

Advancements in the application of cardiopulmonary exercise testing for overweight and obese populations

Tingshuai Fu^{1,2} | Mingzhong Xiao³ | Jiajia Ding⁴ | Chenxia Lu³ |
Peiran Wang² | Jingjing Yang² | Qing Zhang³

¹Department of Bone and Joint Rehabilitation, The Affiliated Hospital of Hubei Provincial Government, Wuhan, Hubei, China

²School of Acupuncture and Bone Injury, Hubei University of Chinese Medicine, Wuhan, Hubei, China

³Hubei Provincial Hospital of Traditional Chinese Medicine, Wuhan, Hubei, China

⁴Guangdong Hospital of Traditional Chinese Medicine Zhuhai Hospital, Zhuhai, Guangdong, China

Correspondence

Qing Zhang, Hubei Provincial Hospital of Traditional Chinese Medicine, Wuhan 430060, China.

Email: 15121210@qq.com

Abstract

Objective: To evaluate the advancements in cardiopulmonary exercise testing (CPET) among overweight or obese patients.

Methods: Reviewed the recent studies on clinical trials of CPET in overweight and obese patients, thought about the CPET advantage in obesity, while CPET equipment use for elucidating the principles underlying obesity and using CPET kinematic scheme to explore fat metabolism.

Results: The exercise program developed by CPET is scientific, sustainable and advantageous. With this trial, we can develop a relatively effective, fast and measurable amount of exercise, on the basis of the exercise test in obese people, CPET can provide scientific and digital motion reducing weight for overweight patients. At the same time, the trial has become widely applied in research into drug and surgical treatments for overweight patients. It is possible to quantify the efficacy of a trial and ultimately assess the merits of CPET.

Conclusion: CPET is considered as a fundamental criterion for designing motion schemes. Despite limitations of equipment errors and patient endurance, the benefits of CPET in program formulation have been gradually recognized, which made it a promising tool in the field of obesity management.

KEYWORDS

bicycle test, cardiopulmonary exercise testing, exercise test, obesity, overweight, sports medicine

INTRODUCTION

Obesity mainly refers to the excessive accumulation of fatty components in the body and abnormal distribution of metabolic balance, resulting in a dramatic increase in body mass index (BMI). It is a chronic, full-body adipose metabolic disease that directly induced by a variety of

factors [1]. An earlier survey in the United States (2016) showed that the overall prevalence of human obesity diseases and the population level of obese people have continued to increase globally, with the overweight population rate and the overall population obesity rate increasing by an average of 50.7% per year [2]. A recent survey (2021) in China showed that

Tingshuai Fu, Mingzhong Xiao and Jiajia Ding are first authors.

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approximately half of the country's residents are overweight/obese [1], more than half of residents in some area or neighborhood are overweight/obese [3, 4].

According to the report [5], many new diagnostic programs have been developed for various types of obese patients, such as functional exercise training [2], and comprehensive assisted therapeutic exercises [6]. To verify the effectiveness and safety of these training procedures, the cardiopulmonary exercise testing (CPET) and its devices can be used as a preferred method. At present, the mainstream equipment used is treadmill and sports bike [7]. They are safe and non-traumatic current clinical detection with the advantages of objective, quantitative, continuous and multi-function [8–10], and specific clinical application scopes, which played essential roles in the study of exercise treatment programs for obese people [5].

THE BRIEF INTRODUCTION OF CPET

CPET is a combined exercise test for respiratory metabolism. Patients are commonly placed in CPET systems in the form of exercise machines such as bicycles or treadmills. A series of metabolic test data such as oxygen uptake (VO_2), carbon dioxide discharge (VCO_2) and electrocardiogram (ECG) indexes were measured under continuous exercise load power state. Comprehensively reflect the blood oxygen exchange and metabolic activity in the patient's body, and evaluate cardiopulmonary reserve and cardiopulmonary function [11]. Major areas of research for technological applications include: evaluation of patient exercise tolerance and intolerance, and comprehensive assessment of exercise capacity in patients with cardiopulmonary disease. At present, CPET can comprehensively and quantitatively evaluate the overall changes in the multi-skeletal-muscle-joint movement system in a single test, which is also one of the latest technical equipment for clinical motion quantitative detection [12, 13].

