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Review Article

From Cardiopulmonary Resuscitation, Cardiopulmonary Exercise Test and Cardiopulmonary Coupling to New Theory of Holistic Integrative Physiology and Medicine

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Abstract

The Holistic Integrative Physiology and Medicine (HIPM), which was firstly purposed by Xing-Guo Sun since 2011 at APS conference, is a brand-new concept of physiology and medicine for human being. It originated from the philosophy of traditional Chinese and Western medicine and culture. It steps upon the coupling ideas of systems, such as cardiopulmonary resuscitation (CPR) by Yuan-Chang Wang and Kouwenhoven, cardiopulmonary exercise testing (CPET) by Karlman Wasserman and cardiopulmonary coupling (CPC) and integrated physiology. HIPM's concept is always combining not only "Holistic" but "Integrative" (rather than integrated), not only time but space, not only normal (i.e. physiology) but abnormal (i.e. pathophysiology and medicine) for human physiology and medicine: only one inseparable set in whole contenting the all functional systems and their control and regulation in human being are internally integrative altogether, rather than the integrated one-by-one system of two or more systems as integrative physiology in systemic physiology. HIPM approaches the mechanism of neurohumoral control and regulation with the integration of all systems in the human body. We described the rough constructural frame of HIPM theory and clearly explained many unique questions in physiological and medical and pathophysiological mechanism of patients with chronic diseases (CDs). With HIPM, we can widely apply the methods of CPET, CPC and continuous functional monitoring for accurate diagnosis and differential diagnosis, evaluation, training, treatment, rehabilitation, prognosis and prevention in clinical medicine. We also can accurately and quantitatively manage CDs and do initial successful practice of integration of optimized traditional therapy, rehabilitation, health care and management, eating, drinking, exercise, sleep and lifestyle modification in China. The implementation and popularization of HIPM has the excellent opportunity and prospect. HIPM is the future of human physiology and medicine.

Keywords: Holistic Integration Physiology and Medicine (HIPM); Cardiopulmonary Resuscitation (CPR) Cardiopulmonary Coupling (CPC); Cardiopulmonary exercise testing (CPET).

Using time and space, the new theory of Holistic Integrative Physiology and Medicine (HIPM) approaches the physiological mechanism of control and regulation for respiration, circulation, digestion, absorption, excretion, and metabolism etc. altogether for human being; explains the pathophysiological mechanism of patients with chronic diseases (CDs); and guides the safe and effective converting CDs' abnormalities to normal and health, combing of traditional physiology and culture with modern science, scientific technology, systemic physiology and medicine [1-26].

Origin of HIPM Theory

Origin of Chinese traditional philosophy, culture and medicine

The HIPM has been constructing by Xing-Guo Sun [1-26] since 2011 the first introduction at APS conference. [9-10] Combining with modern science, scientific technology, systemic physiology and Western medicine, [27,28] HIPM theory mainly originated from the traditional Chinese philosophy and culture embodying the balance and imbalance among human, nature, society and culture, such as "Yi-Jing"(I-Ching) [29],"Dao De Jing"(Tao Te Ching), [30] and traditional Chinese medicine such as "Inner Canon of Huangdi" [31] and "Treatise on Exogenous Febrile Disease"[32]. All of these emphasize "the theory of human is an integral part of nature" which considered human as an indivisible integral whole should be in harmony with nature. These traditional Chinese philosophy and culture have influenced the Chinese people from generation to generation for thousands of years [33].

Origin of Western traditional philosophy, culture and medicine

Hippocrates, ancient Greek physician who is traditionally regarded as the father of traditional medicine. He has been respected for his ethical standards in medical practice, mainly for the Hippocrates Oath. Moreover, his views of philosophy and medicine had deemed as the origin and inspiration of doctrines of Empiricism and Rationalism in ancient time, and further influenced on the development of Western medicine in terms of medical views and practices, especially his humoral theory that relate to the theory of health as balance.[34, 35]In the 2nd century BCE, Galen, a doctor of Rome, purposed the theory of temperament, and realized that the difference between arterial and venous blood was that the arterial blood mixed with the vital energy from outside of body. Furthermore, he divided body fluids into three types, related to veins, arteries and nerves, was a classic in the Middle Age.[36]He developed his magnificent medical system and dominated the western medicine for nearly 15 centuries.

