Cardiovascular autonomic control after short-duration spaceflights

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Abstract

After spaceflight, astronauts sometimes suffer a variable degree of reduced orthostatic tolerance. Although many studies have addressed this problem, many aspects remain unclear. Also, it is unknown how long the cardiovascular system needs to recover from short duration spaceflights.

The scope of the present study was to determine a long-term follow-up of cardiovascular control up to 25 days after spaceflight under control conditions in five astronauts using heart rate variability, blood pressure variability and baroreflex sensitivity (BRS) indices.

In standing position heart rate after spaceflight was significantly higher compared with pre-flight (R+1: 99 (SD 9) BPM vs L-30: 77 (SD 3) BPM; \( p < 0.001 \)). At the same time high frequency modulation of heart rate was extremely depressed (R+1: 70 (SD 334)ms\(^2\) vs L-30: 271 (SD 68)ms\(^2\); \( p < 0.01 \)), as was BRS: (R+1: 5 (SD 1) vs L-30: 10 (SD 2) ms/mmHg, \( p < 0.05 \)). These changes had largely recovered after 4 days upon return to Earth. Orthostatic blood pressure control was well maintained from the first day after landing.

The decrease in BRS and in vagal heart rate modulation following short-duration spaceflight appear to constitute an adequate autonomic neural response to restored gravity. After 4 days upon return to Earth, vagal heart rate modulation is almost completely recovered to the pre-flight level. The findings of the present study demonstrate that the decrease in vagal heart rate modulation in standing position should not be characterised as some kind of cardiovascular deconditioning, but rather as the normal response to orthostatic stress after spaceflight.

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1. Introduction

Spaceflight induces many changes in the human body [1,42,41]. Especially after return to Earth, this causes physiological problems for astronauts. The inability to stand for prolonged periods, with the risk of fainting, and reduced orthostatic tolerance [34] can be considered as some of the most problematic conditions from an operational point of view. The degree of lack of orthostatic tolerance varies a lot from subject to subject. Despite the large amount of studies devoted to solving this problem, or to elucidate the mechanisms behind it, many aspects are still unclear.

In space, most studies agree on diminished vagal baroreflex gain together with an increase in vagal heart rate control [13,24], which is probably due to an
increase in stroke volume (SV) in the first days of spaceflight [31,33]. At the same time however, muscle sympathetic nerve activity (MSNA) has been shown to be higher in microgravity, as demonstrated with lower body negative pressure (LBNP) experiments, Valsalva manoeuvres, handgrip and cold pressor tests [13,22,17,15]. The increased sympathetic drive was supported by measurements of platelet norepinephrine in space [10].

After return to Earth the human body has to readapt to gravity. At this moment, the most likely cause of decreased orthostatic tolerance after spaceflight is a limitation of compensatory elevation in vascular resistance upon standing [9,21]. This can be related to a hypoadrenergic responsiveness as supported by lower or equal values of plasma noradrenaline (NA) levels postflight compared to preflight in orthostatic intolerant subjects [40]. At the same time changes in the baroreflex might contribute to reduced orthostatic tolerance [12,20,11,18]. Reduced vagal–cardiac efferent neural outflow in combination with reduced cardio–vagal baroreflex gain have been described in relation with reduced orthostatic tolerance [20]. On the contrary, astronauts that are able to complete a stand test show increased levels of plasma NA after spaceflight [21,40]. The sympathetic dominance after spaceflight might result from the decreased SV and cardiac output (CO) upon standing [31,39].

Although symptoms of reduced orthostatic tolerance disappear rather quickly after return from space, the autonomic control system may recover more slowly, the duration of which is still unclear. Yet, most studies have performed a follow-up of astronauts and cosmonauts from the first day after landing up to 1 week [13,19,22,9,29,35,16,27]. However, some studies have shown that cardiovascular control mechanisms were not yet restored in full by that time. Nevertheless, only very few studies have performed post-flight measurements up to between 10 and 18 days.