During the CPET trial, Domestic and foreign researchers mainly observe the Maximum oxygen consumption (VO_{2max}), maximum heart rate (HR_{max}), and anaerobic threshold (AT) measured on the equipment threshold (ET), ventilation threshold (VT), lactate threshold (LT), VO_2/VCO_2 , ventilation (VE)/ VCO_2 and other parameters and ratios, These were the core data of all trials [14].

Among the data analysis, the current authoritative systematic review and retrospective meta-analysis [15] show that the VO_{2max} is the most significant data, and the statistical analysis of the research is also the most [14, 16]. Typically, the average value of the data of 30–90 s before the final exercise is taken [17, 18]. The data of CPET can provide a reference for clinicians in the design of programs, and develop appropriate exercise

programs with relatively rigorous and accurate CPET [19]. In various studies, the advantages and disadvantages of different programs, and standardized judgments were assessed by the CPET [7, 20, 21]. Besides, CPET can also be directly tested on the equipment to replace these low, medium and high intensity exercises, which further contribute to explore the relationship between exercise intensity or other directions [17, 22].

ERROR STUDY OF CPET TRIALS IN OBESE PEOPLE

In the study of CPET, Davila [23] and Löllgen et al. [7] found that most overweight patients and some healthy people could not get satisfactory and complete data in this test besides the errors of instrument (impurity test gas, aging equipment, operating system failure, etc.). The European Society of Cardiology points out that an essential reason is that the maximum exercise capacity of overweight patients is generally lower than the preset maximum in the current analysis due to the restriction of cardiovascular risk [24]. Secondly, the differences in body strength and ethnicity of testers in various regions of the world such as Asia, Europe, and America result in differences in data among different regions [25]. The American Thoracic Society suggests that the research should choose similar population properties as the reference of predicted values [13]. Secondly, the ECG connecting to the chest during exercise usually been affected by strong muscle electrical signals, which lower the reliability of the ECG to a certain extent [26]. Finally, whether these patients take treatment drugs before the test also has a great impact on the results [27, 28]. Because of metabolic problems in obese people, the intervention period of drugs and exercise will also be longer than that of general trials, which are at least 6 weeks [29], and at least three [30] or even 6 months [30] if more complete and reliable data are to be obtained. It can be seen that this trial has the shortcomings of lengthy period and extreme cost, which leads to the elevated difficulty of carrying out the current research trial [7].

LATEST HARDWARE FOR CPET FOR THE OBESE

At present, the most advanced main equipment of the CPET should be the ergonomic power bicycle, which is also the core component of the test [31]. Participants sit upright on a bicycle-like contraption. Both hardware and software operating systems are equipped with state-of-the-art system software, which intelligently modulated the motor resistance continuously and robustly. Another type of supine bicycle is commonly used in

echocardiography and magnetic resonance imaging to conjointly record the cardiac imaging changes under exercise [32, 33]. The airflow metabolism sensor was also a must-have device in the tests, showing real-time ventilation during exercise and regularly attached to a mask. Subjects were asked to wear a mask to collect gas data if they accepted the exercise test, or to only measure lung function if they did not accept the test. During exercise, these gas data can be used to evaluate lung function together with finger blood oxygen data, and if combined with ECG data, cardiopulmonary function during exercise can be analyzed [8, 34]. The ECG lead device is of secondary importance in some trials [26] because of the interference of the muscle electrical signal, sometimes only the heart rate data (HR) are taken for analysis, if the interference can be overcome, the test should be used in a larger number of patients.

