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ORIGINAL ARTICLE

Effects of long-term fasting and confinement on the cardiovascular activity

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Abstract

Fasting has been demonstrated to improve health and slow aging in human and other species; however, its impact on the human body in the confined environment is still unclear. This work studies the effects of long-term fasting and confined environment on the cardiovascular activities of human via a 10-day fasting experiment with two groups of subjects being in confined (6 subjects) and unconfined (7 subjects) environments respectively and undergoing the same four-stage fasting/feeding process. It is found that the confinement has significant influences on the autonomic regulation to the heart rate during the fasting process by altering the activity of the parasympathetic nervous system, which is manifested by the significant higher pNN50, rMSSD, and Ln-HF of heart rate variability (HRV) ($p < 0.05$) and slower heart rate ($p < 0.01$) in the confined group than that in the unconfined group. Furthermore, the long-term fasting induces a series of changes in both groups, including reduced level of serum sodium ($p < 0.01$), increased the serum calcium ($p < 0.05$), prolonged QTc intervals ($p < 0.05$), and reduced systolic blood pressures ($p < 0.05$). These effects are potentially negative to human health and therefore need to be treated with caution.

Keywords Fasting · Confinement · Cardiovascular system · Parasympathetic nervous system

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1 Introduction

The cardiovascular system is one of the critical systems of the human body, responsible for delivering oxygen and nutrients to tissues and organs and for transporting carbon dioxide and wastes out [1]. In recent years, fasting has received wide attention of both academics and the public for its potential benefits to the health of human and other species [2, 3]. In a fasting diet, a person drinks water only or eats very few calories (usually less than 200 kcal/day) during several days, weeks, or months. Previous studies have suggested that fasting has a range of beneficial effects on the cardiovascular system, including the reduction of blood pressure [4, 5]; decreased incidence of acute cardiac diseases [6, 7]; and improved cardiovascular risk factors, e.g., obesity [8] and diabetes [9].

The adaptability of the human body to low or even zero energy intake also undoubtedly benefits the survival of a person in extreme conditions, e.g., food shortage. However, the safety and benefits of fasting for human have not been fully validated especially when the fasting period is prolonged (1 week or longer). Besides, little is known about the effects

of fasting in extreme environments, such as microgravity, confinement, and isolation. Consequently, understanding possible effects of fasting in the extreme environments on the cardiovascular system is critical to maintaining the human health and ensuring the success of missions.

Previous studies have been conducted to identify and understand the impact of the confinement on the autonomic regulation of the cardiac activity. In a 105-day confinement study (Mars105) with 6 healthy male subjects, it was found that the parasympathetic activity was increased during wakefulness in the confined environment [10]. As an extension of Mars105, a 520-day confinement study (Mars500) with the same 6 subjects analyzed the sleep–wake difference of heart rate variability (HRV), and revealed a progressive decrease of the difference during the confinement, especially for the parasympathetic activity [11]. However, the combined effects of confinement and fasting on the cardiovascular system have not been investigated in previous studies.

This study focuses on the impact of long-term fasting and confined environment on cardiovascular system. In the study, we organized a fasting experiment with 13 subjects participating a water-only fasting program of 10 days. The subjects were grouped by the housing environment during the experiment: The unconfined group (7 subjects) lived in a lab building with relative moving freedom, while the confined group (6 subjects) was confined in a closed cabin. In order to find out the effects of fasting and confinement on the functions of cardiovascular system, we tracked a series of physiological indices during the experiments, including body weight, blood pressures, serum electrolytes, QT/QRc intervals, and HRV indices. In the rest of this paper, we will describe the experimental design, the data analysis methods, and our findings in detail.

2 Methods

2.1 Experimental design

We recruited 13 healthy male subjects to participate in this study. These subjects were divided into two groups: confined group (6 subjects; mean ± STD: age 39.7 ± 8.7 years; height 171 ± 3.6 cm; weight 74.7 ± 12.2 kg; BMI 25.5 ± 3.9 kg/m^2) and unconfined group (7 subjects; mean ± STD: age 39.6 ± 8.3 years; height 172.9 ± 6.1 cm; weight 69.9 ± 11.1 kg; BMI 23.3 ± 2.7 kg/m^2). The two groups experienced the same fasting process, with the only difference being their housing environment. The confined group was confined to a closed cabin (204.3 m^3 and 50 m^2) during fasting, while subjects in the other group lived in a lab building and were allowed to move around with relative freedom.

This experiment consists of 4 stages, which include S1, pre-fasting stage (3 days, PF1 to PF3); S2, complete fasting stage (10 days, CF1 to CF10); S3, calorie restricted stage (4 days, CR1 to CR4); and S4, fully recovery stage (7 days, FR1 to FR7). At the beginning of the S1 stage, subjects of each group entered to their respective environment and maintained their normal diet. Then, during the S2 stage, they were only allowed to drink water, except for a small amount of sugar in case of hypoglycemia. At the end of S2 stage, the confined group got out of the cabins and entered the same environment as the unconfined group. During the following calorie restricted stage S3, each subject was allowed to eat only a limited amount of food. After this phase of adjustment, they were free to eat during the S4 stage.

The study was approved by the Ethics Committee of the SPACEnter Space Science and Technology Institute. All experiments were performed in accordance with the relevant guidelines and regulations stated in the Declaration of Helsinki. All subjects gave written informed consent to participate in the study. To minimize the risks of fasting, subjects were given advice and information on fasting and its possible risks and were informed to immediately report to researchers and stop fasting if they felt unwell.

2.2 Measurements

To investigate the effects of long-term fasting in the confined environment on the functions of cardiovascular system, we performed some predefined measurements, as discribed below, during the experiment. All the clinical data were collected by physicians.

2.2.1 Body weight and blood pressure

Body weight and blood pressure, including systolic blood pressure and diastolic blood pressure, are important indicators of physical health. The body weights of the subjects were recorded at 6 time points, namely, the 1st day in the S1 stage (PF1), the 6th and 10th days in the S2 stage (CF6 and CF10), the 2nd day in the S3 stage (CR2), and the 2nd and 4th days in the S4 stage (FR2 and FR4). The body weights were measured in the morning after voiding and in the nude. The blood pressures were recorded on PF3, CF3, CF6, CF9, CR3, and FR4. Blood pressure was measured in the morning in sitting position by using upper arm blood pressure monitor manufactured by Omron, Japan.