Influence of HIPM from modern science, technology, systemic physiology and medicine

The modern science, technology and systemic physiology

Under the background of systematology and reductionism, the theory of blood circulation was established to lay a foundation for modern systemic physiology. In the early 17th century, William Harvey, who purposed a brand-new direction of physiological research, thinking of the cardiovascular system as one unified system in the time of ancient Greeks' view were dominated as human body was a group of separate organs and systems, each with its own independent function. [37,38] The innovative theory, which elaborate in his book "Anatomical Exercise on the Motion of the Heart and Blood in Animals", has identically influenced modern physiology and western medicine for ages. Even though William Harvey obtained huge achievement in modern systemic physiology and medicine, it reveals some limitations for explanation of human physiology from HIPM's view. The technologies of initial coupling of two or more systems are demonstrated as bellow.

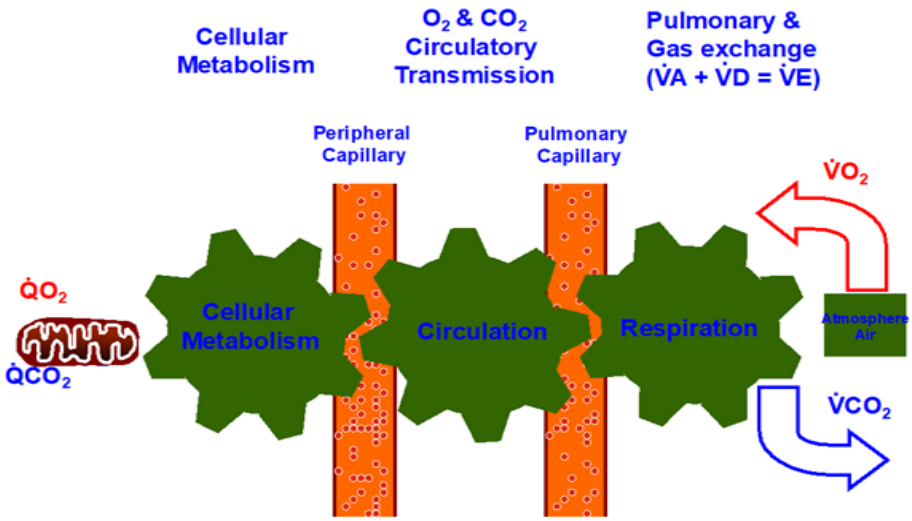
Cardiopulmonary resuscitation (CPR)

Yuan-Chang Wang (Tianjin, China) who initially created the idea of chest compression on patient with sudden cardiac arrest in 1955, and published it in 1957, [39] which is 3 years earlier than Kouwenhoven in USA. Synthesized with mouth-to-mouth resuscitation and electric defibrillation technology, established the basic content of the present cardiopulmonary resuscitation technology.

Cardiopulmonary exercise testing (CPET)

Since 1960-70s, owing to the development of measuring instruments (the invention of oxygen and carbon dioxide measuring technology of faster reaction around 50~200 Hertz), exercise equipment and the computer technology carried out accurate, real-time and continuous measuring (breath-by-breath) technology, which achieved the goal of collection, store and analysis of gas exchange during the exercise. Karman Wasserman, who purposed the theory of coupling of external (external respiration) to cellular metabolism (internal respiration) linking by circulation during exercise, [40,41] (Figure 1) combined with these technologies and finally created modern CPET for clinical practice. [42,43] CPET also received widespread attention for clinical medicine. Therefore, it can not only evaluate the overall functional state of human body, but also guide the prevention, treatment and rehabilitation of the disease for the health, sub-health, and ill people nowadays [6,43]. In our hospital, we follow the protocol of Harbor-UCLA CPET Laboratory and strictly conducted with calibration of environment, volume, flow and gas, and also correct them by metabolic simulator before the CPET [43-46]. In addition, the data collection abide by the standard operating process to offer the foundation of accurate data calculation, analysis, and plot drawing. We also further apply HIPM in guiding interpretation of CPET and clinical practices [45,46]. Besides, Max test is commonly applied when we suspect the exercise extremity of patients, and well confirms the accurate and reliable of test [47].

Figure (1): Animation (PPT format) of circulatory gas transport coupling cellular metabolism (internal respiration) and pulmonary (external) respiration.



