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REVIEW

Physiological effects of weightlessness: countermeasure system development for a long-term Chinese manned spaceflight

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Abstract The Chinese space station will be built around 2020. As a national space laboratory, it will offer unique opportunities for studying the physiological effects of weightlessness and the efficacy of the countermeasures against such effects. In this paper, we described the development of countermeasure systems in the Chinese space program. To emphasize the need of the Chinese space program to implement its own program for developing countermeasures, we reviewed the literature on the negative physiological effects of weightlessness, the challenges of completing missions, the development of countermeasure devices, the establishment of countermeasure programs, and the efficacy of the countermeasure techniques in American and Russian manned spaceflights. In addition, a brief overview was provided on the Chinese research and development on countermeasures to discuss the current status and goals of the development of countermeasures against physiological problems associated with weightlessness.

Keywords countermeasure; physiological effects of weightlessness; effect evaluation; long-term manned spaceflight

Introduction

China will step into the space station era around 2020. By that time, a routine spaceflight duration will last for six months. Such long-term manned spaceflights will inevitably induce serious physiological effects, associated with space and weightlessness, on astronauts. In fact, astronauts who previously experienced flights displayed multiple physiological symptoms, including sensorimotor disturbance, cardiovascular deconditioning, loss of muscle mass, loss of muscle strength, loss of bone mineral density, and visual impairment due to intracranial pressure (VIIP) [1,2]. Thus, developing countermeasures against the effects of weightlessness is essential to the long-term maintenance of human performance in space.

Technical capabilities and challenges of the physiological effects of long-term manned spaceflights

Physiological challenges during long-term manned spaceflights

In view of the effects of long-term spaceflights, the physiological adaptation and medical problems relating to the musculoskeletal system have drawn considerable attention. Zange *et al.* reported after 6 months in space, astronauts experienced a 48% decrease in soleus peak force, 20% reduction in muscle volume [3,4], 10%–20% loss in arm strength, and 20%–30% loss in thigh strength [5]. Such muscular atrophy and skeletal unloading results in a 1%–2% reduction of bone mineral density at selected skeletal sites each month, and weight-bearing bones are more affected than non-weight-bearing bones [6]. Postflight orthostatic intolerance was experienced by approximately 20% of astronauts after short-term spaceflights and 83% of astronauts after long-term spaceflights [7–9]. The maximal oxygen consumption (VO_{2max}) decreases by 17% after the first two weeks of flight and then gradually increases; however, it never returns to its preflight level [5]. A different study demonstrated that the VO_{2max} decreases

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to below its pre-flight levels during the first 10 days of spaceflight and then returns to its preflight levels after one month [10]. Approximately 60%–80% of crews experiences space motion sickness during the first two or three days of spaceflight [11]. According to the data from NASA, visual impairment was experienced by 29% of crews who returned from short-duration spaceflights and 60% of long-duration mission astronauts. Furthermore, NASA currently lists VIIP as the top gravity-related health risk [2,12].

Mission performance challenges in long-term spaceflights

Extravehicular activity (EVA) is vital for supporting daily life under constant weightlessness during long-term spaceflights. Most EVAs are performed with the upper body muscles such that VO_{2max} and metabolic efficiency are lower than that during leg exercises [13]. Preserving or mitigating the loss of aerobic capacity is essential to protecting the ability of an astronaut to perform strenuous extravehicular tasks [14]. Astronauts reported experiencing height vertigo and felt temporary acrophobia when they performed EVAs. Such experiences may be related to weightlessness-induced neurovestibular disturbances [15].

The inability of astronauts to stand because of postflight orthostatic intolerance can lead to life-threatening injuries during emergency egress from a spacecraft [16].

A 10% loss of bone mineral density in elderly men and women results in a two- to threefold increase in risk of fracture [17]. A 2.5%–2.7% loss of trabecular bone mineral density per month in a space station presents a serious medical risk of skeletal fracture [18]. Decreased muscle mass and muscle strength are associated with a 68%–82% decline in postural stability [19], which increases the risk of fracture [20]. In addition, skeletal unloading during spaceflights may impair the healing of fractures [21].