Using a simple paced-breathing protocol, we recently showed that 25 days of recovery after short-duration spaceflight is sufficient to restore vagal–cardiac outflow to pre-flight conditions [38]. However, the time course of recuperation within this period of 25 days remains uncertain. The scope of the present study was to determine a long-term follow-up of cardiovascular control up to 25 days after spaceflight under control conditions.

We studied heart rate modulation, blood pressure modulation and baroreflex sensitivity (BRS) before, during and after spaceflight using heart rate variability (HRV) and blood pressure variability (BPV) indices in five astronauts who had spent 10–11 days in space [3]. According to the above information, the hypothesis was tested that decreased vagal–cardiac control early post-flight will last more than 2 weeks after return but will be restored completely upon 25 days after landing.

2. Methods

2.1. Subjects

This study was performed during three scientific ESA-Soyuz missions to the International Space Station (ISS) (Odissa, Cervantes and Delta: 10–11 day missions). Five male astronauts were studied before, during and after spaceflight. Mean age of the subjects at the time of the pre-flight data collection was 40 (SD 3) years, height 180 (SD 4) cm and weight 76 (SD 10) kg. In space the astronauts had a busy scientific schedule and had no physical exercise programme. Upon return there was also no specific rehabilitation programme, in their spare time they were advised to rest.

The experiment protocol was approved by the local ethical committee and the ESA Medical Board. Each subject was informed of the experimental procedures and signed an informed consent form. The study complies with the Declaration of Helsinki.

2.2. Experimental protocol

Pre- and post-flight: during the pre- and post-flight data collections a stand test was performed in the morning (before 11 AM). This test consisted of a supine period of at least 10 min for instrumentation, calibration and hemodynamic equilibrium, and 10 min recording in rest, followed by a 3–5 min sitting period and a 10 min standing period. Subjects were instructed to maintain their regular breathing depth and rhythm, which was verified by the operators and a respiratory sensor. The stand test was terminated after 10 min.

Pre-flight data collection was performed 1 month before launch (L-30). Post-flight data collections were performed at 1, 4, 9, and 25 days after return to Earth (R+1, R+4, R+9 and R+25). The tests were performed at ambient room temperature (21–23°C) in a quiet room at the Gagarin Cosmonaut Training Center in Moscow, Russia. Late post-flight R+25; between 25 and 28 days after landing) data collection was performed in a temperature-controlled laboratory (21–23°C) in the University Hospital Gasthuisberg of Leuven, Belgium. The subjects were asked to refrain from alcoholic or caffeinated beverages from at least 9 h before the measurements.
In-flight: Astronauts were carefully trained to perform the in-flight measurements by themselves. They were guided through the experiment by dedicated software allowing standardisation of test procedures [7]. Data collection in space was performed in the morning during 10 min in floating conditions with the feet of the astronauts under a belt to keep position on day 8 in the ISS. During the experiment video footage and pictures were taken by a second astronaut to assure of the experimental circumstances.

2.3. Measurements and data processing

Pre- and post-flight: ECG was measured continuously in the supine, sitting and standing position (amplifier/programmer: Medtronic 9690, Minneapolis, MN, USA). Arterial blood pressure was measured three times in each position by means of an automated sphygmomanometer (STBP-780, Colin, Komaki, Japan) placed at the left arm. The average of three readings was calculated to obtain representative values of systolic (SAP) and diastolic arterial pressure (DAP). Mean arterial pressure (MAP) was calculated by adding a third of the pulse pressure (PP) to diastolic blood pressure. Beat-to-beat oscillations in arterial blood pressure were derived from finger blood pressure measurements (Portapres Model 2, Netherlands Organisation for Applied Scientific Research, TNO-BMI, Amsterdam, The Netherlands) at the midphalanx of the right middle finger. During the stand test, the hand was held at heart level using an arm sling. In the supine position the hand was relaxed next to the body. Respiration was measured by an abdominal pressure sensor connected to the MR10 Respiration Monitor (Graseby Medical Limited, Hertfordshire, UK). ECG, continuous finger blood pressure and respiration were sampled using an external A/D converter (DI220PGH, 12 bit precision, Dataq Instruments, Akron, OH, USA) at a frequency of 1000 Hz per channel, thus giving a time resolution of 1 ms and stored on a PC for later off-line processing.