Since 1960s, Wasserman used three gears to represent the functional interdependence of the physiologic components of the human systems during exercise. Pulmonary (external) respiration implies gas exchange between room air and lung ventilation, matters for O_2 uptake ($\dot{V}O_2$) and CO_2 output ($\dot{V}CO_2$). The internal metabolism in the cells, in order to match the increasing of O_2 consumption ($\dot{Q}O_2$) for energy requirement. The increasing of cardiac output, by the local circulatory blood flow redistribution, is proportion to this of $\dot{Q}O_2$. Circulatory response has to be dependent on the energy requirement. In the cells, CO_2 production ($\dot{Q}CO_2$) is generated from the $\dot{Q}O_2$. The ratio of $\dot{Q}CO_2$ over $\dot{Q}O_2$ (RQ) in the cells is dependent on three factors: the kind of metabolic energy materials, percentage of materials combination and balance status of metabolic rate with O_2 supply. First, it is 1.00 for glucose, 0.70 for fatty acid, and 0.80 for amino acid. Secondly, our cells commonly use combination of metabolic energy materials and the RQ is dependent on eachone's percentage of combination. Thirdly, based on the balance status of metabolic rate with O_2 supply, we describe cell metabolic status as aerobic and anaerobic. During below AT exercise intensity, which is aerobic stage, CO_2 elimination from lung ventilation($\dot{V}CO_2$) almost equals to$\dot{Q}CO_2$, however, above AT exercise intensity, the $\dot{V}CO_2$ will be over the $\dot{Q}CO_2$ due to the extraction of lactic acidosis buffering by bicarbonate radical, generating from body fluids and blood. In other words, $\dot{V}CO_2$ =$\dot{Q}CO_2$+buffer from the bicarbonate above AT. Thus, the [HCO3]-buffering system plays a crucial role in eliminating the production of lactic acid. In addition, the development of metabolic acidosis during heavy workload accelerates the increasing of ventilation, which meets the ventilation compensatory point (VCP), provides respiratory compensation for the metabolic acidosis. Ventilation must increase at an even greater rate than $\dot{V}CO_2$ to constrain the fall in pH by reducing arterial PCO_2 and maintains balance of acid-base. Finally, the whole gas transport mechanism has accomplished by coupling among respiration, circulation and cells.

Q˙O2, oxygen consumption; Q˙CO2, carbon dioxide pr0duction;V˙O2, oxygen uptake; V˙CO2,carbon dioxide output; PCO2, partial pressure of carbon dioxide; [HCO3]-, bicarbonate ion; AT, aerobic threshold;VCP,ventilation compensatory point.

(Modify from Wasserman K, Stringer WW, SunX-G and Koike A. **Circulatory coupling of external to muscle respiration during exercise**. In Wasserman K ed. Cardiopulmonary exercise testing and cardiovascular health. Futura Publishing Company, Armonk, NY, 2002; p2-25.)

In our hospital, we follow the protocol of Harbor-UCLA CPET Laboratory and strictly conducted with calibration of environment, volume, flow and gas, and also correct them by metabolic simulation before the CPET. [43,46] In addition, the data collection abide by the standard operating process to offer the foundation of accurate data calculation, analysis, and plot drawing. We also further apply HIPM in guiding interpretation of CPET and clinical practices. [45,46] Besides, Max test is commonly applied when we suspect the exercise extremity of patients, and well confirms the accurate and reliable of test [47].

Cardiopulmonary coupling (CPC)

In 1973 from Harbor-UCLA (University of California at Los Angeles) Medical Center, Brain J.Whipp published the theory of CPC during exercise which considered the control of respiratory and circulatory responses during exercise is highly mediated by both neural and humoral mechanisms: a crucial control link appears to couple the responses, via feedforward ventilatory control of cardia origin [48]. From Harvard Medical School, Robert Joseph Thomas published the measurement algorithm of CPC during the sleep in 2005 based on the CPC theory, which was applied in evaluating sleep quality and respiratory rhythm disorder. [49-51] Moreover, CPC theory has also applied in the medical monitoring devices such as continuous pulse wave, continuous pulsating blood pressure, etc.

Establishment of HIPM Theory

The limitation of traditional physiology and Western medicine

Traditional physiology and Western medicine have continuously penetrated into the various of systems, organs, cells, genes and molecules for hundreds of years, and deviated from the reality that the human

whole is indivisible. Under this background of reductionism in the modern science, physiology and medicine are stepwise refined into separated parts of human body. Although clinical medicine, only service in whole human object, obviously brought tremendous progress, it also appeared obvious defects and limits at the same time [4].