Countermeasures in long-term spaceflights

Along with neural signals to the skeletal muscles, powerful neural feedforward signals are transmitted to cardiovascular, respiratory, cellular, and endocrine systems during physical excise. In turn, neural feedback is received from the contracting skeletal muscles [22]. Exercise is generally used in space as a physical countermeasure against the physiological effects of weightlessness [23]. By investigating the effects of weightlessness on the cardiovascular and musculoskeletal systems and the role of different types of exercises, researchers achieved significant progress in the field of in-flight countermeasure systems [24]. For example, Gemini launched a flight expander, while the Skylab mission had on-board exercise devices (including a bicycle ergometer and a Teflon plate), and the space shuttle carried a Thornton passive treadmill in Extended Duration Orbiter Medical Project (EDOMP). The International Space Station (ISS) was equipped with a treadmill vibration isolation and stabilization system (TVIS), cycle ergometer with vibration isolation (CEVIS), and interim resistive exercise device (iRED) [25], demonstrating that exercise countermeasures have progressed with advances in spacecraft technology. In 2008, an advance resistive exercise device (ARED) was launched to the ISS to replace the iRED. Similarly, the TVIS was updated to a T2 combined operational load-bearing external resistance treadmill (T2/COLBERT) in 2009 [26].

Apart from exercise, gravity loading countermeasures (such as muscle loading and fluid loading) [27], pharmaceutical, and nutritional approaches have been tested for their potential health benefits to astronauts [23]. Conventional drugs have been used to treat chronic and transient neurovestibular effects, such as space adaptation syndrome and headaches induced by cephalad shifts. Meanwhile, previous Earth-analog studies tested the efficacy of supplementation with various substances, including vitamin D and calcium, hormone replacements, selective estrogen receptor modulators, and antiresorptive drugs, in countering muscle atrophy and bone demineralization [23]. The evidence suggests that resistance exercise coupled with adequate energy intake and vitamin D can maintain bone density in most bodily regions from four to six months of spaceflight [25]. Russian cosmonauts on the ISS utilized special countermeasures, such as the Chibis suit, Kentavr G-suit, occlusion cuffs, and penguin-3 loading suit [28]. Notably, nutrition not only supplements exercise-orientated countermeasures [29] but also counters space-related immune dysfunction [30].

Technical development of countermeasures in international space exploration

The main goal in the development of countermeasures is to maintain crew health and optimize their performance during long-term missions. In assessing the feasibility of long-term spaceflight, the most paramount objective should be to validate countermeasures against deconditioning [31]. Validating countermeasures mainly involves developing high-efficacy countermeasure devices, designing appropriate countermeasure protocols, and constructing effective testing techniques.

Development of exercise systems

The development of exercise hardware is important for the maintenance of crew health with respect to weightlessness. In recent years, space scientists have gained deeper insight into weightlessness-induced physiological changes in humans and countermeasures against its negative effects on the cardiovascular and musculoskeletal systems; they have consequently identified exercise as the primary countermeasure against such negative effects during long-term spaceflights [32].

Gravity replacement and vibrational isolation are the key techniques in the development of exercise systems. During treadmill exercises, astronauts must wear a subject load device (SLD) to restore their body weight (BW). This device is installed through a shoulder-and-waist harness that pulls the exercising subject toward the treadmill surface. The SLD largely influences the running experience, biomechanics, and the effects of countermeasures. The comfort of a subject and the functionality of the device were extensively evaluated during the development of the SLD. The SLD provides a loading of 40–220 lbs (18–100 kg). NASA scientists conducted short-term (5 min) [6], long-term (30 min × 12 sessions) [33], and in-orbit (15 min × 12 sessions) [34] functional evaluation tests on various SLDs. Subjective comfort ratings indicated that the subjects can tolerate SLDs loaded with their full BW, and the overall ratings for harness discomfort, particularly in the back and hip regions, eventually decreased with repeated test sessions because of habituation. The most common forms of discomfort reported by astronauts are hip and back pains, suggesting that further testing is required to realize custom-fitted designs with the desired loads and optimal shoulder-to-waist load ratios.

A treadmill can be stabilized against excessive motion by using a vibrational isolation and stabilization (VIS) system to isolate the vibrations from the space station and provide a flexible mechanical connection to the space station [35]. A VIS system is important in maintaining the microgravitational level for in-orbit scientific experiments. A VIS system consists of a gyroscope, four linear slide-mass stabilizers, four motor controllers, and a VIS controller. Four linear stabilizers are assembled on four corners to realize stability against linear motion and pitch. In a previous study, treadmills with a VIS system on the ISS were evaluated, and the results revealed that the peak linear and angular displacements are less than 2.5 cm and 2.5°, respectively [36]. Furthermore, the damper systems of such treadmills tolerate a maximum displacement of 12 cm and rotation of 2.5° relative to any axis [37].

