MEDS Chinese Medicine (2024)
Clausius Scientific Press, Canada

DOI: 10.23977/medcm.2024.060310
ISSN 2616-1753 Vol. 6 Num. 3

Review of the Research on Animal Models of Heart-Kidney Disharmony in Traditional Chinese Medicine

Guoliang Xiong[1], Jing Ma[2,*]

[1]*Shaanxi University of Chinese Medicine, Xianyang, Shaanxi, 712046, China*
[2]*First Affiliated Hospital of Air Force Military Medical University, Xi'an, Shaanxi, 710032, China*
[*]*Corresponding author*

Keywords: Heart-kidney Disharmony, Heart-kidney Correlation, Syndrome and Symptom, Animal Model, Chinese Medicine

Abstract: As a typical syndrome of Chinese medicine, heart-kidney disharmony may be the cause of a series of diseases. The current established animal models of heart-kidney disharmony include animal models of heart-kidney disharmony insomnia, animal models of heart-kidney comorbidity, and animal models of heart-kidney co-treatment to prove heart-kidney correlation. Most of these animal models have only partially simulated some symptoms, rather than truly reflecting the syndrome of heart-kidney disharmony in Chinese medicine. In future, when further improving the animal model of heart-kidney disharmony, both main and concomitant symptoms of heart-kidney disharmony should be included in the animal model as much as possible, and the method of "determining the syndrome by specific prescriptions" should be used to determine whether the syndrome of the established model is correct.

1. Concept of Heart-Kidney Disharmony in Traditional Chinese Medicine

The theory of heart-kidney disharmony discusses the relationship between the heart and kidneys from the perspective of physiological functions and pathological changes, and is one of the important contents of the theory of Zang-Fu in traditional Chinese medicine. "Heart-kidney disharmony" is a pathological concept relative to the normal physiological state of "heart-kidney harmony". It was first seen in the compilation of Yan's Jisheng prescriptions: "Gorgon fruits are round in shape, which are used to treat heartburn caused by worry, kidney damage caused by fatigue, heart-kidney disharmony, premature ejaculation, dull complexion, palpitations and forgetfulness, and restless dreams". The basis of the theory of "heart-kidney disharmony" is the generation, restraint and transformation of the five elements and the rise and fall of yin and yang, water and fire. Its essence is the mutual restraint relationship between the substances and functions of the heart and kidneys [1]. Compared with the normal physiological state of heart-kidney interaction, heart-kidney disharmony is a manifestation of heart-kidney dysfunction. In a narrow sense, heart-kidney disharmony refers to the imbalance of the rise and fall of water and fire in the heart and kidneys [2]. According to the five elements of the internal organs and the infinite divisibility of yin and yang, the heart and kidneys can be further divided into heart yin, heart yang, and kidney yin, kidney yang. Therefore, heart-kidney disharmony represents the disorder caused by the pathological changes of one of the yin and yang of the heart and

kidney, which affects the other aspects. For example, insufficient heart yang affects heart yin, kidney yang, and kidney yin, and insufficient heart yin also involves heart yang, kidney yang, and kidney yin [3]. In short, any imbalance in the relationship between the heart and kidneys, yin and yang, water and fire, qi and blood, essence and body fluids, meridians, consciousness, exterior and interior, and ascending and descending trends can be extended to "heart-kidney disharmony".

2. Modern Research on Relationship between Heart and Kidneys

2.1. Physiological Connection between Kidneys and Heart

Modern research shows that the heart and kidneys in traditional Chinese medicine (TCM) not only include the cardiovascular system and organ kidneys in modern anatomy, but also include the functions of the nervous, endocrine, reproductive, hematopoietic, and immune systems [5]. The heart and kidneys are closely connected and influence each other in the above aspects. The kidneys play an important regulatory role in cardiovascular function through neural and humoral factors. It is well known that the kidneys are an important organ for maintaining normal body fluid volume and composition. When the body adapts to changes in the internal or external environment, the heart is regulated by many neural and humoral factors and then adapts to various changes by constantly changing the stroke volume, rhythm, etc. [6]. However, such changes in heart function often require normal kidney function as a background. The kidneys affect cardiovascular function by regulating the volume and osmotic concentration of extracellular fluid. The kidneys secrete antidiuretic hormone through the osmotic pressure receptor-hypothalamus-pituitary system to control plasma osmotic concentration and multiple variables in the cardiovascular system [7].

