. Galloway, et al., Repolarization abnormality for prediction of all-cause and cardiovascular mortality in American Indians: the strong heart study, J. Cardiovasc. Electrophysiol. 16 (2005) 945–951.
[28] T. Yamazaki, V.F. Froelicher, J. Myers, S. Chun, P. Wang, Spatial QRS-T angle predicts cardiac death in a clinical population, Heart Rhythm 2 (2005) 73–78.
[29] H.H. Draisma, M.J. Schalij, E.E. van der Wall, C.A. Swenne, Elucidation of the spatial ventricular gradient and its link with dispersion of repolarization, Heart Rhythm 3 (2006) 1092–1099.
[30] G.E. Dower, A lead synthesizer for the Frank system to simulate the standard 12-lead electrocardiogram, J. Electrocardiol. 1 (1968) 101–116.
[31] F. Badilini, P. Maison-Blanche, R. Childers, P. Coumel, QT interval analysis on ambulatory electrocardiogram recordings: a selective beat averaging approach, Med. Biol. Eng. Comput. 37 (1999) 71–79.
[32] M. Merri, M. Alberti, A.J. Moss, Dynamic analysis of ventricular repolarisation duration from 24-hour Holter recordings, IEEE Trans. Biomed. Eng. 40 (1993) 1219–1225.
[33] H.C. Burger, A theoretical elucidation of the notion ventricular gradient, Am. Heart J. 53 (1957) 240–246.
[34] C.E. Kossmann, D.A. Brody, G.E. Burch, H.E. Hecht, F.D. Johnston, C. Kay, E. Lepeschkin, H.V. Pipberger, G. Baule, A.S. Berson, S. A Briller, D.B. Geselowitz, L.G. Horan, O.H. Schmitt, Report of committee on electrocardiography, American Heart Association, recommendations for standardization of leads and of specifications for instruments in electrocardiography and vectorcardiography, Circulation, 35, 583–602.
[35] R.W.C. Scherptong, I.R. Henkens, S.-C. Man, S. Le Cessie, H. W. Vliegen, H.H.M. Draisma, A.C. Maan, M.J. Schalij, C.A. Swenne, Normal limits of the spatial QRS-Tangle and ventricular gradient in 12-lead electrocardiograms of young adults: dependence on sex and heart rate, J. Electrocardiol. 41 (2008) 648–655.
[36] M. Kozàkovà, E. Malshi, C. Morizzo, S. Pedri, F. Santini, G. Biolo, M. Pagani, C. Palombo, Impact of prolonged cardiac unloading on left ventricular mass and longitudinal myocardial performance: an experimental bed rest study in humans, J. Hypertens. 29 (2010) 137–143.
[37] E.G. Caiani, P. Massabuau, L. Weinert, O. Laerez, M. Berry, M. Sotaquira, P. Vaida, R.M. Lang, Cardiac adaptation to deconditioning after 5-days of head-down bed-rest: a Doppler-echocardiographic study, Eur. Heart J.–Cardiovasc. Imaging 13 (Suppl 1) (2012).
[38] J.M. Fritsch, J.B. Charles, B.S. Bennett, M.M. Jones, D.L. Eckberg, Short-duration spaceflight impairs human carotid baroreceptor-cardiac reflex responses, J. Appl. Physiol. 73 (1992) 664–671.
[39] J.V. Meck, C.J. Reyes, S.A. Perez, A.L. Goldberger, M.G. Ziegler, Marked exacerbation of orthostatic intolerance after long- vs. short-duration spaceflight in veteran astronauts, Psychosom. Med. 63 (2001) 865–873.
[40] P.M. Rautaharju, Z.M. Zhang, Linearly scaled, rate-invariant normal limits for QT interval: eight decades of incorrect application of power functions, J. Cardiovasc. Electrophysiol. 13 (2002) 1211–1218.
[41] C. Haarmark, C. Graff, M.P. Andersen, et al., Reference values of electrocardiogram repolarization variables in a healthy population, J. Electrocardiol. 43 (2010) 31–39.
[42] L. Johannesen, U.S.L. Grove, J.S. Sørensen, M. Schmidt, C. Graff, J.P. Couderc, Analysis of T-wave amplitude adaptation to heart rate using RR-binning of long-term ECG recordings, Comput. Cardiol. 37 (2010) 369–372.
[43] J. Bolea, E.G. Caiani, E. Pueyo, P. Laguna, R. Almeida, Microgravity effects on ventricular response to heart rate changes, Proc. Ann. Int. Conf. IEEE Eng. Med. Biol. Soc., EMBS (2012) 3424–3427.
[44] E. Pueyo, Z. Husti, T. Hornyik, I. Baczkó, P. Laguna, A. Varró, B. Rodríguez, Mechanisms of ventricular rate adaptation as apredictor of arrhythmic risk, Am. J. Physiol.–Heart Circ. Physiol 298 (2010) 1577–1587.
[45] C.A. Schreurs, A.M. Algra, S.-C. Man, S.C. Cannegieter, E.E. van der Wall, M.J. Schalij, J.A. Kors, C.A. Swenne., The spatial QRS-T angle in the Frank vectorcardiogram: accuracy of estimates derived from the 12-lead electrocardiogram, J. Electrocardiol. 43 (2010) 294–301.
[46] D.L. Cortez, T.T. Schlegel, When deriving the spatial QRS-T angle from the 12-lead electrocardiogram, which transform is more Frank: regression or inverse Dower? J. Electrocardiol. 43 (2010) 302–309.