A zero-gravity locomotion simulator (ZLS) is a platform in which test subjects are suspended horizontally in midair while running on a vertical treadmill. The forces exerted by the foot while running on a ZLS and on the ISS were measured to evaluate the effects of altered mechanical loading environments on the musculoskeletal system. The mean active peak force for the ZLS with a 100% BW load was 2.5 ± 0.13 BW, whereas that for running on the ground was 2.56 ± 0.17 BW [6]. Comparison of the forces exerted on the shoes during treadmill walking and running on the ISS with those on Earth revealed that the mean in-orbit left foot and right foot forces on the ISS were reduced by 25% and 46%, and the bone mineral density on the ISS was decreased by 0.71% and 0.83% per month in the femoral neck and lumbar spine, respectively [38]. The maximum in-orbit and single-leg load for the treadmill while running at 8 mph (~12.87 km/h) was 1.77 BW, which was approximately 75% of the typical active peak force on Earth [34]. All of the published data suggest that a subject running in space cannot support the same loads as when performing the same exercise on Earth [39].

Resistive exercise devices (RED) are designed to prevent muscle atrophy and neuromuscular deconditioning in a microgravity environment. Depending on its design, REDs can perform one of the following main functions: supplying the force, adjusting the force, and transmitting the force to the user. REDs must be designed such that the device is suitable for its intended purpose while satisfying the required volume and weight of the confined cabin of a spacecraft. These specific design requirements have been realized by employing various force supply methods, including pneumatic springs, hydraulic mechanisms, magnetic elastic bands, clutches and band brakes, bending rods, constant force springs, and standard springs [40]. Isokinetic exercises, such as free-weight training, were used in building a RED on the ISS. Elastic polymer systems were used in the design of an iRED [41], and the movement of pistons within a pair of vacuum cylinders provided the resistance of the ARED [42]. The ARED enabled the crew to exercise at a load of up to 272 kgf, whereas the iRED had a 0–136 kgf load range. In addition to providing a more constant load than the iRED, the ARED can simulate inertia, which can be felt during free-weight training [43]. A VIS was also developed for the ARED [44].

Development of exercise protocols

Exercise protocols have been developed with exercise systems, and the effectiveness of countermeasures has been evaluated. At present, the prescribed aerobic exercise regimen implemented on treadmills on the ISS includes steady-state and interval protocols. The steady-state protocol involves running at 60%–80% of the maximum heart rate for 30 min, and the interval protocols include 4 and 2 min interval protocols. The 4 min interval protocol comprises a 5 min warm-up at 50% of the maximum oxygen uptake (VO_{2max}), followed by four times of 4 min sets at 90% of the maximum heart rate with 3 min active rest interval periods. The 2 min interval protocol consists of a 5 min warm-up at 50% VO_{2max}, followed by six times of 2 min stages at 70%, 80%, 90%, 100%, 90%, and 80% VO_{2max}. The first five stages are separated by 2 min active rest stages at 50% VO_{2max}, and the interval between the fifth and the final stage is a 5 min active rest at 40% VO_{2max} [45,46]. Matsuo *et al.* designed an aerobic cycling protocol for controlling energy expenditure. The recommended protocols were interval training, which comprised seven sets of 30 s sprint cycling at 120% VO_{2max} with a 15 s rest in between sets, and high-intensity aerobic interval training, which comprised three sets of 3 min cycling at 80%–90% VO_{2max} with a 2 min active rest at 50% VO_{2max} [47]. Strength training using the iRED consisted of four trials of single- and double-leg squats, single- and double-leg heel raises, bent-over rows, upright rows, straight-leg deadlifts, and deadlifts [34]. A periodized exercise protocol was excluded because of the maximum load of the iRED (136 kg). The ARED in-flight protocol with an increased load capacity (272 kg) was incorporated into a periodized protocol with two distinct three-month macrocycles. Each cycle consisted of three individual exercise sessions with a rotating order of heavy, light, and medium days [45]. The exercise prescription was customized to an astronaut's needs based on individual aerobic fitness, personal preferences, flight career status, and in-orbit exercise hardware specifications [24]. An exercise protocol can be modified according to the routine physical assessment results during spaceflight [45].

The exercise countermeasure support implemented on the ISS has been extensively reported since 2015 [48–50]. Prescriptive exercise begins one year prior to a flight. Preflight exercises include cardiovascular conditioning, strength training, training on in-flight exercise hardware, estimation of in-flight exercise loads, and pre-flight exercise-related evaluations. For each week, inflight crew members perform exercises for six days and rest for one day. On active days, astronauts perform 1 h of resistance training and 30–45 min of aerobic training per day. Resistance training is divided into two phases, namely, acclimatization and formal training. This type of exercise emphasizes lower body conditioning. Aerobic training is prescribed according to the test results of the capacity of an individual. Postflight exercise support continues for 45 days after a flight. Crew members perform 2 h of reconditioning exercises per day for six to seven days per week. Reconditioning training includes exercises for regaining flexibility, balance, agility, coordination, muscular strength, muscular endurance, and cardiorespiratory function. Even though 50 years had passed since the first manned spaceflight, the minimum fitness level that should be maintained in orbit has yet to be determined; various factors, such as the exercise hardware, inflight contingencies, and the schedules of crew members (i.e., availability for exercise) may potentially contribute to the determination of the appropriate minimum fitness level [5,51,52].