APPLICATION OF THE CPET TO OVERWEIGHT AND OBESE PATIENTS

Obesity complicated by cardiovascular disease

CPET is one of the effective methods to evaluate cardiac function in overweight patients [24, 35]. At present, the positive effects of exercise on the cardiovascular system have been widely confirmed [36], and CPET trials have proved that the safety and technical risks of cardiovascular patients in exercise are higher than those of the general population [37–39]. Studies have shown that obesity is an independent risk factor of cardiovascular disease [24, 40], in addition, people with higher BMI generally have slower rate of recovery of heart rate reserve (HRR). Rosa et al. [41] performed CPET on 17 adult patients with congenital heart disease. The results shown that CPET could provide information of the severity of coronary heart disease (CHD) patients and assess the relevant therapeutic efficacy. Therefore, CPET has the potential to assist physicians to assess the functional capacity and severity of adult patients with CHD for the better development of personalized treatment plans.

Comparison of the effects of motion

Most researchers have focused on improving exercise programs in patients with varying BMI and cardiovascular disease. Lan et al. [42] found that different types of exercise programs can improve body composition and cardio-pulmonary health through CPET in a group trial of college students, but the program based on aerobic exercise may be more effective. Jurio-Iriarte et al. [43] experimented with different exercise training

programs for overweight/obese adults with hypertension with the help of CPET equipment. It is believed that different exercise training regimens can improve cardiorespiratory fitness in overweight/obese patients with hypertension, meanwhile, the combination of aerobic exercise and strength training may provide greater benefits in this process.

Drug, perioperative, and operative applications

There are few studies on drugs [28] and differences in central arteriovenous pressure [44] in patients with different BMI by CPET alone, and most of them are combined with preoperative and postoperative or exercise in the form of auxiliary methods. The observational study by Borasio et al. [45] were assessed by resting respirometer before and after surgery, followed by maximal incremental CPET on a treadmill UK NGC [46]. systematically introduced the basic knowledge of CPET and discussed its application in preoperative testing, including the measurement of gas exchange variables, ECG, pulse oxygen saturation, and heart rate. Otto et al. [47] reviewed the role of CPET in preoperative evaluation, including providing personalized risk assessment, guiding shared decision-making, comorbidity optimization and preoperative exercise training, as well as guiding perioperative patient management. Zumerkorn et al. [48] Systematic review CPET in the long term effectiveness of surgical and non-surgical treatment of obesity. Levett et al. [49] discussed the use of perioperative CPET to assess the risk of adverse perioperative events and provide information for the perioperative period. Nelson et al. [50] studied the application of CPET in assessing surgical risk factors in severely obese children, especially before pediatric bariatric surgery. Salgado-Garcia et al. [51] studied the effects of BMI and type of low-intensity exercise on the side effects of recognition under the CPET. The results showed that patients with a higher BMI were more likely to experience side effects such as headaches and vomiting after regressive therapy. In addition, walking reduced the adverse effects of relapse in patients with higher BMI.

Cardiac imaging

In terms of cardiac imaging, CPET can be combined with other examination methods, such as radionuclide myocardial perfusion imaging (MPI), echocardiography and cardiovascular magnetic resonance, to improve the accuracy of heart disease diagnosis. Katsikis and colleagues [52] investigated and analyzed the patients with myocardial perfusion imaging (SPECT) using the CPET, and investigated the gender differences and

hemodynamics after receiving the regadenoson-like receptor agonist regadenoson. AlJaroudi et al. [53] evaluated the safety and tolerability of regadenoson in 514 patients undergoing SPECT MPI under the CPET trial. In conclusion, CPET is an objective, quantitative and non-invasive examination method, it can assess the global functional status and prognosis of patients with heart failure, CPET's results are complementary to the indicators in cardiac imaging.