In-flight: A log-file was automatically created containing the blood pressure readings obtained with an automatic sphygmomanometer (Puritan Bennett D500, Pleasanton, CA, USA) aboard the ISS. A spaceflight certified device (Cardioscience) was used to record beat-to-beat finger arterial pressure and ECG simultaneously (Cardioscience, TNO-BMI, Amsterdam, The Netherlands). The respiratory frequency was derived from a stretch sensor that was worn around the abdomen. The in-flight data were sampled at 100 Hz per channel and stored on a flash memory for off-line analysis.

2.4. Data analysis HRV/BPV

After peak detection on the ECG and finger blood pressure signals, a file consisting of consecutive RR intervals (RRI, tachogram) and systolic blood pressure values (systogram) was created. The operator controlled adequacy of peak detection before the time series were exported as a spreadsheet file. Subsequent analysis was performed off-line with methods previously published [4]. Briefly, beat-to-beat hemodynamic time series were interpolated using a third order cubic-spline approximation and resampled at 2 Hz to construct equidistant time series. Power spectra were obtained using a Fast Fourier transform (FFT). FFT was calculated in windows of 256 points with 50% overlap. Power spectral density (PSD) in ms$^2$/Hz for tachograms and mmHg$^2$/Hz for systograms was then computed. The spectral resolution for all estimates equalled 0.0078 Hz. Two frequency bands were defined as recommended by the Task Force [36]: a low frequency (LF) band from 0.04 to 0.15 Hz and a high frequency (HF) band from 0.15 to 0.4 Hz. To correct for large variations in total power (TP: 0.078–0.5 Hz), LF and HF are also expressed as a low- to high-frequency ratio (LF/HF). The data of the breathing frequency was used to verify that the respiratory frequency was within the HF limits. On average, this was the case for all recordings (see Table 2).

2.5. Data analysis: spontaneous BRS

BRS was calculated using the sequence method [8]. This method considered the slope between changes in heart rate and changes in systolic blood pressure as the index of BRS. A baroreflex sequence was defined by a series of at least three consecutive heart beats in which systolic pressure and the following RR-interval either both increased or both decreased. Sequences with at least three intervals of 1 mmHg BP changes and 5 ms RR interval changes were analysed only if the correlation coefficients were higher than 0.7. To find the highest coefficient, systolic BP was correlated with the same RR interval changes were analysed only if the correlation coefficients were higher than 0.7. To find the highest coefficient, systolic BP was correlated with the same RR interval changes were analysed only if the correlation coefficients were higher than 0.7. To find the highest coefficient, systolic BP was correlated with the same RR interval and the following RR interval either also expressed as a low- to high-frequency ratio (LF/HF). The data of the breathing frequency was used to verify that the respiratory frequency was within the HF limits. On average, this was the case for all recordings (see Table 2).

2.6. Statistical analysis

Statistical analysis was performed using SPSS for Windows version 11.5. Data are provided as mean ± SEM. A repeated measures ANOVA was performed with Tukey’s post-hoc correction for multiple measures. An additional test was performed for the
significant levels of the responses upon standing with a one-sample \( t \)-test. Values of the responses of the HRV, BPV and BRS indices were tested for normal distribution with the Kolmogorov–Smirnov test. The level of significance was set at \( p < 0.05 \).