Development of technologies for evaluating the effects of countermeasures

The guidelines for the general physical preparedness of crew members pre-flight have been established in the American College of Sports Medicine Guidelines, NASA-STD-3001A (Volume 1) and the Canadian Physical Activity, Fitness, and Lifestyle Approach and related standards. Aside from receiving weekly data from a cycle ergometer and inflight treadmill training, periodic fitness evaluations must also be conducted. Postflight recovery schedules are based on NASA's standardized postflight protocols [45]. The Johnson Space Center of NASA has established an unrelated protocol for evaluating cardiorespiratory fitness [53]. According to this protocol, VO_{2max} can be calculated by considering the subject's physical activity rating (PAR) scale [54], body mass index (BMI), and gender.

(1) The equation used for male subjects is
$VO_{2max}\ (mL\cdot kg^{-1}\cdot min^{-1}) = 67.350 - (0.381 \times \text{age [year]}) - (0.754 \times BMI) + (1.951 \times PAR)$.

(2) The equation used for female subjects is
$VO_{2max}\ (mL\cdot kg^{-1}\cdot min^{-1}) = 56.363 - (0.381 \times \text{age [year]}) - (0.754 \times BMI) + (1.951 \times PAR)$.

Feiveson posited that the efficacy of countermeasures for long-term space missions should be quantitatively assessed because of the small number of participants in clinical research trials [55]. In his proposal, the performance criteria are determined as markers of outcomes in comparison with the per-subject-mission level. Performance is categorized under three levels, namely, success, failure, and undetermined. The efficacy of the countermeasures is evaluated by X and Y, where X represents the success on at least 90% of astronaut missions, and Y denotes the failure on 5% of astronaut missions. If $X \geqslant 90$ and $Y \leqslant 5$, then the countermeasure package is satisfactory. By contrast, if $X < 90$ or $Y > 5$, the countermeasure package is insufficiently effective, and corrective action must be performed. This evaluation strategy is limited by sample size, individual differences, variable degrees of countermeasure compliance, differences in missions, repeatability of test methods, and measurement errors, among other factors.

Simulation has been widely used for evaluating the risks to the human body and the effects of exercise during spaceflight. In 2002, the National Space Biomedical Research Institute convened an exercise workshop to determine the effectiveness of human exercise simulations on the evaluation of the effects of countermeasures against the effects of weightlessness [56]. In addition, the NASA Digital Astronaut Project implemented a series of computational models for predicting and assessing health during spaceflight, performance risks, and the efficacy of countermeasures [57]. Models of cardiovascular and muscle changes, bone remodeling, and biomechanical computations have been developed under this project, and free software, such as OpenSim and quantitative circulatory physiology [58,59], have been widely used for the computation of mathematical models for analysis [60,61].

Specific technical considerations for countermeasures in Chinese long-term spaceflight

Although the success of other countries in countermeasure systems for the past 50 years can serve as reference, China must develop its own countermeasure systems. The first step in establishing a successful countermeasure system is identifying the key factors. We propose that the main factors in constructing a countermeasure system are features, physiological targets, devices, evaluation of efficacy, and countermeasure programs. The objective of producing a countermeasure system is to establish a complete set of research and development process. The four main factors of the development process are countermeasures, zero-gravity simulation platforms, countermeasure protocols, and effect evaluation techniques (Fig. 1).

Numerous design boundaries, such as the volume, shape, power consumption, and weight of the device, must be strictly considered at the research and development stages during the designing of a countermeasure device. In addition to these restrictions, human applicability must also be assessed. Subject-oriented requirements are given particular importance in the hardware design of countermeasure products in China. Thus, the design requirements for exercise devices, physical protection measures, gravity replacement devices, and vibration and isolation units must be clarified.

Zero-gravity simulation platform are essential in the assessment of countermeasure devices and programs, and thus simulations are important during the validation of a countermeasure. Given that the developed countermeasure devices are mostly physical training devices, newly developed simulation methods have mainly focused on the microgravitational environment on the lower extremities of the musculoskeletal system and locomotion function. Suspension and supine training techniques are used to simulate reduced gravitational load on lower extremities. The −6° head-down bed rest model has been widely used as a comprehensive verification method for testing the integrated effects of countermeasure systems. Parabolic flight experiments were performed as supplemental test methods for in-orbit device development. Given its complex technical support requirements, the neutral buoyant simulator has yet to be considered a microgravitational simulation method in countermeasure development.