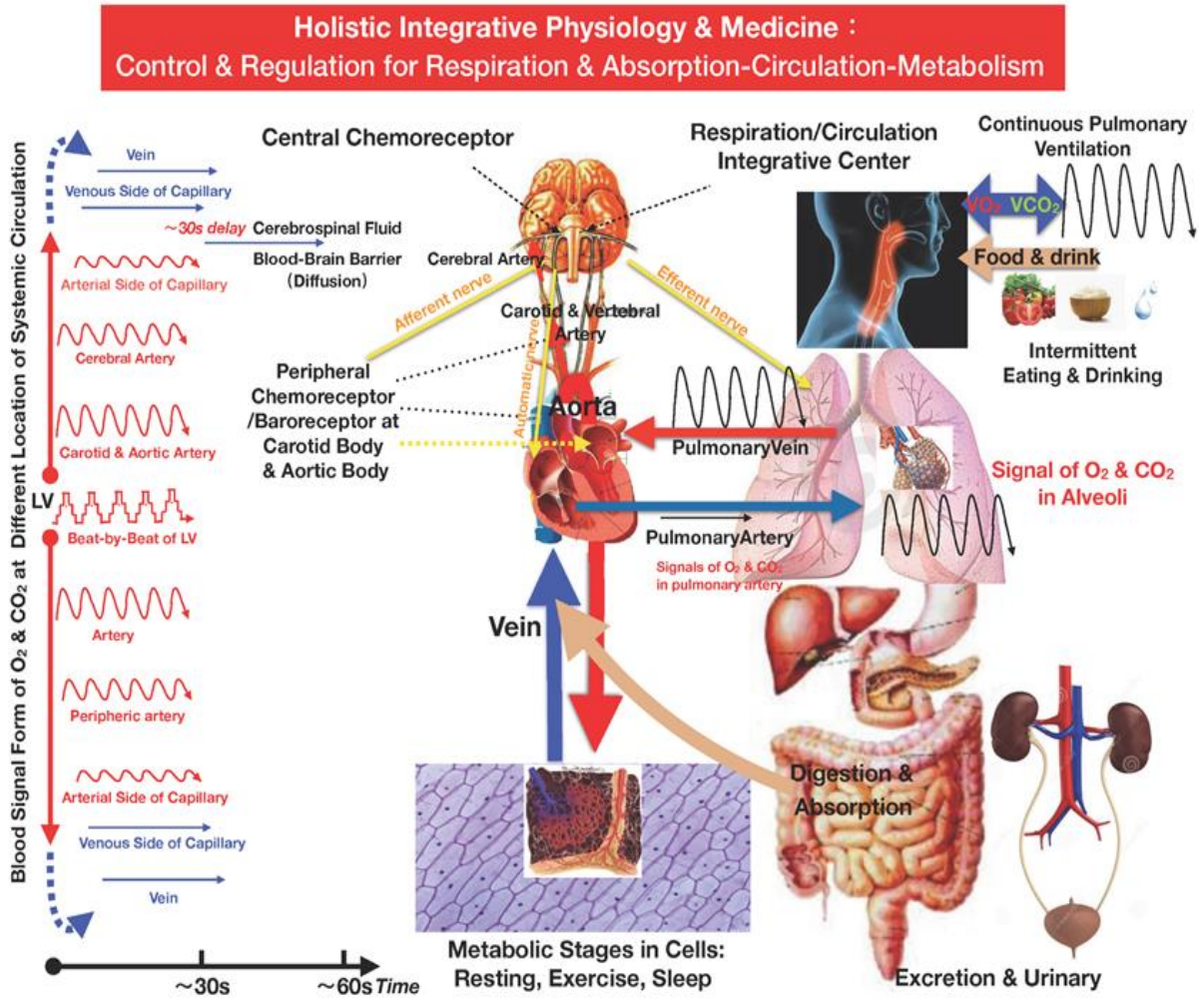
Xing-Guo Sun's HIPM, step-by-step

Since1980s, Xing-Guo Sun, as an anesthesiologist in modern Western medical service system, recognized some limitations, overlooks and shortcomings in systemic physiology and medicine, due to he is deeply influenced by traditional Chinese and Western philosophy, culture and medicine. In order to further lucubrate, he went to Harbor-UCLA Medical Center to follow Karman Wasserman, who is father of CPET and CPC, engaged in researches for exercise, metabolism, sleep, diet and rehabilitation in normal subjects and patients with chronic diseases (CDs) for more than 20 years. Based on the traditional philosophy and culture, combined with some systemic medicine and advanced scientific technology, he spent more than 30 years to established a rough structure of HIPM for human body and subsequently went back to China for guiding the clinical application.