3. Results

The astronauts body weight had decreased from 76 (5) kg before spaceflight to 73 (5) kg after return to Earth \( (p = 0.042) \). Body weight had already fully recovered after 4 days. Respiratory frequency did not differ between the pre-flight measurements (average: 15 breaths/min \( \sim 0.25 \) Hz; min: 12 breaths/min; max: 18 breaths/min), the in-flight measurements (average: 15 breaths/min \( \sim 0.26 \) Hz; min: 15 breaths/min; max: 17 breaths/min) and the post-flight measurements (see Table 2 for details).

Tables 1 and 2 summarise cardiovascular data before, during and after flight. Fig. 1 shows the individual values of HR before, during and after flight. Individual transitions from Earth gravity to microgravity and back to Earth gravity are shown using both the standing and supine body positions as a reference.

3.1. In-flight autonomic control

On average in all subjects, HR and BP values were significantly suppressed in space as compared with the pre-flight standing level. No differences were observed compared with the supine position on Earth (Table 1). HR in space adapted to a level in between the pre-flight standing and supine values in two subjects, maintaining the pre-flight supine level in three subjects (Fig. 1). Despite the observed in-flight adaptations of HR and BP to the pre-flight supine level, most of the HRV and BPV parameters fell in between the pre-flight standing and supine reference values (Table 2). This was also true for the cardiac BRS in space (Table 1).

3.2. Autonomic control at R+1

At the first day after landing standing heart rate was significantly higher compared to pre-flight conditions \( (p < 0.001, \text{Fig. 1}) \). HR exceeded 100 beats per minute.
Table 2
Frequency domain analysis of heart rate variability, blood pressure variability and respiratory frequency before, during and after spaceflight.

<table>
<thead>
<tr>
<th></th>
<th>Pre-flight</th>
<th>In-flight</th>
<th>Post-flight</th>
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<tbody>
<tr>
<td></td>
<td>L-30</td>
<td>FD8</td>
<td>R+1</td>
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<tr>
<td><strong>HRV</strong></td>
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<tr>
<td>Total power (ms²)</td>
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<td></td>
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<tr>
<td>Supine</td>
<td>3106 (1264)</td>
<td>3317 (1082)</td>
<td>2791 (1310)</td>
</tr>
<tr>
<td>Standing</td>
<td>4580 (1104)</td>
<td>1777 (960)</td>
<td>2000 (895)</td>
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<tr>
<td>LF (ms²)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Supine</td>
<td>1317 (575)</td>
<td>1492 (423)</td>
<td>1370 (765)</td>
</tr>
<tr>
<td>Standing</td>
<td>2560 (628)</td>
<td>1126 (612)</td>
<td>1758 (552)</td>
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<td>HF (ms²)</td>
<td></td>
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<td></td>
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<tr>
<td>Supine</td>
<td>462 (167)</td>
<td>435 (166)</td>
<td>373 (182)</td>
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<tr>
<td>Standing</td>
<td>271 (68)</td>
<td>70 (34)*</td>
<td>111 (29)</td>
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<tr>
<td>LF/HF</td>
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<tr>
<td>Supine</td>
<td>3 (1)</td>
<td>7 (4)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Standing</td>
<td>11 (2)</td>
<td>14 (2)</td>
<td>15 (2)</td>
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<tr>
<td><strong>BPV</strong></td>
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<tr>
<td>Total power (mmHg²)</td>
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<tr>
<td>Supine</td>
<td>104 (72)</td>
<td>33 (8)</td>
<td>34 (10)</td>
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<tr>
<td>Standing</td>
<td>50 (13)</td>
<td>63 (14)</td>
<td>45 (7)</td>
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<tr>
<td>LF (mmHg²)</td>
<td></td>
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<tr>
<td>Supine</td>
<td>10 (3)</td>
<td>18 (6)</td>
<td>15 (8)</td>
</tr>
<tr>
<td>Standing</td>
<td>25 (7)</td>
<td>39 (8)</td>
<td>27 (4)</td>
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<tr>
<td><strong>RESP. FREQ</strong> (min⁻¹)</td>
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</tr>
<tr>
<td>Supine</td>
<td>15 (1)</td>
<td>15 (1)</td>
<td>16 (1)</td>
</tr>
<tr>
<td>Standing</td>
<td>15 (1)</td>
<td>17 (1)</td>
<td>17 (1)</td>
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Fig. 1. Evolution of heart rate before and after spaceflight in standing (●) and supine position (○) (values mean ± SEM) and during spaceflight (□).