2.2. Pathological Connection between Kidneys and Heart

When kidney function declines, the ability to participate in the regulation of cardiac function will inevitably decline, resulting in the inability to effectively regulate the myocardium when the myocardium is severely loaded, causing heart damage. Among them, severe hypertension that often occurs in kidney disease is an important factor that makes the heart vulnerable to damage [4]. There are many reasons for the close relationship between kidney and heart diseases: hemodynamic changes, activation of the renin-angiotensin-aldosterone system (RAAS), metabolic disorders, anemia, high expression of inflammatory factors, and glomerular filtration barrier disorders are the main reasons [8].

3. Diagnostic Criteria for Heart-Kidney Disharmony Syndrome in Traditional Chinese Medicine

The seventh edition of the textbook on TCM diagnosis defines it as: "Heart-kidney disharmony refers to the deficiency of yin fluid in the heart and kidney, and the internal disturbance of virtual fire. It is a virtual heat syndrome with irritability, insomnia, nocturnal emission, tinnitus, and low back pain as the main manifestations. It is also known as heart-kidney yin deficiency and yang hyperactivity or heart-kidney yin deficiency and fire excess syndrome" [9]. The main symptoms of heart-kidney disharmony are insomnia and sleeplessness. Therefore, ancient and modern literature often uses sleeplessness and its associated symptoms to explain the syndrome of heart-kidney disharmony.

As there are few studies on the manifestations of other diseases of heart-kidney disharmony syndrome, there is no clear diagnostic standard. Researchers mostly define the judgment criteria based on the clinical manifestations of heart-kidney disharmony insomnia. Mei Yuanting et al., referring to

the national textbook "Diagnosis of Traditional Chinese Medicine" (11th edition) for general higher education in the "14th Five-Year Plan" and the relevant chapters of the "Guidelines for Clinical Research of New Chinese Medicines" formulated and issued by the Ministry of Health of the People's Republic of China in 2002, defined that the main symptoms of heart-kidney disharmony syndrome should be: palpitations, chest tightness, chest pain; secondary symptoms should be: irritability, insomnia, forgetfulness, soreness of waist and knees, dizziness, tinnitus, dry throat and mouth; tongue and pulse patterns should be: red tongue with little coating, deep and fine pulse. Patients who meet at least one of the main symptoms and at least two of the secondary symptoms, and meet the corresponding tongue and pulse patterns at the same time, can be identified as this syndrome [10].

4. Diseases Related to Heart-Kidney Disharmony

As a syndrome of TCM, heart-kidney disharmony does not correspond to one or several particular diseases. Syndrome classification is mainly based on if the patient's symptoms meet one particlular syndrome. Clinically, the following diseases have been attributed to heart-kidney disharmony syndrome, including insomnia [11], palpitations [12], cardiac neurosis [10], chronic renal-cardiac syndrome [13], diabetic nephropathy [14], psychological heart disease [15], chronic kidney disease with heart failure [16], premature ejaculation [17], recurrent oral ulcers [18], anxiety disorders [19,20], etc.

