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基于中西医临床病证特点的扩张型心肌病动物模型分析

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【摘要】 扩张型心肌病(dilated cardiomyopathy,DCM)是导致心力衰竭、心律失常和猝死的常见疾病之一。DCM 病因复杂多样,机制尚未完全阐明,现有干预措施对患者的预后改善有限,10 年存活率不足 25%。本研究基于 DCM 动物模型国内外研究成果,结合西医临床诊断标准与中医辨证分型,总结 DCM 动物模型构建特征并评价模型中西医临床吻合度。研究发现,DCM 造模方法主要涉及基因编辑、药物诱导、免疫诱导、病毒感染、快速起搏诱导等,实验动物主要包括鼠、斑马鱼、果蝇、猪等,以小鼠和大鼠为主。基因编辑是最常用的 DCM 造模方法,其次是阿霉素诱导造模。目前同一类型 DCM 动物模型所选实验动物、实验用药及其单次或累积剂量、给药方式、造模周期等均有差异,中西医临床吻合度水平参差不齐,同一模型中医临床吻合度普遍较西医临床吻合度低。此外,DCM 动物模型成模标准多以西医理论为基础,而中医证候模型辨证标准及四诊信息采集标准尚未规范统一,未来有待建立稳定、均一、临床吻合度高的病证结合动物模型,为 DCM 机制研究和新药研发提供依据。

【关键词】 扩张型心肌病;中西医结合;病证结合;动物模型
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Analysis of dilated cardiomyopathy animal models based on clinical characteristics of traditional Chinese and Western medicines

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【Abstract】 Dilated cardiomyopathy (DCM) is a common disease leading to heart failure, arrhythmia, and sudden death. The etiology of DCM is complex and diverse, and the mechanisms have not been fully elucidated. Conventional interventions have a limited ability to improve the prognosis of patients, who have a 10-year survival rate of less than 25%. This study aimed to summarize the construction and characteristics of a DCM animal model and evaluate the clinical compatibility of the model with traditional Chinese and Western medicines. Analysis was based on domestic and overseas research into DCM animal models, Western clinical diagnostic criteria, and traditional Chinese medicine syndrome

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differentiation. The DCM modeling method mainly involved gene editing, drug induction, immune induction, viral infection, and rapid pacing induction. Experimental animals included muroids, zebrafish, *Drosophila*, and pigs, of which mice and rats were most commonly used. Gene editing was the most commonly used method for modelling DCM, followed by doxorubicin-induction. In the literature, the experimental animals, drugs, single or cumulative doses, administration method, and modeling period used varied among studies involving DCM animal models. The level of clinical anastomosis according to traditional Chinese and Western medicines varied considerably, being generally lower in traditional Chinese medicine than Western medicine in the same model. In addition, the modeling standards for DCM animal models were mostly based on Western medicine theories. The differentiation of syndrome models and information collection for the four diagnoses have not been standardized and unified. In the future, stable and homogeneous animal models of high clinical consistency combining both disease and syndrome need to be established to provide a basis for DCM mechanism research and drug development.

【Keywords】 dilated cardiomyopathy; combination of Chinese traditional and Western medicine; combination of disease and syndrome; animal model

Conflicts of Interest: The authors declare no conflict of interest.

扩张型心肌病(dilated cardiomyopathy, DCM)是由遗传因素和(或)非遗传因素作用所致的异质性心肌病,发病率约 1/2500[1-2]。病机复杂,心肌纤维化是 DCM 的重要病理特点,临床表现主要为进行性心力衰竭[1,3]。现代医学治疗研究取得了较大进展,药物治疗、免疫吸附、超滤技术、左室辅助装置、心脏移植等治疗措施极大地延长了患者寿命,但治疗副作用、疗效不稳定、低依从性等局限性一定程度上影响了治疗效果,患者预后改善有限。研究显示,DCM 的 5 年死亡率为 15% ~ 50%,严重危害人类健康[4]。中医药在 DCM 领域的认识和研究不断发展进步,稽其病机,以本虚标实为要,多为正气亏虚,复感邪毒、痰瘀、水湿,分早、中、晚 3 期辨证论治。发病之初,邪盛则以祛邪之品以折其势,或合养心育阴之药以护其心;病久而深者,邪入血络、痰瘀胶着、阳气衰微、五脏俱虚,惟化痰祛瘀、理气通滞、培补脾肾、温振心阳,其证可愈[5-6]。研究表明,中医药对改善 DCM 心室重构[7]、心功能[8]、免疫功能[9]等均有积极作用。