In three subjects, while orthostatic BP control was well maintained during the 10 min stand test early postflight. No symptoms of an impending syncope were reported; however, there was a large reduction in PP upon standing compared with pre-flight values. This was associated with a significant fall in the cardiac BRS (Table 1). The HF power of HRV was significantly depressed in the standing position after spaceflight.
(p < 0.01) while no differences were observed in the LF powers of both HRV and BPV when compared with pre-flight values. The LF/HF ratio of HRV was not significantly different between pre- and post-flight sessions (Table 2).

3.3. Autonomic recovery up to R+25

Although the orthostatic tachycardia response largely disappeared at R+4, standing HR remained slightly elevated up to 25 days after landing in three subjects (Fig. 1). The HF modulation of HR was restored at pre-flight level after 4 days upon return to Earth, as did the cardiac BRS. No significant trends were observed in the evolution of BP and BPV up to 25 days after landing.

4. Discussion

In this study a long-term follow-up of five astronauts up to 25 days after their 10-day spaceflight was performed. We found a profound effect of short duration spaceflight on heart rate and HRV after spaceflight in the standing position only. There was a strong decrease in vagal heart rate modulation upon standing early post-flight while blood pressure and blood pressure control were not affected and remained stable at pre-flight levels. Cardiovascular control during spaceflight adapted to a level similar to the ground-based supine position. The observed changes in heart rate modulation and BRS early post-flight seem to represent a normal adaptation mechanism to restored gravity.

4.1. Effects of microgravity on cardiovascular function

As in previous studies we found that heart rate in space was significantly lower than pre-flight standing conditions on Earth, but similar to pre-flight supine conditions [13,16,31]. This effect on heart rate has also been observed during a very long term mission of 438 days in a Russian cosmonaut [25,26] and during the Neurolab missions [30]. The same observations were also made during the ultra short periods of microgravity (20s) elicited during parabolic flights [2,6,37].

The resemblance with the supine Earth condition is also in HF power of HRV. This means that cardiac autonomic modulation during spaceflight mimics the vagal predominance of the supine position. This is in agreement with previous Neurolab missions [24,30]. These results point to the advantage of the methods of HRV, being able to demonstrate vagal–cardiac dominance, while experiments measuring MSNA have found increased sympathetic activity during spaceflight, both in baseline conditions and during stress tests [15,16,24].

The present finding that arterial BP in space adapts to a pre-flight supine level is in line with a recent report of systemic vasorelaxation after 8 days into spaceflight, as compared with the ground-based upright (seated) posture [31]. Such systemic cardiovascular relaxation is difficult to merge with previous reports of increased sympathetic drive in space. Further studies should provide an answer here.

4.2. Recovery after spaceflight

Interestingly, the first day after return to Earth presented with the most outspoken changes in heart rate control in standing position, while in supine position no differences were observed compared to pre-flight conditions. Standing upright after spaceflight is difficult for most astronauts and is known to provoke dizziness or even fainting. In our population, in order to cope with the orthostatic stress, we observed an increased standing heart rate after spaceflight. Especially HF of HRV was significantly lower compared to pre-flight values leading to a sympathetic dominance of heart rate control. Also previous studies, in which increased levels of NA [21,29,32,40] and MSNA [16,22,28] were observed after spaceflight confirm this. Gisolf et al. and Verheyden et al. also described recently an increased sympathetic influence on heart rate after spaceflight, demonstrated by the increased RRI-SAP lag after spaceflight [23,38]. In our study we observed no significant differences in LF power of HRV with the pre-flight condition. Blood pressure levels and blood pressure control were similar to pre-flight values. Also, in a study of Meck et al., the orthostatic tolerant subjects did not present differences in the upright position for systolic BP, with an increased heart rate during standing on landing day [29]. Sigaudo-Roussel et al. [35] found higher SAP values after spaceflight, but their subjects were in space between 90 and 198 days, which could explain these differences. Baevsky et al. [5] found similar results after 180 days in space.