5. Treatment of Heart-Kidney Disharmony

5.1. Huanglian Ejiao Decoction

Huanglian Ejiao Decoction comes from the Shaoyin Disease chapter of Treatise on Febrile Diseases: "Shaoyin disease, if it lasts for more than two or three days, when the heart is upset and unable to sleep, Huanglian Ejiao Decoction is the main treatment." It is composed of coptis chinensis, scutellaria baicalensis, peony root, donkey-hide gelatin, and egg yolk [21]. Zhang Zhongjing originally designed it to treat the heart-kidney disharmony caused by insufficient kidney water and hyperactivity of heart fire, i.e. Shaoyin heat syndrome. It has the functions of nourishing yin, clearing heat, and connecting the heart and kidneys. In the formula, coptis root and scutellaria root can clear the heart fire and eliminate irritability and heat, which is the so-called purging the south; peony root and donkey-hide gelatin can nourish kidney yin and replenish essence and blood, which is the so-called replenishing the north; egg yolk can nourish blood and moisten dryness. All these herbs together can actually purge heart fire, nourish kidney water, and connect the heart and kidney, so it is also called the method of purging the south and replenishing the north.

5.2. Jiaotai Pills

Jiaotai Pills are recorded in Han's Medical Manual. They are composed of coptis root and cinnamon in a ratio of 10:1. They are clinically used to treat insomnia, depression, menopausal syndrome, arrhythmia and other diseases caused by disharmony between the heart and kidneys [22]. Coptis chinensis is bitter and cold in nature and enters the heart meridian. It can clear the heart fire and connect with the kidney water. It has the effects of clearing away heat and dampness, purging fire and detoxifying. Cinnamon bark is pungent, sweet and hot in nature. It enters the kidney meridian, warms up the kidney water and restrain the heart fire. It also has the effects of replenishing fire and yang, dispersing cold and relieving pain, warming the meridians and unblocking the vessels, and guiding fire back to the origin. The two medicines, one cold and one hot, one yin and one yang, work together to connect the heart and kidneys and regulate emotions and calm the mind.

6. Animal Models of Heart-Kidney Disharmony

6.1. Animal Model of Insomnia Due to Heart-Kidney Disharmony

6.1.1. Injection of p-chlorophenylalanine

Intraperitoneally injection with 300 mg/kg p-chlorophenylalanine (PCPA) into rats in one shot [23]. Quan Shijian et al. determined that injection of PCPA is a conventional modeling method for establishing an animal model of insomnia caused by heart-kidney disharmony.

6.1.2. Multifactorial Stimulation Combined with Injection of p-chlorophenylalanine

Gao Hongli et al. subjected rats to random discontinuous stimulation for 5 weeks, including separation of mother and infant rats, limb restraint for 2h, swimming in 4℃ iced water for 5min, fasting for 24h, water deprivation for 24h, tail clamping for 1min, light-dark reversal, foot shock, cage tilt at 45 °for 24h, and moist bedding for 24h. After that, PCPA was injected intraperitoneally to establish a rat model of insomnia with TCM heart-kidney disharmony and hypothalamic-pituitary-adrenal (HPA) axis disorder [24].

6.1.3. Water Environment Small Platform Method

Qian Lili et al. established a TCM animal model of insomnia caused by heart-kidney disharmony by using a special water environment small platform method [25]. In a 30.0cm×30.0cm×40.0cm rat box, a small platform with a diameter of 6.3cm and a height of 8.0cm was set up. The platform was filled with water, and the water temperature was maintained at about 20℃. The water surface was about 1.0cm away from the platform. The rats were placed on the platform and allowed to eat and drink water on their own. If they fell asleep, they would fall into the water due to the relaxation of muscle tension. When the rats entered rapid eye movement sleep, the muscle tension of the whole body decreased, and they would suddenly wake up when their faces touched or dipped into the water. This behavior would cause insomnia if it occurred repeatedly.

6.2. Animal Model of Heart-Kidney Comorbidity

6.2.1. Building Cardiac Disease Model and Proving Successful Establishment of Heart-Kidney Comorbidity Model by Measuring Changes in Renal Indicators

Lin Wenqiu et al. established a severe myocardial fibrosis model by intramuscular injection of isoproterenol (2.4 mg/kg, 7 days) into rats [26]. After 6 weeks, decreased renal vascular endothelial growth factor (VEGF) expression and increased 24-hour urinary albumin excretion were observed, hematoxylin-Eosin (HE) staining of rat kidney tissue also showed a significant kidney impairment.