For countermeasure programs, in-orbit exercise protocols must be established for maintaining or improving aerobic exercise capacity, anaerobic exercise capacity, muscular strength and endurance, muscular explosive power, finger strength, respiratory muscle strength, bone mineral density, *g*-tolerance, and orthostatic tolerance.

Countermeasure protection assessment techniques provide a systematic evaluation of the effects of countermeasures. These assessments involve testing various physiological factors, such as the cardiovascular system, musculoskeletal system, neuro-endocrine/immune system, neurovestibular function, structure and function of the brain, and sleep–wake biological rhythm. These techniques conduct measurements in static and dynamic states. A comprehensive evaluation of the used methods depends on the mathematical models or the simulation techniques from

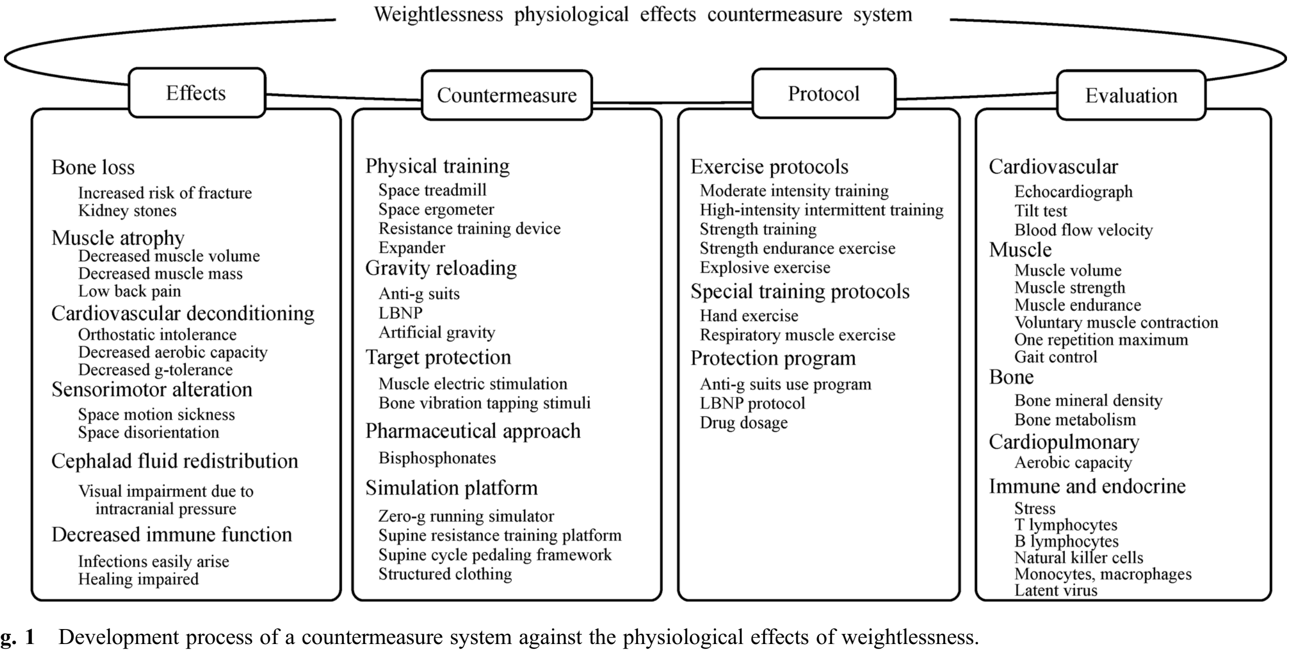

Fig. 1 Development process of a countermeasure system against the physiological effects of weightlessness.

a large database, with a sample library of data collected from manned spaceflights and zero-gravity simulation experiments.

Current situation of countermeasure studies in China

The success of the Shenzhou missions marked the establishment of a countermeasure system for short-duration spaceflights in China. Ergometer, lower body negative pressure (LBNP), thigh cuffs, expanders, and elastic suits were the main in-orbit devices utilized in Chinese short-term spaceflight. The countermeasure protocol was designed based on the results of several head-down bed rests [62,63] and tested in a series of head-down bed rest experiments [64,65]. An efficacy evaluation system was accomplished on the basis of this series of head-down bed rests and Shenzhou missions. New countermeasures should be developed for long-term spaceflights, and the development of novel simulated weightlessness platforms, countermeasure protocols, and effect evaluation techniques for long-term spaceflights must also be considered.