BRS was significantly decreased during a 10min stand test at the first day after flight. This again is an indication of lower vagal heart rate modulation during orthostatic stress early post-flight. In previous reports baroreflex function has been reported to be reduced after spaceflight; however, it is especially the hypotensive buffering of the response that was affected [18,20], while the hypertensive buffering remained intact [29]. The spontaneous baroreflex, including both hypotensive and hypertensive buffering, as was measured by Sigaudo-Roussel did not show significant differences
after spaceflight during standing [35]. Fritsch et al. [18] found an impaired baroreflex response after return from a 5-day Shuttle mission. Later, they showed further evidence of both decreased vagal modulation of heart rate and increased sympathetic control of the heart after return from an 8–14-day mission. [20]. Di Rienzo et al. found no deconditioning in the baroreflex control of the heart and even return to baseline in the later phases of spaceflight [14].

The observed changes in heart rate modulation and BRS early post-flight seem to be related with a postural reduction in PP. These data are suggestive of thoracic hypovolemia early post-flight, requiring an increased heart rate and sympathetic drive to maintain orthostatic blood pressure. The loss in absolute body weight after spaceflight supports this hypothesis. The most likely explanation of the weight loss at R+1 is the suboptimal intake of food and water during the flight.

Our study shows that vagal autonomic heart rate control in baseline standing conditions after short-duration spaceflight is already restored from about 4 days after return to Earth, while blood pressure control is maintained immediately after spaceflight. In three subjects, however, HR is affected up to 25 days after return, indicating still some residual adaptations to gravity that require lower vagal modulation during standing. Such slow (vagal) recovery after return to Earth was also confirmed by others after short duration missions [18] and long duration missions [5,12]. Whether this recovery period after return to Earth is related to the duration of the space mission is still an open question. Some of the differences in post-flight recovery described in the literature could also be a result from the differences in characteristics between the Space shuttle (position: sitting; max g force: \(\sim 2g\)) and the Soyuz capsule (position: laying on back; g force: \(\sim 3–4g\)) during the re-entry procedure.

4.3. Study limitations

The number of subjects available in spaceflight experiments is very limited. All agencies involved with human space flight (ESA, Roskosmos, NASA, Chinese Space Agency), impose limitations upon the accessibility and time slots available to life science researchers. Since the accident with space shuttle Columbia, the available subjects and the time these subjects are available to participate in experiments is restricted even more. Although we have imposed a standardisation the experiments between the different missions, we cannot control differences in workload between these missions. Also, changes in sleep–wake cycles, personal exercise regimens, quantity and quality of sleep, fluid intake and nutrition before, during and after the flight could not be controlled.

5. Conclusion

The importance of this study, in which multiple time points up to 25 days after landing with strict standardisation of measurements between the different space missions were obtained, was to demonstrate that especially the first days after spaceflight the spontaneous vagal autonomic control (without interventions like paced breathing, Valsalva, ...) of heart rate is affected, resulting in a sympathetic dominance. After 4 days this control is largely recovered, although the effects on heart rate may remain visible up to 25 days after spaceflight in some astronauts. The effect of spaceflight on vagal heart rate modulation in standing position should not be characterised as some kind of cardiovascular deconditioning, but rather as the normal response to orthostatic stress with a steeper reduction in PP after spaceflight.

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