6.2.2. Building Renal Disease Model and Proving Successful Establishment of Kidney-Heart Comorbidity Model by Measuring Changes in Cardiac Indicators

6.2.2.1. 3/4 Nephrectomy in Rats

Lin Wenqiu et al. established an early-to-mid-stage renal failure model by 3/4 nephrectomy in rats [26]. After 6 weeks, increased cardiac left ventricle weight / whole heart weight ratio (LVW/HW) and left ventricle weight to body weight ratio (LVW/BW) indexes, and high expression of TGF-β1 in cardiac immunohistochemistry were observed, the myocardial HE staining of rats in the model group also showed severe myocardial fibrosis.

6.2.2.2. Hydrocortisone Injection into Rats

Chen Jiewen et al. established kidney yin deficiency (1.8 mg/100 mg, 5 days) and kidney yang deficiency (3.6 mg/100 mg, 9 days) models by intramuscular injection of large amounts of hydrocortisone into rats [27]. After 5 days, the plasma atrial natriuretic peptide (ANP) level of rats in the kidney yang deficiency model group increased and the serum testosterone level decreased significantly, indicating impaired cardiac function; after 9 days, the atrial and plasma ANP levels of rats in the kidney yin deficiency model group decreased, the hypothalamic ANP level increased, and the serum testosterone level decreased significantly, indicating impaired cardiac function.

6.2.2.3. Rabbits Fed with Hydroxyurea

Chen Jiewen et al. established a kidney yang deficiency model by feeding rabbits with hydroxyurea (500mg/10ml/kg, 7-10 days) [27]. After 10 days, the left ventricular pressure peak (LVSP), maximum rate of rise of left ventricular pressure (+dp/dt max), pressure and velocity changes during isovolumetric contraction and rapid ejection (CFLI+I) of the model control group were lower than those of the normal group, the left ventricular end-diastolic pressure (LVEDP) was higher than that of the normal group, the maximum rate of fall of left ventricular pressure (-dp/dt max) was lower than that of the normal group, and the pressure and velocity changes during isovolumetric relaxation and rapid filling (CFL VI) were higher than those of the normal group; the arterial systolic pressure, diastolic pressure, and mean arterial pressure of the model control group were lower than those of the normal group; the testosterone and estradiol levels of the model control group were lower than those of the normal group; all of the above indicated that the heart function was impaired.

6.3. Animal Model of Heart-Kidney Co-treatment to Prove Heart-Kidney Correlation

6.3.1. Building Cardiac Disease Model to Verify Heart-kidney Correlation by Heart-Kidney Co-treatment

6.3.1.1. Oral Administration of Furazolidone to Rats

Gao Hongshan et al. established an animal model of dilated cardiomyopathy by orally administering furazolidone and sodium carboxymethyl cellulose (0.2 g/g, 8 weeks) to rats. After modeling, they divided the model into a pure Chinese medicine experimental group administered with Zhenwu capsule [1.8 g/(kg*d)], a combined Chinese and Western medicine experimental group administered with a combination of Zhenwu capsule [1.8 g/(kg*d)] and benazepril [3.33 mg/(kg*d)], and a pure Western medicine group administered with benazepril [3.33 mg/(kg*d)] alone as the positive control group [28]. After 8 weeks, results showed that the combination of Chinese and Western medicine group was better than the pure Chinese medicine group and the pure Western medicine group.