疾病的发生发展复杂难测,直接以人本身作为实验对象来探索疾病的发生机理和演变趋势十分困难。疾病动物模型是利用模式动物来模拟人体各种复杂的生物学问题及疾病特征和过程,可通过基因编辑、药物诱导、免疫诱导、病毒感染、快速起搏诱导等方法构建,对明确疾病的基本规律和研发新药有重要意义[10-11]。故本研究通过梳理文献,参考西医临床诊断标准与中医辨证分型标准,依据动物模型评价新方法,总结 DCM 动物模型构建特征,并评价模型中西医临床吻合度,以期为 DCM 动物模型的合理选用和设计优化提供借鉴。

1　扩张型心肌病病因病机

1.1　中医病因病机

传统医学中无对 DCM 病名的明确记载,根据历代医家学者对 DCM 的认识,可将其归属于心胀、心水、怔忡、心悸、喘证、水肿、胸痹心痛等范畴。《灵枢·胀论》记载:“夫心胀者烦心短气,卧不安”[12]。《金匮要略·水气病脉证并治》中对心水描述如下:“心水者,其身重而少气,不得卧,烦而躁,其人阴肿”[13]。《素问·评热病论篇》记载:“诸水病者,故不得卧,卧则惊,惊则咳甚也”[14]等表现与 DCM 的临床症状表现极为类似。虽历代学者医家对 DCM 的病机演变认识不完全一致,然主要思想可概括为:DCM 发病基础是先天不足或正气亏虚,复感六淫邪气,或因饮食不节、情志失调、劳逸失度等,致气血阴阳虚衰,脏腑功能失调,心失所养,心血不运,痰饮、瘀血、水湿阻遏心阳[15-16]。疾病本质为本虚标实,病位在心,五脏相关。病程初期以心气亏虚、痰瘀阻络为主,中期多为心肾两虚、阳虚水泛,后期则五脏阴阳俱损,证候多虚实夹杂,各证型间可相互转化[16-17]。

1.2　现代医学认识

DCM 的病因主要涉及遗传因素和非遗传因素 2 部分。遗传因素在各年龄段的发病中都占据重要地位[18-19]。临床筛查证据表明,20% ~ 35% DCM 患者存在家族性传播倾向[20-22]。约 60%的家族性 DCM 患者显示与 DCM 相关的 60 个基因之一的遗传学改变,其中肌联蛋白基因(titin, TTN)突变频率达 25% ~ 30%[23-24]。非遗传因素包括感染、药物、毒素以及内分泌紊乱等[3]。在儿童中,DCM 的常见

病因是基因突变、心肌炎和先天性代谢缺陷[25-26]。此外,围生期心肌病发生于妊娠最后 1 个月或分娩后 5 个月内,发病机制不明,50%以上的患者病情逐渐加重,康复比例不到 1/4[27],多见于撒哈拉以南非洲地区[28]。

2 扩张型心肌病动物模型评价标准

2.1 中医辨证分型与临床表现

目前 DCM 辨证分型尚无统一标准,本研究参照《中药新药临床研究指导原则(试行)》[29]、《中医内科学》[30]及《中医病证诊断疗效标准》[31-34]辨证分型标准,将 DCM 分为心肺气虚证、气阴两亏证、心肾阳虚证、气虚血瘀证、阳虚水泛证、痰饮阻肺证、阴竭阳脱证 7 种证型,见表 1。依据动物模型评价新方法[11],中医临床诊断标准分为主症和次症,中医吻合度权重各占 60%和 40%。主症包括:(1)心悸气短,或喘息不得卧;(2)神疲乏力,精神萎靡;(3)畏寒肢冷;(4)胸腹水;每项赋值 15%。次症包括:(1)尿少肢肿;(2)胁下痞硬;(3)唇甲青紫或毛发枯槁;(4)燥热多饮;每项赋值 10%,总分值 100%。

2.2 西医诊断标准与临床表现

参照《中国扩张型心肌病诊断和治疗指南(2018)》[24]和《2023 年 ESC 心肌病管理指南》[35],拟定 DCM 动物模型西医诊断标准,见表 2。依据动