Obesity and respiratory disorders

It has been extensively documented that obesity affects lung function and gas exchange [54] and imposes mechanical ventilation restrictions during exercise [55]. Meanwhile, Cavalheri et al. [56] found through exercise training that the activation of respiratory muscles and exercise play an essential role in the respiratory system of patients. At present, it is difficult to determine the training intensity suitable for patients' respiratory muscle endurance with objective indicators, so the patients' parameters of respiratory training are mostly determined according to their own subjective judgment, and it is easy to see that the respiratory frequency, breathing depth and training time cannot meet the actual situation of patients [57]. The CPET will refer to the respiratory parameters under exercise to formulate a relatively objective and reasonable training amount for patients [58].

Innovation in the formulation of respiration-metabolism

The CPET system integrates respiratory metabolism and movement and has the conditions to investigate breakthroughs and innovations in the formulation of ventilation conversion efficiencies. According to these data of the machine, the American Cardiothoracic Society summarized the ventilation-oxygen consumption formula [13] and the early Baba et al. [59] proposed the oxygen uptake efficiency slope (OUES). Johnson [34], in an article published in December 2020, provided an improved parametric equation for the parameters of CPET to process and analyze the data, combined the relationship between lipid metabolism and exercise to a certain extent, and explained the positive correlation between lipid metabolism and oxygen consumption [60–62]. These formulas may better inform future research. However, the above equations and formulae still do not adequately account for energy loss errors during locomotion, and when it comes to medication intervention, there is still no proper provision for timing and dose administration. Better equations still require large amounts of clinical data and summaries.

Exploring the treatment of respiratory diseases

Obesity, especially the abdominal obesity, can lead to increased intrathoracic pressure, thereby limiting the expansion of lungs and affecting respiratory function. The accumulation of fat in the neck and throat of obese people may lead to upper respiratory tract stenosis and increase the risk of apnea, which is one of the main risk factors for sleep apnea syndrome (OSA). Cytokines secreted by adipose tissue, such as tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6), may cause inflammation of the respiratory system and impair the function of respiratory organs, thereby increasing the risk of asthma and chronic obstructive pulmonary disease [63–65]. Arzt et al. [66] compared the effects of nocturnal continuous positive pressure ventilation (CPAP) and oxygen therapy on VE/VCO₂ slope, and the results showed that CPAP and oxygen therapy had similar relief effects on central sleep apnea (CSA). However, only CPAP therapy improved respiratory efficiency and had a beneficial effect on left ventricular ejection fraction (LVEF) in CPET trials. Moreover, Hebestreit et al. [67] conducted CPET on 74 patients with cystic fibrosis, and concluded that under the same BMI, the maximum oxygen uptake, maximum running speed, maximum cardiopulmonary load and additional indicators of patients were significantly related to the survival rate. These results suggest that the CPET is a simple and effective way to help physicians to better assess the prognosis of patients with cystic fibrosis.

Applied to middle-aged and older obese people, obese adolescents, women and obese people during pregnancy

A study of a middle-aged and elderly patient population

In the study of middle-aged and elderly obese population, it was found that with the increase of exercise load, the respiratory function of people aged 40–59 tended to decline steadily, which was significantly lower than that of young people. At the same time, the obese elder endurance is rapidly declining [68].

The exercise stress ECG of CPET has a strong clinical significance for the occurrence of perioperative cardiovascular complications in the elderly [69]. To reduce the risk of anesthesia in older patients, surgery should be delayed or treated with alternative methods when the percentage of VO_{2max}/VCO_2 is less than 75%. The ratio of FEV₁/FVC, an indicator of respiratory function, can more effectively reflect lung function in the elderly and effectively predict lung function under stress. CPET can be used as an examination data

index for the elderly during the perioperative period [18], and the elderly with a ratio lower than 80% should also delay the operation. Opina et al. [70] explored the relationship between respiratory reserve and body composition and physical function in elderly obese people. There was a significant correlation between respiratory reserve and body fat content, body weight, skeletal muscle mass, and physical function.