2.2.2 Serum electrolytes

The cardiac electrophysiological activities involve a series of electrolytes, such as sodium (Na), potassium (K), and calcium (Ca). Electrolyte disturbance will affect the electrophysiological activities of the heart and even lead to arrhythmias [12]. Because the body needs to maintain a balance of electrolytes through diet, fasting may cause electrolyte

disturbance and further affect the body's electrophysiological activities. Therefore, the test and analysis of these substances will help us to understand the influence of fasting on cardiovascular system. During the experiment, we collected blood samples at 6 time points, namely, PF1, CF3, CF6, CF9, CR2, and FR4. The blood samples were taken from the elbow vein of subjects in sitting position before dawn of the day. Then, the blood samples were sent to the Longgang Central Hospital, Shenzhen, China, for analysis. Serum sodium and potassium were measured by the ion-specific electrode (ISE) technology [13], and the serum total calcium is determined with Arsenazo III method [14].

2.2.3 QT interval

QT interval, defined as the time interval between the beginning of the QRS complex and the end of the T wave, reflects the total time for cardiac depolarization and repolarization. Since QT interval is dependent on the heart rate, it is common to use the QT interval corrected for heart rate (QTc) for diagnostic and comparative purposes. The QT and QTc intervals are important indicators of cardiac electrophysiological activity and are associated to the risk of malignant arrhythmias and sudden death [15, 16].

In this study, we recorded 12-lead resting ECG (1000 Hz, device: PCECG-500, Carewell, Shenzhen, China) of each subject during wakefulness at 6 time points, namely, PF3, CF3, CF6, CF9, CR3, and FR4, during this experiment. Each recording lasts for 5 minu, whereby short-term HRV analysis could be applied. The QT intervals were measured by physicians from the collected ECG signal of lead II and alternatively lead V5. If the signals of both leads were distorted severely by noise, one of the other leads was chosen. The waveforms of 3 consecutive heart beats in normal sinus rhythm were selected for the measurement, where the tangent method [17] was used to determine the end of the T wave. Then, we used the Bazett's method [18] to correct QT interval for heart rate: $QTc_{(ms)} = QT_{(ms)} / (RR_{(sec)})^{1/2}$, where RR denotes the preceding RR interval.

2.2.4 Heart rate variability

Autonomic nervous system (ANS) plays a key role in the modulation of cardiac rhythm. ANS consists of two parts: the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS). In response to stress, human body is mainly controlled by SNS, while, during rest or sleep, PNS dominates the autonomic regulation [19]. The interaction of SNS and PNS is reflected by the variations of heart rate, i.e., heart rate variability (HRV) [20]. Therefore, HRV is commonly used to analyze the autonomic regulation of cardiovascular activity [21–24].

To calculate the HRV indexes, we should first extract the time series of beat-to-beat intervals from the ECG signals. Generally, the heart beats are temporally located based on the R-waves, which typically have the largest amplitudes compared to surrounding waveforms (including P, Q, S, and T) and thus are easiest to identify. In this study, we detected the R peaks from raw ECG signal using the Pan-Tompkins algorithm and then computed the RR intervals by differential operation of the R peak locations [25] to represent the beat-to-beat intervals. In addition, RR intervals that are derived from ectopic and lost beats were identified by visual check of raw ECG signals and removed from the time series to make sure the remaining ones are all from normal sinus rhythms. Then, we use the HRVAS [26] software to calculate the HRV indices.

The HRV indexes that are used in our study include time domain indexes, frequency domain indexes, and entropy indexes [20]. The time domain HRV indexes can be calculated directly from the RR intervals. As the ECG was recorded for just 5 min in our experiment, we selected some indexes that were suitable for short-term HRV analysis, namely, the standard deviation of RR intervals (SDNN), the root mean square of differences between successive RR intervals (rMSSD), and the proportion of pairs of successive NNs that differ by more than 50 ms (pNN50). Among them, the SDNN measures the total HRV and reflects the integral influence of ANS (including both SNS and PNS), while rMSSD and pNN50 mainly reflect the regulation of parasympathetic nerve to heart rate.

Frequency domain HRV indexes quantify the variation of heart rate in different frequency bands. As for the short-term recording in our study, the total power (i.e., signal energy) of heart rate variation (TP), the power in a very low frequency band from 0.0033 to 0.04 Hz (VLF), a low frequency band from 0.04 to 0.15 Hz (LF), and a high frequency band from 0.15 to 0.4 Hz (HF) are generally evaluated. TP, encompassing all of the bands together, reflects the overall excitability of the autonomic nervous system. VLF is affected by a variety of activities, including PNS activity, physical activity, thermoregulatory, renin-angiotensin, and endothelial influences on the heart [20]. Experimental evidences also suggest that SNS can modulate the amplitude and frequency of its oscillations [27]. VLF is also an important health indicator of which the low value is associated with all-cause mortality [28]. LF reflects both the sympathetic and parasympathetic modulation of heart rate and is also related to the baroreceptor function. HF, on the other hand, is believed to be an indicator of the heart rate changes resulting from respiratory sinus arrhythmia that are mediated by parasympathetic nerve [29]. In this paper, we report the natural logarithms (Ln-TP, Ln-VLF, Ln-LF, and Ln-HF) and normalized values [nLF = LF / (LF + HF); nHF = HF / (LF + HF)] of these two indexes. Besides, the ratio between LF and HF (LFHF) is

a frequently used index to denote the ratio between sympathetic and parasympathetic activity. However, recent studies have shown the irrationality of this approach [27, 30]. For the comprehensiveness of the information, this index was also reported in this study. The method we used to calculate these frequency-domain measures is the Burg autoregressive method which is able to resolve the closely spaced sinusoids in low-noise signals [31].

No-linear measurements are also frequently used in the HRV analysis. A previous study has suggested that the regulation of ANS on the cardiovascular system is a non-linear dynamic and chaotic process [32]. Thus, it is believed that no-linear methods are more adequate than linear methods for the HRV analysis [33]. No-linear HRV analysis methods can be classified as chaotic analysis, graphical representation, and complexity analysis [32]. Among these methods, chaotic analysis and graphical representation methods need a very long time series, while the complexity analysis methods, mainly including different kinds of entropy measures, can be used to analyze a much shorter time series [34]. In this study, we calculated two kinds of entropy measures, namely, sample entropy (SampEn) and fuzzy measure entropy (FuzzyMEn). SampEn quantifies the regularity and complexity of signals [35]. FuzzyMEn extends traditional entropy measures for HRV analysis and has been suggested to provide a more reliable measurement [36].