Development of new countermeasures for Chinese long-term spaceflights

The development of exercise countermeasures, such as treadmills or resistance training devices, was prioritized. The development processes for the exercise systems established throughout the Shenzhou-9 and Shenzhou-10 missions provided useful reference points. The development of exercise countermeasure device for Chinese space station missions has mainly focused on the human-oriented design concept, and experiments that consider the human aspect have been the main approach for resolving the key elements of the human-oriented design of countermeasures. These elements include efficacy, compliance, research and development cycle required for countermeasures, and zero-gravity simulation capability.

The ergonomic and functional evaluations of countermeasure products involve the assessment of compliance and efficacy. Various factors, such as mode of exercise, size, weight, and installation location, must be considered in the development of exercise hardware. The optimal exercise load, space for exercise, and exercise expenditure should be determined. The minimal effective exercise requirements that can ensure the dynamic effectiveness of the countermeasure must be implemented. The three main factors in hardware development are space station load, available space, and power capacity. In general, experiments and hardware improvements are performed in three iterations to satisfy the requirements of human-oriented hardware development. Subsequent improvements in the hardware are guided by recommendations based on in-orbit performance.

A classic development framework can be realized through the investigation of the design requirements for a space treadmill. For treadmill development, physical indexes (the length, width, height, weight, size of walking area of the treadmill), biomechanical requirements (static axis loading, adjustable load range, adjustable load interval, etc.), exercise mode (speed range, heart rate monitoring, etc.), operating mode (active or passive treadmill), ergonomics, and subject-safety requirements must be determined in advance on the basis of preliminary results, published data, and space pre-assigned to treadmills. The weight and power capacity supplied to a device must be also examined. Physiological and biomechanical experiments can be designed to test whether the hardware design satisfies the human-oriented design requirements. The hardware design and human-oriented design requirements should then be modified according to the test results. The next round of requirements should be proposed, followed by test experiments. The target requirements should be reached after three rounds of tests.

New weightlessness simulation platform for exercise

Ground-based, zero-gravity exercise simulation platforms are the most essential tool in the development of exercise systems, because an effective simulation determines the quality of the test experiments and the validity of the subsequent guidelines for hardware development and for pre-evaluating the efficacy of a countermeasure.

The vertical treadmill was first developed at Russia's Institute of Biomedical Problems [66]. NASA, the German Aerospace Center (DLR), and the Astronaut Center of China (ACC) established similar systems to the vertical treadmill [67,68]. The simulation capability of these systems is strongly related to the subject loading of the device and the application pattern of an external 1 *g* load. The results of the test experiments depend on a specific system. Therefore, the results are fit for specific missions, and the ability to generalize is limited.

The ACC established a zero-gravity running simulator, supine resistance training platform, supine cycle pedaling framework, and structured clothing to facilitate a comprehensive test of countermeasure products. These simulation platforms have been widely used in the development of space treadmills, space resistance training devices, space ergometers, gravity loading suits, and endurance/strength exercise prescription studies.

New exercise protocols

When an SLD generates gravity replacement loads while an astronaut is running, biomechanical and physiological differences in the effects of running exercises occur between 1 *g* and zero gravity. In a previous study, gait, electromyography (EMG) of leg muscles, oxygen consumption, and foot ground reaction force variations were investigated when subjects were running or jogging at 3, 7, or 10 km/h in a 1 *g* or zero-gravity locomotion simulator with a 100% BW external load [69]. The results revealed that when running in a simulated microgravity, the stride length was increased by 165–204 mm, the gait cycle was shortened by 43–62 ms, the stance phase was shortened by 10–155 ms, and the knee angle was reduced (by −3° to −5° for the forward angle and by −4° to −11° for the backward angle). Only the RMS EMG of the rectus femoris was strengthened. The maximal impulse force in the foot was decreased by 35%–42%. The VO_2 expenditure was higher at lower speeds but was reduced at speeds higher than 7 km/h (Fig. 2). Given that decrease in the maximal impulse force was not dependent on speed (Fig. 3), simply increasing the running speed would not resolve the problem of dropping force. The VO_2 expenditure increased when the subject was running at less than 4–5 km/h on a vertical treadmill in comparison to that when running on a normal treadmill, and the VO_2 consumption decreased when the subject exercised at speeds higher than 7 km/h. Given that a light or medium workload was more typical for astronauts working in space stations, VO_2 expenditure may be larger than that for the same workload under 1 *g* conditions. This phenomenon must be considered in countermeasure protocol design and countermeasure device development. That is, VO_2 consumption in a light or medium workload must be reduced at the countermeasure design stage. Exercise protocol studies were performed at less than 1 *g* with a vertical treadmill and reduced weight gait systems. The exercise protocols explored were as follows: (1) a moderate-intensity training protocol consisting of a 3 min warm-up, five sets of running at a peak of 65% VO_2 for 4 min with a 2 min interval at 50% VO_2 peak, and a 3 min cool-down for five times a week; and (2) a high-intensity intermittent training protocol consisting of a 5 min warm-up, 15 sets of running at 90%–120% VO_2 peak for 1 min with an interval when the heart rate returns to its original level, and a 5 min cool-down for three times a week. After six weeks of training, the aerobic capacity was increased in all training groups, and supine running in a ZLS could reach only half of the efficacy of that in a reduced weight gait system. The moderate-intensity training protocol may offer better effects on knee flexor strength than the high-intensity intermittent training protocol. Further studies on exercise