The efficacy of aerobic exercise was assessed by the CPET. After 12 weeks of aerobic exercise, the population showed significant reductions in LDL cholesterol. The result can be inferred that aerobic exercise sufficiently improves blood lipid indicators. The research found that BMI, waist circumference, waist-hip ratio, body weight and percentage of body fat were significantly decreased in middle-aged and elderly patients with obese AA and AV genotypes [71, 72].

Dietary control and exercise prescriptions for adolescent patients

In recent years, Carr et al. [73] and Besnier et al. [62] explored the effect of dietary structure (fiber diet) on adolescent obesity from the perspective of aerobic exercise and moderate and low oxygen exercise. Currently, people generally accepted that adolescents and children should be scientific in their exercise dosage. To achieve optimal weight loss, exercise intensity should be moderate, exercise time should be limited to 40–90 min, exercise methods should increase resistance training, stick to exercise for more than three months, and maintain an exercise frequency of three to six aerobic exercises per week. In terms of diet, the intake of high-fat and high-calorie foods should be limited, and the intake of fruits and vegetables and fiber should be increased [74]. Currently, there are still few studies of dietary structural proportions in CPET trials, which provide a potential direction for future research.

Monitoring and control of hypertension, glucose and other diseases in women and obesity during pregnancy

For women and obese women during pregnancy, CPET trials are currently involved in a number of studies, primarily in exercise training research programs in the presence of elevated blood pressure and glucose during pregnancy. Poston et al. [75] study the improvement of elevated blood glucose in pregnant obese women with long-term aerobic exercise and diet control. Dodd et al. [76] studied the effects of different intensities of exercise and metformin on overweight or obese pregnant women. Sorimachi et al. [77] studied the differences of exercise metabolism before and after pregnancy in obese women. CPET can monitor the

change of blood pressure during exercise in obese pregnant women. For patients with gestational diabetes mellitus (GDM), CPET can help doctors understand the effect of exercise on blood glucose control. CPET can not only monitor the cardiopulmonary function of obese pregnant women, but also assess their exercise capacity, helping to develop appropriate weight management and exercise interventions.

DISCUSSION

To guide the health assessment and exercise rehabilitation of obese individuals

Exercise rehabilitation programs for obese patients are often better than simple weight-loss programs. The use of CPET to measure VO_{2Max} can provide a reliable basis for the implementation of corresponding exercise rehabilitation programs. CPET also enables continuous monitoring of an individual's physical function during exercise rehabilitation and timely adjustment of exercise regimens, making rehabilitation regimens more personalized and effective. Using CPET to assess the rehabilitation effects of obese individuals can develop long-term management plans, such as exercise and a normal diet, to promote recovery outcomes.

Obesity causes exercise intolerance due to ventilation limitations

Opina et al. [70] studied the measurement of breathing reserve during peak exercise to explore the mechanisms leading to ventilatory restriction and physiological adaptations related to the ability to accommodate high-intensity exercise that requires elevated ventilatory demands, as well as the ability to improve cardiopulmonary fitness. The adverse effects of ventilation restriction due to increased obesity in the elderly population were minimized. This condition may facilitate the subsequent prescription of appropriate motor training in this population.

Lipid metabolism is proportional to oxygen consumption

Nordby et al. [61] reviewed 41 studies (weighted average of 768 subjects = 40 years, BMI = 48 kg/m²) on pulmonary gas exchange at rest, during exercise, and during weight loss in morbidly obese (BMI ≥ 40 kg/m²) individuals for dynamic monitoring of cardiopulmonary function. In addition, a weight loss of 45 kg (BMI = -13 kg/m²) over 18 months was found to be associated with an improvement in PaO₂ (-10 mmHg, range 1–23 mmHg),

a reduction in PaCO₂ (−8 mmHg, range −3 to −16 mmHg), and PaCO₂ at rest (−3 mmHg, range −3 to −16 mmHg). For every 5–6 kg of weight loss, PaO₂ increases by 1 mmHg and PaCO₂ decreases by 1 mmHg.