2.3 Statistical analysis

Statistical methods were used to test whether there are significant changes in the extracted indicators. Our experiment is in a factorial design involving a within-subject factor (data acquisition time point) and a between-subject factor (environment: confined or unconfined). The questions we would like to answer with the experimental data and the methods we adopted are as follows:

1) Which indicator changed significantly during the experiment under the condition of confined or unconfined environment? To answer this question, we applied one-way repeated measures ANOVA tests [37] on the data of each index and each group by using the IBM SPSS Statistics software. As the ANOVA is based on the assumption of sphericity, we conducted a Mauchly's sphericity [38] test on the data to ensure the validity. For data that did not satisfy the sphericity assumption, the Greenhouse–Geisser (GG) [39] method was applied to correct the epsilon values which were then used to adjust the p values. We also calculated the post hoc study power (1—β) with the G*Power software for each ANOVA test to analyze whether the sample size was sufficient for the test.
2) To answer questions such as when did an indicator change significantly during the experiment, and what patterns did the changes exhibit, we conducted post hoc Tukey's HSD tests [40] on the data between all time pairs to find out which ones are significantly different in terms of mean values. The Tukey's HSD test fully controls for multiple testing and thus prevents the inflation of the probability of making type I errors.
3) To answer the questions such as when the mean values of an indicator were significantly different between the confined group and unconfined group, we used the post hoc Tukey's HSD method to test whether there were significant differences between the data of two groups at each time point.

3 Results

3.1 Body weight and blood pressure

In the results of repeated measures ANOVA test, as shown in Table 1, the changes of body weight were significant ($p < 0.001$) in both confined and unconfined groups. The data that do not satisfy the sphericity assumption are corrected by using the GG method, which is annotated by "(GG)" in the table. Figure 1 shows that the changes of body weight were in a V-shape: The body weight dropped during the period between PF1 and CR2 (from 75.6 ± 13.2 to 67.4 ± 12.2 kg in confined group, from 68.9 ± 11.6 to 62.1 ± 10.0 kg in unconfined group) and then gradually regained (to 72.0 ± 12.6 kg in confined group, and 65.5 ± 9.4 kg in unconfined group) by FR4.

The results in Table 1 also show that the changes of DBP in both groups were not significant, while SBP exhibited

Table 1 F-statistic of body weight and blood pressures along time in each group

Indicators	Unconfined			Confined		
	F-value	p Value	Power	F value	p Value	Power
Weight	25.61	< 0.001 (GG)	1.0	117.98	< 0.001	1.0
DBP	0.25	NS	0.219	2.49	NS	0.994
SBP	3.84	0.008	1.0	4.85	0.028 (GG)	1.0

"GG" indicates that the data do not satisfy the sphericity assumption and are corrected by using the GG method

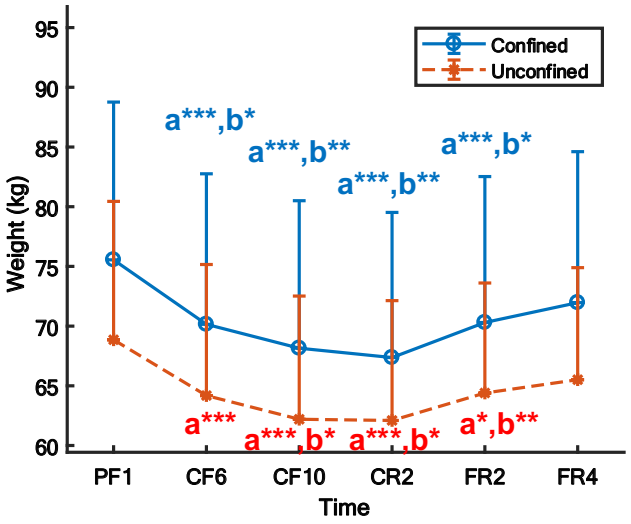

Fig. 1 Changes of body weight during the experimental process. The solid line in each chart indicates the confined group, while the dashed line indicates the unconfined group. The length of a vertical bar presents the standard deviation of the corresponding data of a group at a time point. The marks on the graph show significance of comparisons: "a" indicates significant difference between the current data and that of the first time point (PF1 in this figure); "b" indicates significant difference between the current data and that of the last time point (FR4 in this figure). The asterisk symbols denote the level of significance: *$p<0.05$; **$p<0.01$; *** $p<0.001$

significant changes in confined group ($p<0.05$) and unconfined group ($p<0.01$). As the study power of the ANOVA test for DBP in the unconfined group was just 0.219, the sample size of the unconfined group might be insufficient for the analysis of DBP. By contrast, the study powers of the other tests reached or were close to 1, indicating that the sample sizes for these tests were sufficient. The changing patterns of DBP and SBP are presented in Fig. 2. The SBP in the confined group, as shown in Fig. 2b, had a significant drop ($p<0.05$) from 111.2 ± 10.9 to 95.7 ± 13.2 mmHg during the period between PF3 and CR3. In the unconfined group, there were also significant drops ($p<0.05$) of SBP between PF3 (111 ± 6.1 mmHg) and CF9 (101.1 ± 5.4 mmHg) and between PF3 and CR3 (99.1 ± 7.5 mmHg).

3.2 Serum electrolytes

The time courses of serum electrolytes, including serum sodium, serum potassium, and serum calcium, during this experiment are presented in Fig. 3. Results are shown in Table 2. In addition, we also conducted multiple pairwise comparisons between different time and groups by using the Tukey's HSD method, and the significant changes are annotated in Fig. 3. It is shown that all the tested serum indicators in both groups changed significantly ($p<0.01$, as shown in Table 2) during the whole process. The post hoc powers of these tests all reached 1.0 indicating the sample size is sufficient.

The levels of serum sodium, as shown in Fig. 3a, exhibited a V-shape changing curve: The levels began to decline significantly ($p<0.05$) after CF3 and reached to the minimum on CF9, then kept rising in the remaining S2 and S3 stages, and finally returned to the original level on FR4. The standard deviation of the unconfined group on FR4 was much higher than other time points, which is due to the level of two subjects (133.4 and 139.2 mmol/L) that were obviously lower than that of others (between 141.3 and 145.6 mmol/L). By contrast, serum calcium, as presented in Fig. 3b, showed an almost opposite changing pattern to serum sodium. The levels of serum calcium increased after CF3 and reached the peak on CL9 and then decreased back to near the original values on FR4. It is worth mentioning that, on CF9, the data of a large proportion of subjects in both groups were beyond the reference ranges for serum sodium (137 ~ 147 mmol/L) and serum calcium (2.11 ~ 2.52 mmol/L): in the confined group, 4 subjects (66%) had serum sodium levels (134.5 ~ 136.5 mmol/L)