Key structure of HIPM Theory

HIPM synthesizes the time and space factors, and further analyzes the mechanism of integrative control and regulation for all systems in human physiology. Basically, the framework of HIPM is like a letter of" Y" as the core axes which includes two entrance of human body. In top right axis refers to the oxygen inhalation. Oxygen transports via lung to cells by circulation. In top left axis, represents nutrients (food and drink) enter the digestive system via gastrointestinal tract to cell. Both of them provide materials (oxygen and substrates) for generating energy which body need. In the bottom of axis refers to cellular metabolism in the mitochondria. Furthermore, HIPM theory considered that the regulation of individual function is multi-system and integrated, all systems can affect and participate respiratory regulation signals, and play a crucial role [51]. Exercise makes basal metabolic rate rise, on the contrary, sleep makes it fall. In the process of life, there are three metabolic states of rest, exercise and sleep, which can achieve dynamic balance through the integrated optimization and regulation of respiratory, circulation and neurohumors [27, 28]. The wave signal of alveolar gas which produced by pulmonary ventilation, run through the body, whether it's internal organs (circulatory, respiratory, digestive, nervous, urinary, metabolic system) or different state (rest, exercise, sleep), all can present different amplitude of wave signals. In addition, signals transmit to the peripheral chemoreceptor by blood circulation, and then upward to the respiratory integrative center in the cerebral cortex. Eventually, neural pathways regulate respiratory muscles and sinoatrial node, and formulate a whole regulation and control loop, which is a multi-system participation of the overall loop [1-26]. The system of new HIPM demonstrates in (Figure 2).

Figure (2): The structural frame of human HIPM after birth: All systems are coupling together under effects of time and space.



In the new theory of HIPM, demonstrates a holistic integrative hypothesis which is the mechanism of four systems (respiration, absorption, circulation, metabolism) and two regulations (respiration and circulation) involved. In the respiratory system, it considers that continuous pulmonary ventilation between room air and alveolus generates wave signals and runs through the human body by closed arteriovenous system. On the other hand, nutritious substance which includes substrates (carbohydrate, protein, fat), vitamins, minerals and water, are digested and absorbed by digestive system. The nutrition returns to lung via hepatic vein, inferior vena cava, right atrium, right ventricular, and pulmonary artery. Finally, in order to satisfy the energic requirement of cellular metabolism, the nutritious substance mixes with relatively high-concentration oxygen, which we call" spirit of life" flow through organs, tissues, cells and mitochondria in the body by circulation. Hence the circulation plays a crucial function of connecting these three systems. In the left-hand side of figure, democrats the blood signal form of O_2 and CO_2 at different location of systemic circulation. However, the signal forms become "stair-step" form in the left ventricular (LV) due to the none 100% ejection of left ventricle. (The red dots represent the initial point of blood flow from LV) As long with the blood flow far from the LV, the amplitude of wave form gradually turns small to almost flat at the venous end of capillary. Additionally, it emerges more flat form after diffusing into the cerebrospinal fluid and with around 30 second delay compares with it in the LV. (The black dot of timeline at left-bellow corner represents the beginning of LV

ejection) Furthermore, the regulation of neurohumoral regulation by cerebral cortex which include respiratory and circulatory regulation. In the aspect of respiratory regulation, the peripheral chemoreceptor at the carotid and aortic body, sensors the signal form from LV and upload it to central chemoreceptor through afferent nerves, and download to respiratory muscles (diaphragm, intercostal, etc.) through efferent nerves, eventually, the whole respiratory regulation loop complete. In the circulatory regulation, nerve signal from peripheral baroreceptor upload to the regulative center of medulla spinals and download to sinoatrial node and vessels via automatic nerve (sympathetic and parasympathetic) and meditates the rhythm of heart and vasoconstriction and vasodilation. In general, circulatory system links respiratory, absorbed, metabolic systems and central neural pathways regulate respiratory muscles and sinoatrial node, formulating a whole control and regulative loop, which is an integrative loop with multi-system participation.

HIPM, Holistic Integrative Physiology Medicine; LV, left ventricular.

(Modify from Sun X-G. New Theory of Holistic Integrative Physiology and Medicine. II: New Insight of the Control and Regulation of Circulation. Chinese journal of applied physiology 2015, 31(4):298-301; 302-307; 308-312.).

Holistic integrative control and regulation for respiration

In HIPM, breathing control signals should be transited to peripheral chemoreceptor based on the circulation of blood and then integrated by respiratory center, finally transit to respiratory muscles via neural pathway. Respiratory regulation and breathing switch accomplish through these pathways. However, the whole process need interaction among muti-system includes respiratory, circulatory, neural, metabolic systems. It cannot complete the respiratory regulation by neural signal transmission from only respiratory system. In general, HIPM regards respiratory regulation as the process of coordination and cooperation of multiple systems of human body [1,9,12].

Holistic integrative control and regulation for circulation

The main purpose of circulation is to maintain a stable metabolism of cells, i.e. transport oxygen (from lung) and nutrients (from gastrointestinal tract) to cells and return carbon dioxide and metabolic products back for elimination. Based on this goal, similarly, all respiration and gastrointestinal digestion, absorption, urinary excretion, etc. are integrative together for regulation to maintain the supply-demand balance at any metabolic status of resting, exercise and sleep. In addition, HIPM also make some explanation on the dramatic change of cardiovascular before and after birth, the variant of cardiovascular function, the mechanism of respiratory abnormity in patients with left heart failure, redistribution of blood [2,6].