There was a positive association between obesity and decreased cardiopulmonary function

Song et al. [54] found through CPET that muscle loss accompanied by obesity was closely related to impaired cardiopulmonary function in normal elderly people, and regular exercise and dietary adjustment to maintain muscle mass may help maintain the state of cardiopulmonary function in the elderly.

Survival rate, risk prediction

CPET evaluates a patient's surgical risk and helps physicians determine whether cardiac surgery or alternative treatments are needed. For example, the predictive value of METs for CHD [78]; VO_{2max}, as measured by CPET, is effective in predicting survival and recurrence rates in patients with cardiovascular disease. Before and after pulmonary surgery, indicators such as VO_{2peak} and respiratory reserve ratio (RER) measured by CPET can effectively predict the survival rate of patients and the incidence of postoperative complications [49]. Mora et al. [78] observed asymptomatic individuals with low risk of CHD (risk score <20%) and found that the predictive value of metabolic equivalent (METs) for CHD: If these patients have low target heart rate (tHR) recovery and METs after exercise, tHR is less than 56 beats/min and METs is less than 10.7 in men, and tHR is less than 55 beats/min and METs is less than 7.5 in women, the risk of future coronary heart disease is significantly increased, and this group of patients can be classified as a high-risk group of coronary heart disease.

Attention to the psychological needs of the patient and appropriate encouragement can improve the success rate of the trial

Some patients have a fear and rejection of the training. The CPET typically tests the patient's endurance to the maximum extent without subjective discomfort. When the patient is on the exercise bike with a gradually increased adjustable exercise power, this safe operation mode encourages the patient to try their best to stimulate their potential, which is beneficial to eliminate the patient's fear of training and form a good start in the early stage of the implementation of the training plan. It

provides the conditions for continuous training at a later stage.

ADVANTAGES OF THE CPET IN THE STUDY OF THE OBESE AND IN FUTURE DEVELOPMENTAL STUDIES

Safety and error advantages

The original intention of the CPET to monitor/measure the cardiopulmonary function of patients (or athletes) during exercise [37]. Patients will wear an ECG electrode and face mask to perform work on the device at increasing motor power. Exercise treadmill and exercise bicycle are usually used as a comparison in CPET, and exercise treadmill is also one of the most used test methods in exercise tests [12, 15, 24, 79]. Both of twelve-lead ECG and respirator mask are major components of exercise trials, and both control the intensity of exercise. In a comparison of strengths, exercise machines provided additional muscular activity and better training of leg muscles, while exercise bikes provided extra cardiopulmonary exercise and better training of lung function. In terms of error comparison, the actual exercise power (W) = weight power (G) + exercise power (E) of the exercise plate. After experiments, it is known that under different gaits and different conditions, ordinary runners will have an energy loss of 1.3 kJ/kg, and senior runners will also have a loss of 0.9 kJ/kg [80]. The elevated BMI index of overweight patients makes the power of body weight not equal to the power of exercise tablets, which requires complex calculation and software processing to reduce the error [80–82], while exercise bicycles avoid the influence of gravity on patients. For overweight patients, most will be combined with different systemic conditions. Universally speaking, treadmill exercise, mainly in the form of standing running, has a greater risk of damage to the body and bones and joints and a higher error than exercise bicycle [32, 83, 84]. Strictly speaking, therefore, the closest device to the actual value of cardiopulmonary function is the exercise bicycle.

Compatibility advantages and future developments

Most researchers will use CPET as an exercise mode or intervention factor [20, 51]. Bicycle (or treadmill) data, if used as the only auxiliary test item in the experimental research protocol, is not conducive to the evaluation of the overall data [7, 23], so it is frequently analyzed together with other auxiliary tests. On the basis of the CPET, the measurement of body composition, height and weight of obese people, routine blood biochemical examination, other forms of walking and endurance test combined with medical imaging examination should be

TABLE 1 Current RCT research.