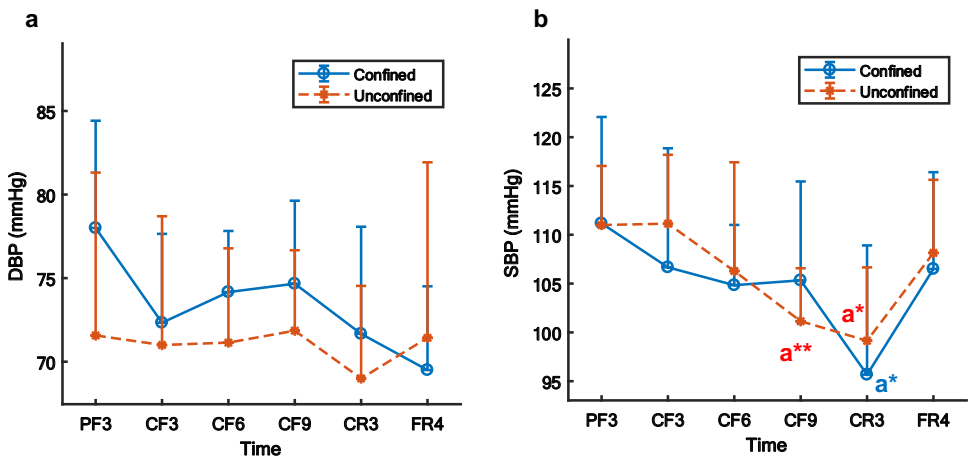

Fig. 2 Changes of blood pressures during the experimental process. **a** Diastolic blood pressure. **b** Systolic blood pressure. The denotations of elements in the graph are the same as Fig. 1

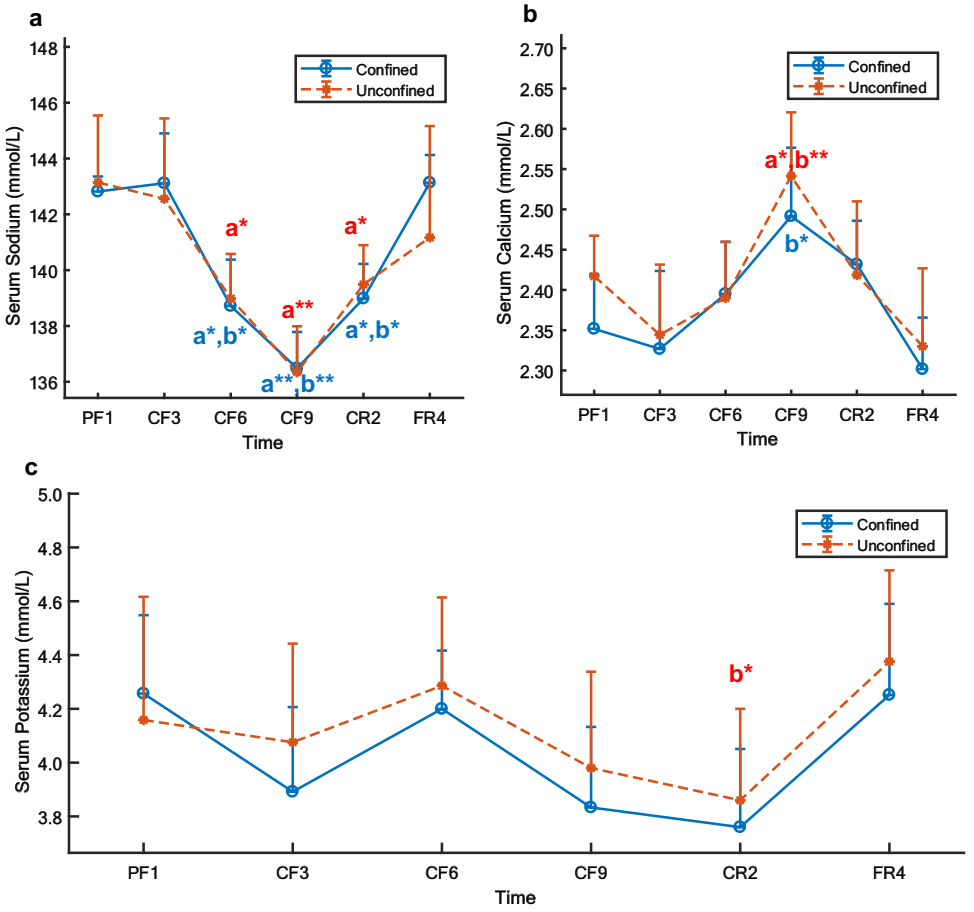

Fig. 3 Changes of serum electrolytes during the experimental process. **a** Serum sodium. **b** Serum calcium. **c** Serum potassium

below the reference range, and 2 subjects (33%) had serum calcium levels (2.54 ~ 2.64 mmol/L) above the reference range; in the unconfined group, 5 subjects (71%) had serum sodium levels (134.8 ~ 136.6 mmol/L) below the reference range, and 5 subjects (71%) had serum calcium levels (2.53 ~ 2.65 mmol/L) above the reference range. In other time points of blood sample collection, abnormal levels of serum sodium and serum calcium were observed only in single or no cases.

The changing pattern of serum potassium, as shown in Fig. 3c, was markedly different from that of others. Though the changing curves of serum potassium in both groups were similar to each other, the levels in the unconfined group dropped significantly between CF6 and CR2 ($p < 0.05$, not shown in the figure) and rose significantly between CR2 and FR4 ($p < 0.05$), while the levels in the confined group did not show significant differences between any two time points. On CR2, 2 subjects (33%) of the confined group and 1 subject (14%) of the unconfined group had serum potassium levels (3.32 ~ 3.49 mmol/L) below the reference range (3.5 ~ 5.3 mmol/L). Only single or no cases of abnormal serum potassium level were observed at other time points.