Holistic integrative control and regulation for digestion and absorption, urinary and excretion

HIPM considers the first cry of infant is owing to open the pulmonary alveoli for first breath, the second cry is for food demand. When fetus in the uterus, they obtain nutrition from maternal circulation and maintain a stable state. However, after delivering from obstetric canal, the digestion and absorption systems start to operation, and subsequent urinary and excretion. The energic substances of digestion and absorption enter the circulation of blood makes the change of blood volume, blood viscosity, blood concentration, blood flow resistance etc. The metabolic state of the body is closely related to the circulatory control and regulation. Urinary, excretion, exercise, mental stress, sleep and so on are possibly change the metabolic state such as changing of concentration of metabolic production, vasoconstriction, changing of hemodynamic indexes. Hence, digestion, absorption, urinary, excretion significantly influence on circulation, all of them closely cooperate to each other for organic life activities [2, 4-8].

Holistic integrative control and regulation for all systems by neurohumoral mechanism

In HIPM, the neurohumoral control and regulation is only a part of the integration of human physiologic functions, and the neurohumoral control and regulation is inseparable from the integrative regulation of the whole function, and only functioning under the coordination of the integrative function. The neurohumoral regulation is holistically integrated and unified for all functions in human body. We briefly explained the mechanism of neurohumoral control and regulation life (respiration and circulation) as the example pattern of sound system. Based upon integrated regulation of life, we described the neurohumoral pattern to control respiration and circulation [1-3]. Additionally, mental, and psychological factors possess obviously influence on human integrative functional state, and closely correlation with diseases. In other words, mental and psychological factors as the risky factors for CDs has been widely discussed. Similarly, HIPM pays attention to the control and regulation of human physiological function by consciousness of cerebral cortex [6-10].

Application of HIPM in Clinical Medicine

HIPM guides CPET widely using in clinical medicine

With the progress of modern science, technology and the improvement of local cognition of human body, the cell metabolism function of oxygen and carbon dioxide molecules as the core combine with the integrative neurohumoral control and regulation of respiration, circulation and metabolism and finally realize the overall function evaluation of CPET. Hence, the testing further induced the thinking of human is an inseparable whole. HIPM theory as a creative concept has widely applied in clinic. Initially, CPET as a best method for assessing integrative functional state is based on the principle of CPC and HIPM theory [52-54]. It can realize the reserve and compensatory capacity of the cardiopulmonary system by detecting the response of the multi-system in the case of increased exercise load [55-57]. Researches had shown closely association with the level of cardiopulmonary function, health condition and exercise ability. Additionally, CPET has been utilized broadly in rehabilitation, cardiology, respiratory medicine, intensive care, sports, fitness and other fields [58- 59]. The main clinical application of CPET describes as follow:

Risk assessment for anesthesia surgery and management of perioperative period

CPET has played a crucial role for risk stratification during perioperative period, especially for those who are assessed to have normal cardiopulmonary function at rest. It is believed that well performance during CPET reveals reduction of surgical risk and postoperative complications [6, 58].

"Pre-early" diagnosis：myocardial ischemia and pulmonary hypertension

Static electrocardiogram and echocardiogram are important methods for early screening of myocardial ischemia and pulmonary hypertension. However, patients are normally without obvious symptoms in the early stages especially in rest status and electrocardiogram usually reveals negative finding. However, CPET could "pre-early" screening out the patients with myocardial ischemia during the incremental loading test of cycle ergometer. Primary manifestations are oxygen uptake ($\dot{V}O_2$) cannot corresponding increase with incremental power, the slop of increasing $\dot{V}O_2$ becomes gentle and oxygen pulse (O_2 pulse) appears plateau when approaching the peak of exercise. These characteristics of myocardial ischemia could emerge earlier than Electrocardiogram (ST segment depression) [6,46]. In addition, we found that patients with trend of Right-to-Left Shunt during CPET could probably progress to pulmonary hypertension at rest couple years later [59,60]. CPET may provide a clinical basis for "pre-early" diagnosis these

kinds of diseases.