Characteristics	Year	Point	References
Obesity & CPET & RCT	2023	Participants underwent echocardiography and CPET at baseline and returned 72 h later for a comprehensive CPET.	[87]
Obesity & CPET & RCT	2021	This study analyzed the results of CPET in adults, compared the performance of obese and non-obese participants on CPET, and mentioned the role of RCTs in research.	[88]
Obesity & CPET & RCT	2019	This literature is about a RCT designed to evaluate the acceptance and effectiveness of a parent support program (more and less) for overweight and obese children.	[89]

Abbreviations: CPET, cardiopulmonary exercise testing; RCT, randomized controlled trial.

carried out [33], which make the final results scientific. Therefore, the development and management of the trial plan are extremely vital [24]. In the future development, CPET has two data advantages, one is machine data including gas data under the breathing mask, and the other is ECG data under exercise [7, 11, 85, 86]. The above two aspects also constitute the main body of the CPET experiment, which records and saves summaries electronically at all times to facilitate data calls. The steady increase in power limited by the machine ensures safety and reproducibility. After continued upgrades and development, CPET will become more complete in terms of data detection, storage, and calling.

With the rise of traditional Chinese medicine (TCM), the combination of CPET with TCM, acupuncture, massage, and other methods in a dynamic assessment model will be more accurate than traditional methods. CPET can evaluate an individual's exercise tolerance, while TCM can improve exercise tolerance through methods such as regulating qi and blood, promoting the flow of meridians, and improving the function of muscles and joints. For example, Chinese herbal medicines, replenishing qi and nourishing blood, can improve the qi and blood status of the body, besides, acupuncture and massage can also improve the function of muscles and joints, and further improve exercise tolerance. Of noted, TCM can also improve heart and lung function by regulating their function. For example, Chinese herbal medicines such as *Astragali Radix* (Huangqi), *Aconitum Carmichaeli* (Fuzi), *Ginseng Rubra Radix* (Hongshen), and *Codonopsis pilosula* (Danshen) have a strong heart effect; formulas such as *Shen Su Yin*, *Si Ni Tang*, and *Qiangxin Dan*, as well as acupuncture and massage, can regulate the function of the respiratory and circulatory systems and improve heart and lung function. TCM treatment can also improve physical condition by regulating metabolism. For example, Chinese herbal medicines such as *Scrophularia ningpoensis* (Xuan Shen), *Astragalus membranaceus* (Huangqi), *Coptidis Rhizoma* (Huanglian), and *Rehmannia glutinosa Libosch* (Shengdi), *Rehmannia glutinosa* (Shudihuang) have hypoglycemic effects and can lower blood sugar and improve the metabolic condition of diabetes patients; acupuncture and massage can also regulate

the metabolic state of the body and improve physical condition.

We also summarized the current randomized controlled trial (RCT) from related studies (Table 1).

CONCLUSION

Based on the literature review, the present studies, focusing on the evaluation of the effects of exercise interventions and training programs in overweight patients, are primarily RCT studies about CPET metabolic power vehicles. In early 2012, the instrument was formally put into clinical practice, with mechanisms related to exercise and obesity has been discussed indirectly or directly during the service period. CPET is more and more widely used in diversiform researches, with being updated constantly and profoundly. Our research will be further improved and applied in clinical guidance after sorting out the numerous divergent directions.

AUTHOR CONTRIBUTIONS

Tingshuai Fu: Data curation; project administration; resources; writing—original draft; writing—review & editing. **Mingzhong Xiao:** Conceptualization; investigation; methodology; project administration; supervision; writing—review and editing. **Jiajia Ding:** Data curation; investigation; writing—review and editing. **Chenxia Lu:** Investigation; supervision. **Peiran Wang:** Investigation. **Jingjing Yang:** Investigation. **Qing Zhang:** Project administration; supervision.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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