6.3.1.2. Rat Left Coronary Artery Ligation

Feng Zhou et al. established a heart failure model by left coronary artery ligation approximately 2mm below the starting point of the left anterior descending coronary artery in rats. After modeling, the heart failure model was divided into high (17.4g*(kg*d)-1; 8 weeks), medium (8.7g*(kg*d)-1; 8 weeks), low (4.4g*(kg*d)-1; 8 weeks) dose experimental groups which were given heart-kidney co-treating Chinese medicine, sham operation group as negative control group, and trimetazidine (1.0mg *(kg*d)-1;8 weeks) group as the experimental control group [29]. After 8 weeks, results showed that the heart-kidney co-treating Chinese medicine could improve the cardiac function of rats with heart

failure with increasing dosage.

6.3.1.3. Rat Coronary Artery Ligation Combined with Exhaustive Swimming

Kong Fanda et al. established a heart failure model by ligating the coronary artery of rats and performing exhaustive swimming. After modeling, they divided the model into experimental group administered with Chinese medicine for nourishing the kidneys and activating blood circulation (9.2g*kg/d; 4 weeks), Western medicine group administered with lisinopril (1.5mg*kg/d). ; 4 weeks) as the positive control group, and the sham operation group as the negative control group [30]. After 4 weeks, results concluded that Chinese medicine for tonifying the kidneys and activating blood circulation can down-regulate the expression of osteopontin and its mRNA, improve ventricular remodeling condition in chronic heart failure (CHF) rats, and the effect is equivalent to that of Western medicine.

6.3.2. Building Renal Disease Model to Verify Heart-kidney Correlation by Heart-Kidney Co-treatment

6.3.2.1. Oral Administration of Retinoic Acid to Rats

Yang Jiezhong et al. established a femoral head avascular necrosis model by orally administering retinoic acid (70 mg/kg for 3 consecutive weeks) to rats. After modeling, the rats were divided into a kidney-tonifying experimental group, a heart-kidney co-treatment experimental group, a model control group, and a normal group [31]. After 3 weeks, results concluded that heart-kidney co-treatment was more effective.

6.3.2.2. Left Kidney Removal Combined with Angiotensin AngII Injection in SHR Rats

Mao Xinjing et al. constructed a hypertensive renal injury model by removing the left kidney of spontaneous hypertensive rats (SHR) and subcutaneously injecting angiotensin AngII (1.46 mg/kg/d, two weeks). After modeling, they divided the model into high and low dose experimental groups of heart-kidney co-treatment, valsartan group as positive control group, and Wistar-Kyoto (WKY) rats as normal control group [32]. After 8 weeks, the conclusion was drawn that heart and kidney co-treatment was more effective.

6.3.2.3. Unilateral Renal Ligation in Rats Combined with Injection of Streptozotocin (STZ)

Zhu Bixiu et al. established a diabetic nephropathy (DKD) model by unilateral renal ligation in rats plus injection of streptozotocin (STZ). After modeling, the rats were divided into an experimental group (16.3 mg/kg*d-1, 12 weeks) administered with heart-kidney co-treating Chinese medicine, a model control group, and a positive control group administered with benazepril (1.0 mg/kg*d-1, 12 weeks) [33]. After 12 weeks, results showed that the effects of heart-kidney co-treating Chinese medicine were similar to that of Western medicine.

6.3.2.4. Large Artery Sclerosis Model in Spontaneous Hypertensive Rats

Zhao Shuying et al. established a large artery sclerosis model using SHR rats. After modeling, they were divided into an experimental group administered with heart-kidney co-treatment Chinese medicine (Yishen Jiangyan prescription, (10.08*kg-1, 6 days/week)), a positive control group administered with amlodipine (1mg*kg-1, 6 days/week), and a normal control group of WKY rats [34]. Results showed that heart-kidney co-treatment Chinese medicine could inhibit the progression of arteriosclerosis and its effect was equivalent to that of Western medicine.