表 1 DCM 中医辨证分型

Table 1 Syndrome differentiation of dilated cardiomyopathy

证型 Pattern type	主症 Primary symptom	次症 Secondary symptom	舌脉 Tongue and pulse
心肺气虚证 Heart and lung qi deficiency	心悸,气短,乏力,活动后加重 Palpitations, shortness of breath, weakness, aggravation after activity	神疲咳喘,面色苍白 Fatigued spirit, panting and cough, somber white facial complexion	舌质淡或边有齿痕,脉沉细或虚数 Pale tongue with tooth marks on the margins of the tongue, heavy and fine pulse, or vacuous and rapid pulse
气阴两亏证 Qi and Yin deficiency	胸闷气短,心悸,神疲乏力,自汗或盗汗 Chest tightness, shortness of breath, palpitations, fatigue, spontaneous or night sweats	五心烦热,口干,两颧潮红,头晕耳鸣,或尿少肢肿 Vexing heat in chest, palms and soles, dry mouth, tidal reddening of the cheeks, dizziness and tinnitus, scant urine and swollen limbs	舌红少苔或少津,脉细数无力或结代 Red tongue with less moss or scant liquid, fine and weak pulse, or bound and intermittent pulse
心肾阳虚证 Heart and kidney Yang deficiency	心悸,短气乏力,动则气喘,身寒腹冷 Palpitation, shortness of breath, asthma, fear of cold and cold abdomen	尿少肢肿,腹胀便溏,面色灰青 Scant urine and swollen limbs, abdominal distention and loose stool, green-blue facial complexion with gray tinge	舌淡胖或有齿印,脉沉细或迟 Pale and enlarged tongue with tooth marks on the margins of the tongue, heavy and fine pulse, or slow pulse
气虚血瘀证 Qi deficiency and blood stasis	胸闷气短,神疲乏力,胸胁作痛,胁下痞块,下肢浮肿 Chest tightness, shortness of breath, fatigue, pain and lump glomus in the rib-side, edema of the lower extremities	面色晦暗,唇甲青紫 Somber facial complexion, green-blue or purple lips and nails	舌质紫暗或有瘀点、瘀斑,脉沉细或涩或结代 Dark purple tongue or petechiae, ecchymosis, heavy and fine pulse, or rough pulse, or bound and intermittent pulse
阳虚水泛证 Yang deficiency and water widespread	心悸,喘息不得卧,神疲乏力,面肢浮肿,尿少,咯吐泡沫痰,畏寒肢冷 Palpitations, hasty panting with inability to lie down, fatigued spirit and lack of strength, puffy face and swollen limbs, scant urine, frothy expectoration, fear of cold and cold limbs	颜面灰白,口唇青紫,腹胀,或胁下痞块坚硬,颈脉显露 Gray face, green-blue or purple lips, abdominal distension, hard glomus in the rib-side, the neck pulse is revealed	舌暗淡或暗红,苔白滑,脉细促或结代 Dark purple tongue with glossy white tongue fur, fine and skipping pulse, or bound and intermittent pulse
痰饮阻肺证 Phlegm and drink obstruct lung	心悸气急,喘息不得卧,咯白痰或痰黄粘稠,胸脘痞闷 Palpitations, rapid breathing, hasty panting with inability to lie down, white sticky phlegm or thick yellow phlegm, glomus and oppression in the chest and stomach duct	头晕目眩,尿少肢肿,或伴痰鸣,或发热口渴 Dizziness, scant urine and swollen limbs, phlegm rale, heat and thirst	舌暗淡或绛紫,苔白腻或黄腻,脉弦滑或滑数 Purple or crimson tongue with slimy white tongue fur or slimy yellow tongue fur, stringlike and slippery pulse, or slippery and rapid pulse
阴竭阳脱证 Yin exhaustion and yang withdrawal	喘悸不休而不得卧,张口抬肩,烦躁不安,大汗淋漓或额汗如油,四肢厥冷 Hasty panting with inability to lie down and catch breath, gaping mouth and raised shoulders, agitated vexation, dripping great sweat or putting forth oily sweat, reversal cold of the limbs	精神萎靡,颜面发绀,唇甲青紫,尿少或无尿肢肿 Lethargy, purple facial complexion, green-blue or purple lips and nails, scant urine, anuria, swollen limbs	舌淡胖而紫,脉微细欲绝或疾数无力 Pale, enlarged, and purple tongue, faint pulse verging on expiry, or racing and weak pulse

物模型评价新方法[11]，西医诊断指标分为核心指标、直接相关指标和间接相关指标，西医吻合度占比分别为 60%、30%、10%。其中，影像与病理①②③每项赋值 20%，实验室检查①②③每项赋值 10%，临床表现每项赋值 5%，总分值 100%。

3　扩张型心肌病动物模型分析

3.1　模型动物的选择

目前用于制备 DCM 动物模型的实验动物有小鼠、大鼠、斑马鱼、果蝇、兔、犬、羊、猴和猪等。由于方法简单、成模率高、重复性强等优势，啮齿类动物是构建 DCM 模型最主要的实验动物，以小鼠和大鼠最为常见，其中 Wistar 大鼠、SD 大鼠、C57BL/6J 小鼠、BALB/c 小鼠、Lewis 大鼠等品种已被成功用于构建 DCM 模型[36]。