Diagnosis and differential diagnosis: differentiate right or left heart failure , cardiogenic or pulmonary

The differential diagnosis of left heart failure and right heart failure is always a challenge for clinical practice, whereas there are significant differences in the performance of CPET. Oscillatory breathing which refers to the oscillatory pattern in the indexes of $\dot{V}O_2$, carbon dioxide output ($\dot{V}CO_2$), ratio of gas exchange (RER) and etc. is the most common pattern of gas exchange in patients with left heart failure during CPET [61, 62]. Nevertheless, Right-to-Left shunt is common abnormality of hemodynamic in patients with right heart failure, the primary manifestations are abruptly increasing of ventilation related to carbon dioxide output ($VE/\dot{V}CO_2$), ventilation related to oxygen uptake ($VE/\dot{V}O_2$), partial pressure of end tidal oxygen ($PETO_2$) and abrupt decrease in partial pressure of end tidal carbon dioxide ($PETCO_2$) and oxygen saturation (SpO_2). Combining with other parameters in CPET, it could provide reliable basis for differential diagnosis and prognostic prediction of heart failure patients [6,63].

Objective quantitative grading of the severity of functional restriction: such as heart failure and COPD

Current methods for assessing the severity of functional limitations in cardiopulmonary diseases include the heart failure functional classification by New York Heart Association (NYHA), 6-minute walk test, CPET. However, CPET is superior to other in its objective and quantitative [6, 63].

Prognostic prediction of death/survival

It is due to the subjectivity and variability of the heart failure functional classification by New York Heart Association. CPET assessment systems are considered more objective and rational. Compared with NYHA and ejection fraction in the echocardiogram, percentile prediction of peak$\dot{V}O_2$ is a favorable independent predicted index of expected lifetime [64-66]. Moreover, recent researches have proved various measuring indexes in CPET are more predictable than traditional indexes (cardiac output, strike volume, pressure and resistance measurement) [65, 66]. Hence, it reveals well prediction of early mortality and rehospitalization rates, diseases severity grading and offers treatment options for patients with heart failure.

Severity of heart/ respiratory failure and cardiopulmonary transplant option

In addition to grade the severity for patients with heart/respiratory failure, CPET provides important indicators for the priority selection of heart and lung transplant which is one of "golden standards" [6].

Monitoring and screening for high-risk population

For certain high-risk diseases, intensive monitoring during CPET could identify potential high-risk population and further provide corresponding suggestion and prevention to reduce the possibility of sudden death at work and home [6].

Measurement of gas exchange effectiveness of cardiopulmonary matching

The indexes of gas exchange effectiveness during CPET include lowest ventilation to carbon dioxide ratio (Lowest $VE/\dot{V}CO_2$),ventilation to carbon dioxide slope ($VE/\dot{V}CO_2$slope) and oxygen uptake efficiency plateau (OUEP) could emerge better prediction of short-term mortality for patients with heart failure [61, 62, 64-65].

Guiding the prescription of exercise rehabilitation：rehabilitation of cardiovascular and pulmonary diseases

Endurance exercise training is beneficial to both normal and cardiovascular and respiratory patients, however, accurate and effective exercise prescription is an important part of exercise

training protocol. CPET could formulate objective and quantitative exercise prescription and also evaluate the effect of exercise training for patients with cardiovascular and pulmonary diseases or even normal people [6, 8].

Objective and quantitative evaluation for various therapeutic effects

CPET has been widely used in the objective and quantitative evaluation of the efficacy of various kinds of surgery, intervention and drug therapy.

Objective quantitative assessment/ identification of labor loss

Most of the clinical functional tests are commonly conducted in resting state. However, when patient's symptoms or subjective ability are different from results of resting function test, CPET might be the best and only way to assess patient's exercise fitness. Additionally, CPET is the "gold standard" for evaluating exercise endurance. It is the most valuable functional examination of the objective and quantitative assessment of labor loss [6].

Identify functional status normal and abnormal , health and sub-health and health management (zero level prevention)

Medical perception for health has been limited in the normal of relevant biochemical indicators and imaging examination at present. Ulteriorly, it pays more attention on evaluating for sub-health people and timely intervention. CPET is an important tool for objectively assessing the functional status of the body which traditional laboratory tests are difficult to approach [6].

Disease prevention and treatment

HIPM theory can be used in the assessment of respiratory health status and respiratory disorders (pulmonary heart disease, chronic obstructive pulmonary disease, asthma, sleep apnea, pulmonary hypertension, pulmonary embolism, pneumonia, lung cancer, etc.) [66-68], cardiovascular diseases (left ventricular systolic functional failure, congenital heart disease, ventricular septal defect, atrial septal defect, patent ductus arteriosus, etc.). Besides, the monitoring of cardiogenic sleep respiratory abnormalities (Cheyne-Strokes respiration during sleep in patients with heart failure) by means of gas exchange during respiratory can further predict the mortality and morbidity of patients with cerebral infarction and heart failure [69,78]. Moreover, The theory has been applied in various aspects from early prevention and treatment to data collection and large sample analysis of healthy population in the present.