3.3 QT/QTc intervals

Figure 4 shows the data for QT and QTc intervals in both groups, and Table 3 shows the results of repeated measures ANOVA test on these two indicators. We can see that during the experiment, both QT and QTc intervals changed significantly in the confined group ($p < 0.05$) and even more

Table 2 F-statistic of serum electrolytes along time in each group

Indicators	Unconfined			Confined		
	F-value	p Value	Power	F-value	p Value	Power
Serum sodium	10.21	0.001 (GG)	1.0	37.13	< 0.001	1.0
Serum potassium	3.83	0.008	1.0	4.38	0.005	1.0
Serum calcium	8.72	< 0.001	1.0	9.64	< 0.001	1.0

"GG" indicates that the data don't satisfy the sphericity assumption and are corrected by using the GG method

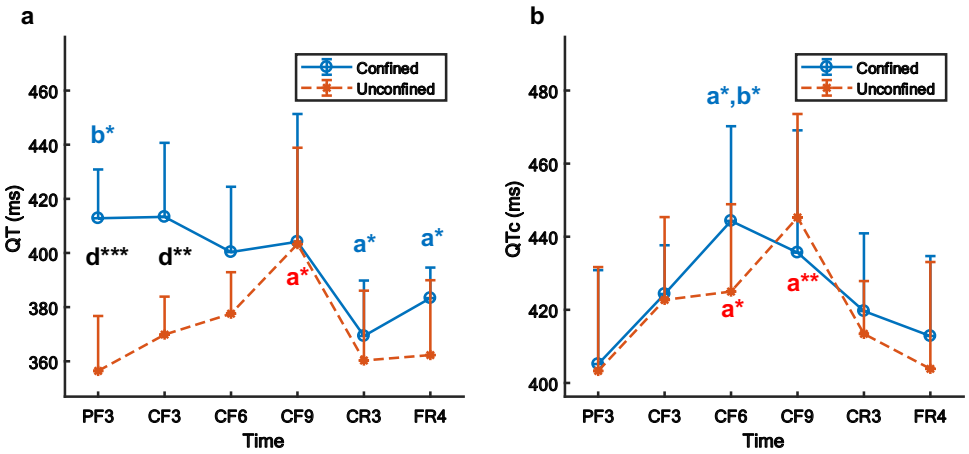

Fig. 4 Changes of QT/QTc intervals during the experimental process. **a** QT interval. **b** QTc interval

significant in the unconfined group ($p < 0.001$). Each test achieved a post hoc study power of 1.0; thus, the sample sizes for these analysis were sufficient. As presented in Fig. 4a, the QT intervals in the confined group were significantly higher than that of the unconfined group on PF3 ($p < 0.001$) and CF3 ($p < 0.01$); then the differences between the two groups were not significant. This pattern is consistent with that of the heart rate mentioned above, since longer RR interval tends to induce longer QT interval. For the same reason, the QTc intervals are more suitable for comparison. The change patterns of QTc intervals in both groups were different from each other, as shown in Fig. 4b. In the confined group, the mean value of QTc intervals increased significantly ($p < 0.05$) from slightly higher than 400 ms on PF3 to above 440 ms on CF6 and then dropt to near the original level on FR4. The QTc intervals in the unconfined group also showed a first up and then down pattern, but they reached the peak on CF9 which was later than the peak of confined group (CF6). This difference indicates that confinement may speed up the changes of QTc intervals during fasting. On CF6, 4 subjects (66%) in the confined group and 2 subjects (29%) in the unconfined group had QTc intervals (443 ~ 472 ms) longer than the reference range (360 ~ 440 ms), while on CF9, 3 subjects (50%) in the confined group and 3 subjects (43%) in the unconfined group had overlong QTc intervals (450 ~ 495 ms). As the QTc interval is susceptible to the serum level of electrolytes [41], these prolonged QTc intervals may be attributed to the electrolyte disturbances induced by fasting as mentioned above.

3.4 HRV indexes

To analyze the influence of fasting and confinement on HRV, characteristics of HRV in the time, frequency and non-linear domains, were computed for different stages of the experiments. The results of repeated measures ANOVA test and post hoc power analysis on all the HRV indexes are presented in Table 4. All the tests made on the confined group had a post hoc study power higher than 0.9 and most of them reached 1.0. Therefore, the sample size of the confined group is sufficient to test the significance of the changes through time. On the contrary, the powers of tests (except that for pNN50 and LFHF) on the unconfined group were lower than 0.9, indicating that the sample size of the unconfined group might be insufficient and the results should be considered as pilot.

During the experiment, the changes of all the time domain HRV indexes were significant in the confined group ($p < 0.01$ for HR and rMSSD, $p < 0.05$ for SDNN and pNN50), but were not significant in the unconfined group. The results of HRV in the time domain are shown in Fig. 5. At the beginning of the experiment (PF3 and CF3), the mean heart rate (HR) of the confined group was significantly lower than that of the unconfined group, $p < 0.01$. The difference between CF3 and PF3 of the confined group is significant ($p < 0.05$), indicating the heart rate increasing

Table 3 F-statistic of QT/QTc intervals along time in each group

Indicators	Unconfined			Confined		
	F-value	p Value	Power	F-value	p Value	Power
QT	6.14	< 0.001	1.0	5.47	0.037 (GG)	1.0
QTc	9.52	< 0.001	1.0	5.62	0.013 (GG)	1.0

"GG" indicates that the data do not satisfy the sphericity assumption and are corrected by using the GG method

Table 4 F-statistic of HRV indexes along time in each group

HRV indexes	Unconfined			Confined		
	F-value	p Value	Power	F-value	p Value	Power
HR	0.87	NS	0.687	9.33	< 0.001	1.0
SDNN	0.64	NS (GG)	0.533	3.89	0.01	1.0
pNN50	1.6	NS (GG)	0.937	6.58	0.03 (GG)	1.0
rMSSD	0.98	NS (GG)	0.748	9.67	0.004 (GG)	1.0
Ln-TP	1.16	NS	0.826	2.89	0.034	0.998
Ln-VLF	1.32	NS	0.877	1.6	NS	0.944
Ln-LF	1.02	NS	0.765	1.56	NS (GG)	0.927
Ln-HF	0.56	NS (GG)	0.475	8.11	0.005 (GG)	1.0
nLF	0.86	NS	0.681	4.14	0.007	1.0
nHF	0.86	NS	0.681	4.14	0.007	1.0
LFHF	1.99	NS (GG)	0.977	3.12	0.025	1.0
SampEn	0.53	NS	0.447	3.90	0.009	1.0
FuzzyMEn	0.93	NS	0.722	3.71	0.012	1.0

"GG" indicates that the data do not satisfy the sphericity assumption and are corrected by using the GG method

with time. In contrast, the changes of HR in the unconfined group were unapparent. Since CF6, the difference of HR between the confined and unconfined groups was not significant anymore, and the data of the two groups showed similar trends. The highest HR of both groups occurred on CR3 of the adaptive feeding stage, then by FR4 of the recovery stage; there was a slight decrease of HR in both groups.