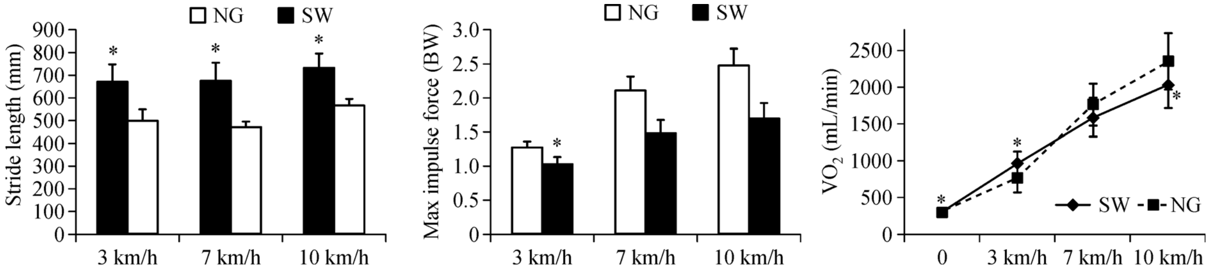

Fig. 2 Stride length, maximum impulse force, and oxygen consumption at different velocities under normal gravity and simulated weightlessness conditions. The longer stride length, decreased maximum impulse force, and relatively higher VO_2 expenditure at lower speeds, lower VO_2 expenditure when running at speeds higher than 7 km/h in simulated weightlessness. NG, normal gravity; SW, simulated weightlessness; *, vs. NG $P < 0.05$.

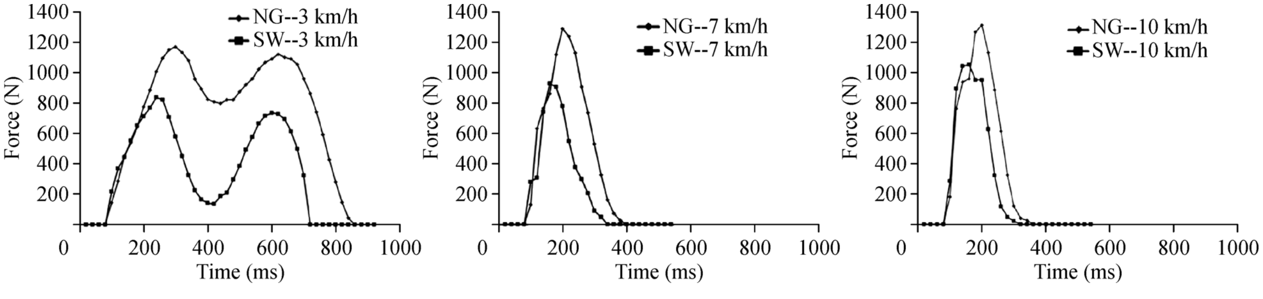

Fig. 3 Plantar force profile changes at different velocities under normal gravity and simulated weightlessness conditions. When the subject was walking at 3 km/h, the double peak curves of the foot force variations can be easily recognized. However, this kind force pattern was not obvious at higher speeds (7 km/h and 10 km/h). Plantar force decreased in SW conditions at any speed. NG, normal gravity; SW, simulated weightlessness. Adapted from Ref. 69, permitted under AAAS's License to Publish.

protocols aimed at determining endurance and strength training are at the data analysis stage. The effects of this exercise training on physiological responses during 90 days of head-down bed rest simulated weightlessness are at the planning stage.