7. Discussion

7.1. Syndrome and Syptom

The biggest difficulty in establishing animal models of TCM is that TCM has the concept of "syndrome", which is not equivalent to "symptom". Heart-kidney disharmony is a type of "syndrome" and not "symptom". (1) One "syndrome" can have multiple "symptoms", the same "syndrome" can have different "symptoms", and the same "symptom" can also be attributed to different "syndromes"; while the establishment of animal models is mostly one "symptom" corresponding to one model, it is very difficult to simulate all clinical manifestations that meet the specific syndromes of TCM at the same time. (2) "Syndrome" is a general term for a series of pathological changes in a certain stage of the disease, including etiology, location of disease, course of disease, and relationship between healthy energy and pathogenic energy. Some diseases have "syndromes" but no "symptoms" at certain stages, and if there are no "symptoms", it cannot be simulated by animals. (3) The same disease can be divided into multiple stages, and different stages belong to different syndromes. Therefore, it is difficult to confirm the attribution of "syndrome" by establishing models based on diseases.

The establishment of TCM disease-syndrome combination models emphasizes the realistic simulation of clinical syndromes. Therefore, when establishing a specific TCM syndrome animal model, as many symptoms as possible should be simulated in order to be closer to the syndrome. However, due to the large physiological and pathological differences between animals and humans, it is still difficult to distinguish behavioral characteristics and physical signs, and the basis for disease evaluation is often insufficient and needs to be further improved.

7.2. Difficulties in Syndrome Differentiation

In the establishment of animal models of heart-kidney correlation, heart-kidney comorbidity, and heart-kidney co-treatment, keeping close to the clinical manifestations of heart-kidney disharmony is the key to successfully replicating heart-kidney disharmony syndrome. The main clinical manifestation of heart-kidney disharmony is insomnia. Therefore, the establishment of animal models of heart-kidney disharmony in the past was mainly based on insomnia models. In terms of concomitant symptoms, heart-kidney disharmony also has symptoms such as irritability, palpitations, dizziness, tinnitus, soreness of waist and knees, hot flashes and night sweats feverish sensation in palms and soles, dry throat and hyposecretion of saliva, enuresis and spermatorrhea. To further improve the establishment of animal models of heart-kidney disharmony, it is necessary to include as many concomitant symptoms as possible while simulating insomnia as the main symptom. However, these are subjective indicators that are difficult to quantify in animal models because it is hard to judge how the animals feel. Moreover, the heart-kidney disharmony syndrome lacks differentiated symptom manifestations clinically, and its concomitant symptoms are common symptoms shared by Yin deficiency syndrome. Even if the model is successfully established, it is difficult to define whether it is Yin deficiency or heart-kidney disharmony syndrome.

7.3. Determination of the Syndrome by Specific Prescriptions

In the establishment of TCM syndrome animal models, blurred determination of syndrome due to overlapping judgment criteria is not an isolated case, and the method of "determining syndrome by prescriptions" to test whether the established model is correct for the targeted syndrome is so far the most sophisticated. This method relies on the properties that specific prescriptions only correspond to the treatment of specific TCM syndromes, through which infers or disproves the syndrome attributes of the established model, which is simple but efficient.

Quan Shijian et al. used the specific properties of Jiaotai Pills for treating heart-kidney disharmony syndrome and compared the effects of Jiaotai Pills and Tianmeng Capsules on rats with insomnia caused by parachlorophenylalanine (PCPA) to establish that injection of PCPA is a conventional method for establishing an animal model of heart-kidney disharmony insomnia [23]. Lin Ye et al. used the properties of Wutou Decoction for treating wind-cold-dampness arthralgia to establish that using an intelligent artificial climate chamber to stimulate wind-cold-dampness is the correct method for establishing wind-cold-dampness arthralgia rheumatoid arthritis [35]. Yang Meng et al. compared the efficacy of different prescriptions on the isoproterenol (ISO)-induced chronic heart failure mouse model and deduced that this method established a heart yang deficiency syndrome heart failure model [36].

Therefore, two points should be grasped in perfecting the establishment of an animal model of heart-kidney disharmony syndrome: (1) The model should include as many symptoms which belong to this syndrome as possible. (2) Use specific prescriptions which are used to treat this syndrome to test whether the model built is correct.

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