The time courses of pNN50 and rMSSD show a similar pattern during the experiment, as they both reflect the

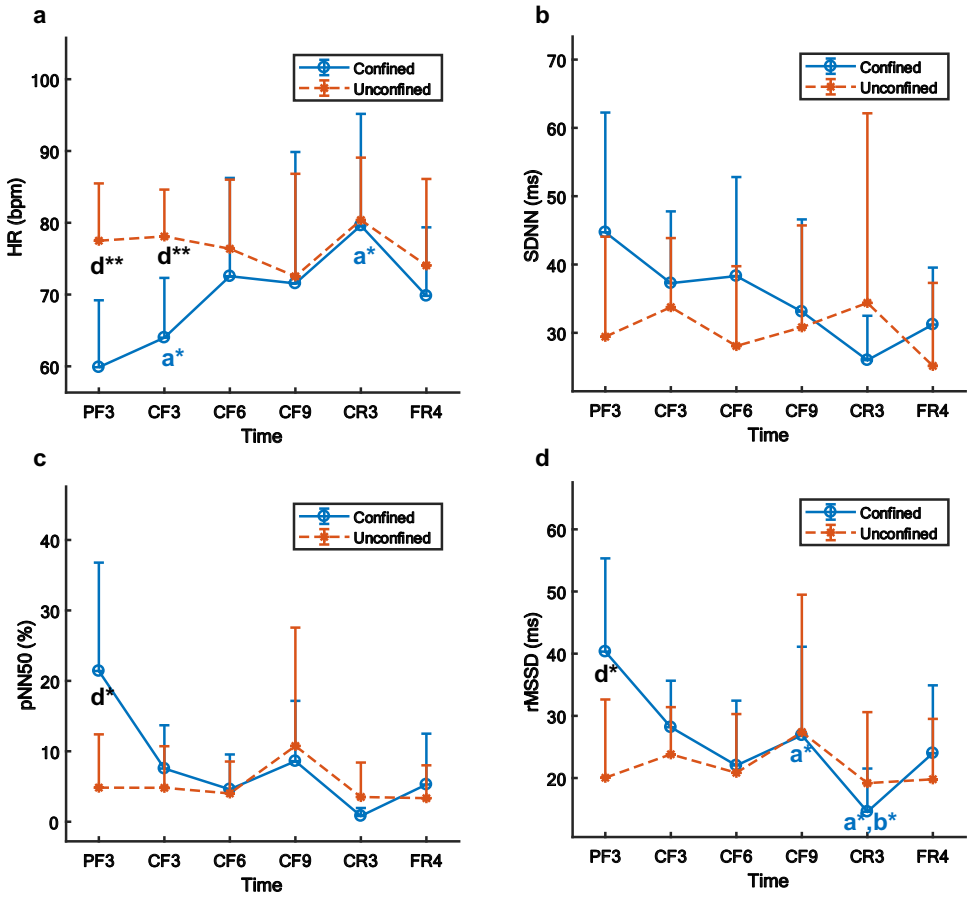

Fig. 5 Changes of the time domain HRV indexes during the experimental process. **a** Heart rate. **b** SDNN. **c** pNN50. **d** rMSSD

parasympathetic regulation to the heart rate. There were also significant differences of these two indexes between the confined and unconfined groups at the beginning of the experiment, $p < 0.05$. Then, after the decrease of values in the confined group, the differences became insignificant, and the trends were very similar between the two groups. Both indexes of the confined group presented the lowest values at CR3 and then became higher at FR4. The changes of rMSSD in the confined group were more significant: CF9 and CR3 were significantly lower than PF3 ($p < 0.05$); CF3 was also significantly lower than FR4 ($p < 0.05$). As for the unconfined group, both indexes did not show significant changes during the experimental process.

SDNN of the confined group also exhibited a roughly downward trend before CR3 and then increased slightly between CR3 and FR4. The unconfined group showed an opposite trend to the confined group. However, there were no significant differences between different time point and between different groups.

The computed characteristics of HRV in the frequency domain, including Ln-TP, Ln-VLF, Ln-LF, Ln-HF, nHF, and LFHF, are presented in Fig. 6. As shown in Table 4, all these indexes changed insignificantly in the unconfined group, but most (except Ln-VLF and Ln-LF) exhibited significant changes in the confined group ($p < 0.05$ for Ln-TP and LFHF, $p < 0.01$ for Ln-HF and nHF) during the whole process. From Fig. 6, we can see that during the time course of the experiment, Ln-TP, Ln-VLF, and Ln-LF presented a very similar changing pattern especially in the unconfined group. However, for each of these indexes, the pattern between the confined group and unconfined group was obviously different. In particular, the differences between the two groups regarding these indexes were significant at the middle of the fasting stage (CF6) ($p < 0.05$ for Ln-TP and Ln-LF, $p < 0.01$ for Ln-VLF).

Ln-HF, on the other hand, showed a changing pattern that differed from the above three. At the beginning of the experiment, Ln-HF of the confined group was significantly higher than that of the unconfined group. Then, the mean value in the confined group dropt gradually during the time period between PF3 and CF6 and rose and fell alternately during the remaining monitoring time. The change of Ln-HF in the confined group was significant during this process: CF3 and CR3 were significantly lower than PF3 ($p < 0.01$); CR3 were also significantly lower than FR4 ($p < 0.01$).

The mean values of nHF in the confined and unconfined groups were both around 0.5 at the beginning of the experiment. Then, nHF in the confined group experienced a significant drop ($p < 0.05$) to about 0.25 by CF6 and then increased slowly through the rest of the experiment, while the change in the unconfined group was not significant during the whole process. According to the principle of normalization, nLF presented a changing pattern opposite to the nHF. It indicated that in the confined group, HF and LF were corresponding at beginning of the experiment, but LF dominated in the subsequent time although its extent was weakened in the latter part of the experiment. The changing pattern of LFHF also conveyed the same massage.

Figure 7 presents the change patterns of entropy measures, including SampEn and FuzzyMEn, during the experimental process. As shown in Table 4, both indexes of the confined group changed significantly ($p < 0.01$ for SampEn, $p < 0.05$ for FuzzyMEn) during the experiment, but that of the unconfined group did not show significant changes. The two indexes followed a similar pattern, but the changing of FuzzyMEn in the confined group was more significant. At the beginning of the confinement, the FuzzyMEn, indicating the complexity of HRV, in the confined group was significantly higher than that of the unconfined group ($p < 0.05$). As the experiment went on, the measures of confined crew decreased gradually and reached the monitored minimums at CF6. Then, the complexity of HRV increased and decreased alternatively: The values increased later in the later fasting period (CF9) and decreased after entering the adaptive feeding stage and then increased again when the normal eating was resumed. During the period between CF9 and CR4, the difference between these two groups at each time point was much lesser then before; the patterns of both groups were very similar to each other.