HIPM guides the development of continuous monitoring technology

Finally, HIPM theory has been carried out in treatment of the CDs patients in China. On the theoretical level, it is based on the HIPM as a framework, however, on the technological application level, it specifically guided the development of accurate monitoring of gas exchange, ECG without the original wave signal filtering, high fidelity (keep slow wave) respiratory wave (original thoracic activity) of the original signal collection, which is totally different from the traditional human physiological signal collection. Moreover, three innovative technology of cardiopulmonary coupling enhancement including pulse wave, traditional electro-cardio signal and autonomic nerve signal could enhance the original signal. On this basis, the team of Xing-Guo Sun is currently devoting in the development of portable, wearable products to comprehensively and continuously monitor human body in different states (sleep, rest, exercise), chest and abdomen breathing, diaphragm, nasal airflow composition, VC, VT, CO_2, O_2, etc. According to the data analysis, physician could make the corresponding adjustment of the treatment protocol.

Along with the invention of new technology guided by HIPM, the mechanism of early disease diagnosis, the prediction and intervention of risk, and CDs management also could apply extensively in the clinic in the near future.

CDs management using HIPM theory

HIPM explains the mechanism of CDs

HIPM considers the essence of CDs from the level of cellular metabolic physiology may primarily result in malnutrition (i.e. imbalance of supply and demand for all or either one of oxygen, energy and nutrition materials), and patients with CDs basically is divided into three types. Firstly, it considers "weakness syndrome" of chronic diseases possibly caused by malnutrition of calorific and or energy deficiency imbalance of supply and demand. Secondly, according to the World Health Organization (WHO) announcement in 2006, cancer should be regarded as one kind of CDs [79]. Hence, "inadequacy" of holistic integrative or local tissues or only fewer cells at important organs, except the heart, are probably the major cause of the cancer. Moreover, invasion of cancer cells is regarded as compensatory response of human body. Thirdly, similarly, the "hyper-" calorific and or energy exceed of many metabolic syndromes such as hyperglycemia, hypertension, hyperuricemia, hyperlipemia, obesity and etc. are the manifestation of compensatory responses of various indexes for the "hypo-" pathophysiological indexes, i.e. imbalance of supply and demand for all or either one of oxygen, energy and nutritious materials.

HIPM guides safe and effective management of CDs

Accurate management of chronic diseases under the guidance of HIPM theory includes initial diagnosis and evaluation by CPET and then we will formulate the exercise intensity of training protocol according the results of it. In addition, exercise frequency will follow the results of continuous monitoring devices (continuous glucose, continuous beat-by-beat blood pressure, continuous pulse wave, sleep monitoring and so forth) [80]. Furthermore, we will conduct "enhanced management" and "weakening management" in different stages for patients with CDs [81]. The training protocol will modulate according to the middle and final assessment. Besides, we also focus on the management of diet and sleep and offer some corresponding advises and treatments. Ultimately, a full-time and all- systems of healthy management platform are accomplished. In recent years, this healthy management platform has obtained initial success and realized a real safe and effective CDs management for many patients with chronic disease [8], notably, under the background of rapid growth of CDs population in China [82].

HIPM guides health management for high risky and normal population

In addition to the management for patients with CDs, we also pay attention to the healthy management of high risky and normal population to avoid the transition from health to illness by omnibearing evaluation and management. Eventually, achieving a consequence of truly disease-free.

HIPM guided the epidemic control of Coronavirus Disease 2019

Coronavirus Disease 2019 (COVID-19) is globe spread and caused over ten millions of people been infected and half of millions of people dead worldwide. Since the early of 2020, Xing-Guo Sun as the National COVID-19 expert, he used the HIPM idea for epidemic control in Zhengzhou City in Henan Province, which is nearest city over ten millions population just north to the Hubei Province. The general principle is individually maintaining the best functional status of everyone to against the COVID-19 and all pathogenic microorganisms, in other words, enhancing the immunity of human body. The specific practices include appropriate exercise, eating rich various nutrients, drinking hot "HULA" soup which is a kind of local spicy soup could supply energy for human body, drinking hot tea, ample sleep and relaxing mind without worry, under these HIPM principles, the merely only 157 people infected and only one died from COVID-19 in Zhengzhou City.

Conclusion

Human physiology has to be HIPM. HIPM synthesized holistic integrative concept of traditional Chinese philosophy and culture combining with modern scientific technology and western medicine. We believe that HIPM will play a key role for people's health management not only in Chinese, but also in the world in the near foreseeable future.

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