Establishment of new protection assessment technology

Establishing physiological evaluation techniques and identifying key detection indicators are key strategies for evaluating the efficacy of countermeasures in microgravity or simulated microgravity. The effects of exercise countermeasures on bone mass, muscular strength, and cardiovascular adaptations were measured before, during, and after a spaceflight. The key physiological parameters were identified and verified through a series of Shenzhou missions and major large-scale ground simulation experiments. The evaluation techniques mainly consisted of functional examinations of three physiological systems, namely, the cardiovascular, musculoskeletal, and neuroendocrine/immune systems. Table 1 lists the partial physiological data before and after spaceflight. The corresponding standard tests and evaluation analysis techniques are ongoing. A database of containing the medical test data, experimental data, and biochemical data of the astronauts and subjects are being collected for the creation of novel scientific evaluation methods. New biological assessment technologies, such as genomics, epigenomics, transcriptomics, proteomics, metabolomics, microbiomics, and phenomics, have become standard tools in terrestrial medicine research. The application of these technologies in space medicine is expected to provide a deeper understanding of human responses in space, a refined characterization of the response to countermeasures, an improved ability to individualize solutions, and added information that may further inform astronaut candidate selection in the future.

Prospective for countermeasure development in Chinese long-term spaceflight

At present, countermeasure system development for Chinese long-term spaceflight is at the technical reserve stage, and our own optimal countermeasure system is currently being examined in depth. Aside from traditional exercise and physical countermeasures, novel physiological countermeasures are gaining considerable attention. According to the literature and our own experiment results, novel concepts of countermeasure development can be considered from at least three viewpoints. The first viewpoint is the establishment and use of artificial gravity. Artificial gravity has been recognized as an integrated countermeasure against the physiological and physical

Table 1 Partial physiological measures before and after the Chinese space program

Discipline	Test performed		Measurement
Cardiovascular	Cardiac function		Echocardiography
	Cardiovascular tilt test		Evaluation of orthostatic intolerance, ECG, finger hemodynamic test
			Laser doppler blood flow detection
			Transcranial doppler test
			Endothelium-dependent and independent vasodilation
Bone	Dual energy X-ray absorptiometry		Bone density of whole body, lumbar spine, proximal femora (hips), calcaneus (heel)
	Bone metabolism markers	Serum chemistry	Calcium homeostasis, gonadal hormones, calcitropic hormones, endocrine regulators, bone turnover markers
		Urinary chemistry	Minerals, bone turnover markers
Exercise physiology	Isokinetic testing		Muscle strength and endurance of the knee and ankle
	Cycle ergometry		Aerobic capacity (VO_2), heart rate, ECG, blood pressure, workload
Skeletal muscle	Skeletal muscular metabolism markers	Serum chemistry	Endocrine regulators, cytokines, and cell signaling mediators
		Urinary measures	Skeletal, muscular, peptide histological spectrum
Immunology	Stress measures		Neuroendocrine hormones and cytokines in response to biochemical and psychological stress
	Oxidative stress measures		Protein oxidative damage, lipid peroxidation damage, nucleic acid DNA/RNA damage
	Immune status		Leukocyte subset distribution, T cell function, T cell cytokine production profiles, antioxidant analysis
Biological rhythm	Serum measures		Epigenetic detection index
	Saliva measures		Melatonin, cortisol

effects of microgravity [70,71]. Given that centrifugal rotation is the main method for generating artificial gravity, studies must explore ways of minimizing the vestibular effects and identify the effective minimum *g*-level, duration, and frequency for maintaining normal physiological function [72]. The second is the development of novel biological techniques that eliminate the effects of unloading. Conventional protective physical training measures always activate a series of physiological responses, in addition to the unloading effects, to counteract the negative physiological effects of microgravity. Given that these two effects occur simultaneously, finding one or multiple routes for switching off the effects of 1 *g* unloading induced by microgravity would be ideal. The third is the application of systems theory, which is the interdisciplinary study of systems in science and society to offer frameworks for describing and analyzing groups of objects that work together to produce results. Traditional techniques in Chinese medicine are a typical example of the application of systems theory [73]. Shi *et al.* successfully used the Taikong Yangxin prescription to treat cardiovascular deconditioning in head-down bed rest in a Chinese space program [74,75]. The development of countermeasures against weightlessness can be promoted by the integration of Chinese medicine (which focuses on addressing the musculoskeletal changes during spaceflight), virtual reality techniques, genetic individuality screening techniques, molecular phenotyping (integrated omics), individualization, and new concepts of functional exercise and technology.

Conclusions

Countermeasure systems that target short-duration spaceflights have been established in Chinese manned space programs. With the looming prospect of long-term spaceflights and deep-space exploration, a systematic investigation was conducted on the current state of countermeasure hardware, protection programs, and the efficacy of such countermeasures were assessed. These plans must be completed with a staged approach.

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Compliance with ethics guidelines

Linjie Wang, Zhili Li, Cheng Tan, Shujuan Liu, Jianfeng Zhang, Siyang He, Peng Zou, Weibo Liu, and Yinghui Li declare that they have no conflict of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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