From the results introduced above, we can find that the changes of examined HRV indexes were not significant in the unconfined group, while most indexes (except Ln-VLF and Ln-LF) exhibited significant changes ($p < 0.05$) in the confined group. It indicates that the fasting itself has no significant influence on the HRV of healthy male adults when they are in the unconfined environment. But when the subjects are in the confined environment, most HRV indexes show significant changes during the experiment process.

4 Discussion

The present study investigated for the first time the impacts of long-term fasting and confinement on the functions of cardiovascular system. In the experiment, participants' energy intake and housing conditions were carefully controlled to ensure the rigor and objectivity of the study, as recommended in a recent perspective [42]. It was found that the long-term fasting caused significant changes of body weight, SBP, serum electrolyte levels, and QTc interval in both the confined and unconfined groups. The abnormal levels of serum electrolytes and the prolonged QTc intervals are worthy of note, as they suggest that the intensity of fasting may be beyond what the body can normally tolerate, which may be harmful to human health. The effects of confinement are mainly reflected in changes of HRV indices, indicating

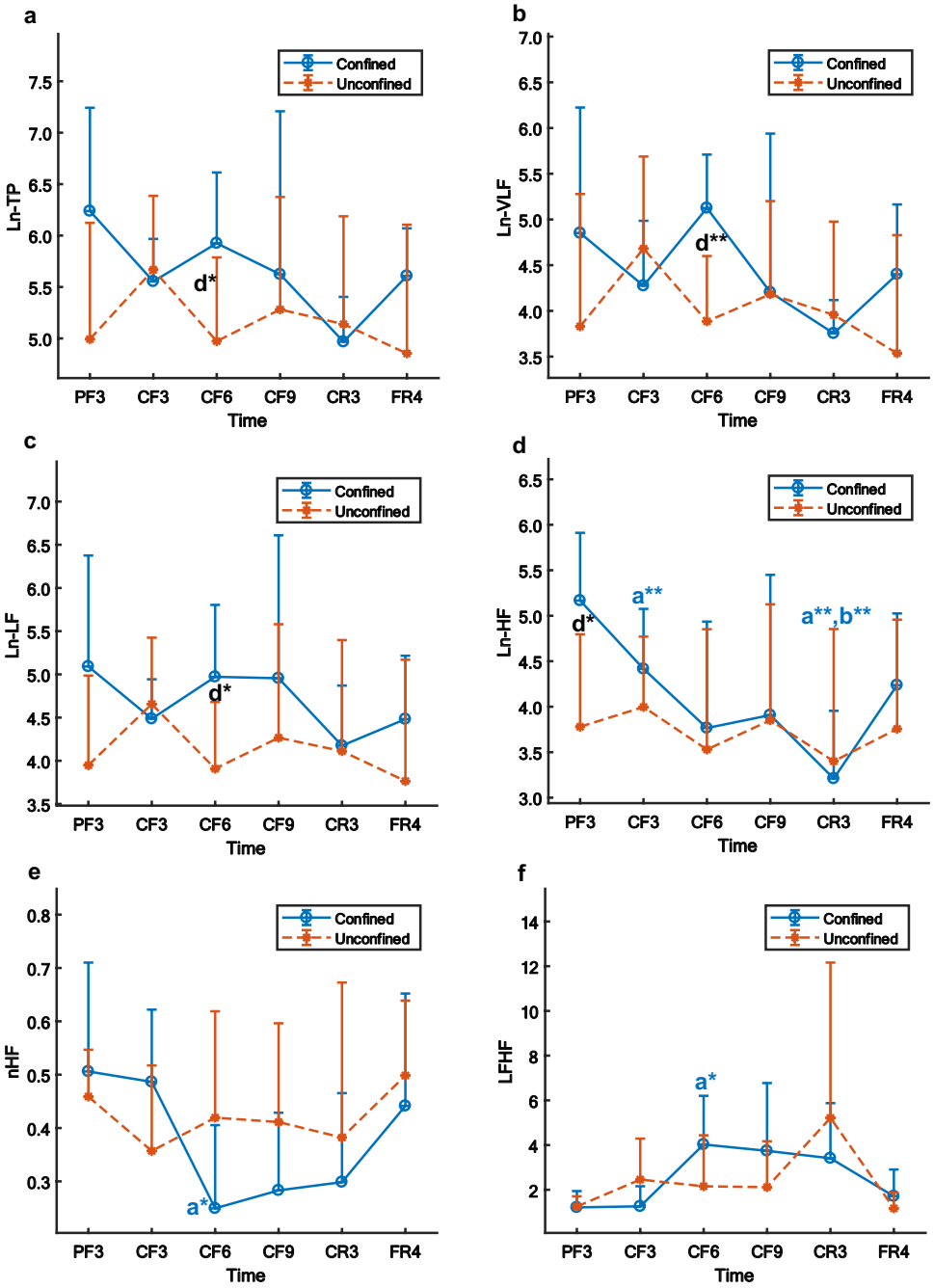

Fig. 6 Time course of the frequency domain HRV indexes during the experimental process. **a** Natural logarithms of TP. **b** Natural logarithms of VLF. **c** Natural logarithms of LF. **d** Natural logarithms of HF. **e** Normalized HF. **f** The ratio of LF to HF

that the autonomic regulation of cardiac rhythm is sensitive to the environmental alteration.

During the fasting process, the weight loss was significant ($p < 0.001$, -7.4 kg in average) in both confined and unconfined groups. Then, after refeeding, the weight began to gain gradually ($p < 0.05$, 3.9 kg in average). Similar results have also been reported in previous studies [43, 44]. In a 10-day starvation experiment including 6 adult males, the average weight loss is -7.27 kg, and after 4-day rehabilitation, the average weight gain was 4.97 kg [44]. The SBP showed a significant decrease in both groups ($p < 0.05$) during the fasting, while the changes of DBP were not significant. The decrease of SBP during fasting was also reported in other fasting experiments [4, 45–47]. In some of these experiments, significant decreases of DBP were also observed [45–47]. According to a recent study including 1422 subjects, both SBP and DBP decreased significantly ($p < 0.001$) during the Buchinger periodic fasting lasting from 4 to 21 days [5]. It should be noted that the subjects in these studies had a higher baseline of blood pressure than that (SBP: 111.1 ± 8.2 mmHg, DBP: 74.5 ± 8.7 mmHg) of our study, which may be one of the reasons of their more

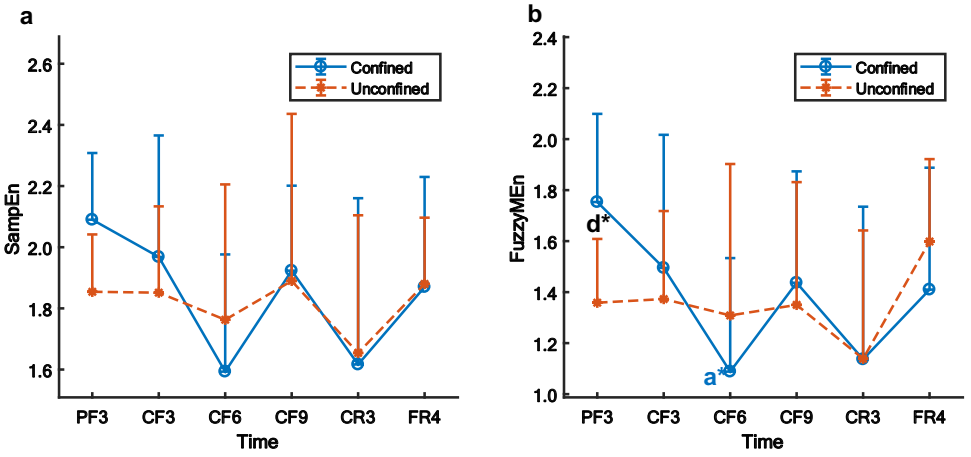

Fig. 7 Changes of entropy measures during the experimental process. **a** Sample entropy. **b** Fuzzy measure entropy

significant decrease in both SBP and DBP. Although the decreased blood pressure has been considered as a beneficial effect of fasting, the influence of the decreased SBP (97.5 ± 10.2 mmHg) in healthy subjects as reported by our results is worthy of further investigation.

From our experimental results, we can see that long-term fasting can lead to disturbances of electrolytes, including decreased serum sodium level and increased serum calcium level. These changes have been reported in other experiments about water-only fasting [48] and Buchinger periodic fasting [5]. However, the changes shown in our results are more dramatic, with a significant proportion of cases outside the reference range. The significantly decreased serum sodium can be attributed to the lack of salt intake and also the natriuresis of fasting as reported earlier [48, 49]. Therefore, a certain amount of salt supplementation during fasting should be beneficial for maintaining serum sodium levels. On the contrary to serum sodium, the level of serum calcium increased significantly during the fasting process, which may be the result of the decalcification of the bone during starvation [44, 50]. These electrolytes are critical to the depolarization and repolarization of electrical action potentials of cardiomyocytes; thus, their disturbances will inevitably affect the electrophysiological activities of the heart [12], which have been reflected by the prolonged QTc intervals in this experiment. After the diet was recovered, all the serum electrolytes returned to their initial levels.

The QTc intervals were significantly prolonged during the fasting in about half of the subjects of both groups. Reports of fasting induced prolonged QT interval can also be seen in the literature [51, 52], including a case of prolonged QTc interval with severely symptomatic paroxysms of torsade de pointes after very low calorie diets [53]. The disturbance of serum electrolytes observed in our experiment may be one of the causes of the prolonged QTc [54]. Given the strong association between prolonged QTc interval and malignant arrhythmias [15], the mechanism by which fasting affects QTc interval deserves further study to avoid possible damage to the cardiovascular system.

Repeated measures ANOVA tests on these indexes suggested a significant change of heart rate and ANS activity (indicated by SDNN and Ln-TP) in the confined group ($p < 0.05$), while insignificant change in the unconfined group. These results indicate that the confinement has a significant influence on the ANS regulation of cardiac rhythm, while the effect of fasting itself on the ANS is not significant. In a previous study, significant decreases of heart rate but no significant HRV changes were observed in amateur weight lifters after 48-h fasting [55]. However, in another study, the HRV indices of healthy subjects were significantly changed after Ramadan fasting [24]. The differences in fasting style and subject may be responsible for the difference in these results.

In the confined group, the heart rates were significantly ($p < 0.05$) slower than that of the unconfined crew in the pre-fasting stage, indicating that the confined environment may stimulate the subjects to slow their heart rate when entering the cabins. In addition, pNN50, rMSSD, and Ln-HF were also significantly ($p < 0.05$) higher than that of the unconfined crew, indicating that the PNS activity was enhanced after the subjects entered the cabins. Then, during the first half the fasting stage, pNN50, rMSSD, and Ln-HF decreased gradually, while the heart rate, Ln-LF, and Ln-VLF increased significantly. Correspondingly, the ratio between LF and HF also increased significantly ($p < 0.05$) during this stage, which indicates that the dominance was shifting from PNS to SNS. After CF3, the differences between the two groups regarding the PNS activity were not significant. And since CF9, the changing patterns of the two groups were much more similar than before. These results suggest that the effects of a confined environment on the ANS seem to be short-term and that

the human body can adapt to it through self-regulation. Of course, the effects of a confined environment may be more subtle and may be reflected in other ways, such as the sleep–wake difference of HRV [11].

There are some possible limitations in the study. First, only the confinement was considered in the experiment, while other factors, e.g., microgravity, were not considered, but may also have impacts for affecting functions of cardiovascular systems in addition to those effects of fasting and confinement [56]. Second, the sample size of the unconfined group is insufficient, as shown by the results of post hoc study presented in Tables 1 and 4. Third, only male subjects were recruited in our experiment, without considering possible gender differences [57]. Therefore, in future studies, these limitations warrant to be addressed.

5 Conclusion

Taken together, the primary outcome of this study is that the long-term water-only fasting can lead to weight loss, serum electrolytes disturbances, prolonged QTc intervals, and decreased SBP of healthy male adults both in and out of confinement. These results indicate that the intensity of fasting may exceed the endurance of the cardiovascular system and a certain amount of calories and inorganic salt supplements may help to ameliorate these conditions. The confinement can stimulate the subjects to increase their parasympathetic activity and slow down their heart rates at the beginning of confinement, but these effects seem to be short-term, since the dominance of PNS gradually disappeared over the course of fasting. Besides, no additional risk associated with fasting was found in confined environments. Additionally, after the normal diet was resumed, all the indicators returned to the original levels in a period about 1 week. In conclusion, the fasting effects on heart functions found in this experiment suggest that long-term water-only fasting in healthy adults is potentially harmful to the cardiovascular system and should be further investigated for safety evaluation.

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Declarations

Conflict of interest The authors declare no competing interests.

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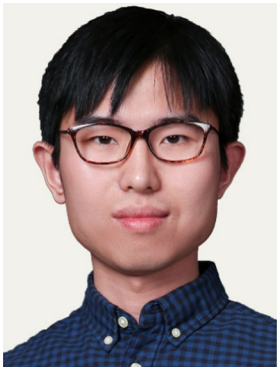

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