3.2　动物模型与临床吻合度

DCM 造模方法主要包括基因编辑、药物诱导、免疫诱导、病毒感染、快速起搏诱导等，其中以基因编辑最为常用，实验动物主要包括小鼠、大鼠、斑马鱼、果蝇、猪等，而药物诱导、免疫诱导与病毒感染动物模型的实验动物以小鼠和大鼠为主，快速起搏诱导法多适于犬、猪和羊等大型动物[36]。除应用基因编辑模型的研究外，其余动物模型相关研究均详细描述了具体造模过程，动物模型与中西医临床病证吻合度见表 3。

结果表明，阿霉素诱导制备 DCM 动物模型最为常见，造模周期 2 ~ 8 周，此模型成本低、操作简单、模型稳定、成模率高、重复性强，其中以 SD 大鼠 DCM 动物模型的中西医临床吻合度最高。然而，目前同一类型 DCM 动物模型所选实验动物、实验用药及其单次或累积剂量、给药方式、造模周期等均有差异，中西医临床吻合度水平参差不齐，同一模型西医临床吻合度普遍高于中医临床吻合度。

表 2　DCM 西医诊断标准

Table 2　Diagnostic criteria for dilated cardiomyopathy

级别 Level	指标 Indicators	表现 Manifestation
核心指标 Core indicator	影像与病理 Imaging and pathology	①超声心动图：提示心脏扩大、或合并二尖瓣和三尖瓣反流及肺动脉高压，左室壁运动减弱、室壁变薄，左室收缩功能下降、左室射血分数和短轴缩短率降低，或有附壁血栓等；②病理学检查：心肌组织病理学诊断提示心肌损伤，炎症细胞浸润，心肌细胞肥大、变形、间质纤维化等；③其他：(1)心脏磁共振：提示左心室腔扩大、室壁变薄及运动功能减低伴室间隔壁间强化。(2)胸部 X 线检查：提示心影扩大，心胸比 > 0.5。(3)心电图：提示心律失常(期前收缩、心房颤动、传导阻滞及室性心动过速等)，或 ST-T 改变、低电压、R 波递增不良，少数可见病理性 Q 波。(4)心脏放射性核素扫描：核素血池扫描可见舒张末期和收缩末期左心室容积增大、左心室射血分数降低 ① Echocardiography: indicated that the heart was enlarged, or combined with mitral and tricuspid regurgitation and pulmonary hypertension, left ventricular wall motion was weakened, ventricular wall was thinner, left ventricular systolic function was decreased, left ventricular ejection fraction and short axis shortening rate were decreased, or mural thrombosis was present, etc. ② Pathological examination: myocardial histopathological diagnosis suggests myocardial injury, inflammatory cell infiltration, cardiomyocyte hypertrophy, deformation, interstitial fibrosis, etc. ③ Others: (1) Cardiac magnetic resonance: indicated left ventricular cavity enlargement, ventricular wall thinning, and reduced motor function with interventricular septal strengthening. (2) Chest X-ray examination: indicating enlargement of the heart shadow, cardiothoracic ratio > 0.5. (3) Electrocardiogram: indicates arrhythmia (premature contraction, atrial fibrillation, conduction block and ventricular tachycardia, etc.), or ST-T changes, low voltage, poor R-wave increase, and a few pathological Q waves. (4) Cardiac radionuclide scanning: nuclide blood pool scanning showed increased left ventricular volume and decreased left ventricular ejection fraction in end-diastolic and end-systolic periods
直接相关指标 Directly related indicators	实验室检查 Laboratory examination	①遗传标记物；②免疫标记物；③心肌酶谱、炎症因子 ①Genetic marker. ②Immune marker. ③Myocardial enzyme profile, inflammatory factors
间接相关指标 Indirectly related indicators	临床表现 Clinical manifestation	①症状：疲劳、乏力、心悸、活动时呼吸困难、活动耐量下降，夜间阵发性呼吸困难、端坐呼吸，食欲下降、水肿等；②体征：心界向左下及双侧扩大，第一心音低钝，可闻及第三心音或第四心音奔马律，或双肺底湿啰音、颈静脉怒张、腹水、肝大等 ① Symptoms: fatigue, weakness, palpitations, dyspnea during activity, decreased activity tolerance, paroxysmal dyspnea at night, upright breathing, decreased appetite, edema, etc. ② Signs: the heart boundary is enlarged to the left lower and bilateral, the first heart sound is low and blunt, and the third or fourth heart sound can be heard, or the wet rales of the bottom of the lungs, the jugular vein irritation, ascites, liver enlargement, etc

表 3 药物诱导、免疫诱导、病毒感染与快速起搏诱导 DCM 动物模型与中西医临床病证吻合度

Table 3 Animal models of DCM induced by drugs, immunity, viral infection and rapid-pacing and the consistency with clinical diseases of traditional Chinese and Western medicine

模型方式 Moulding methods	实验动物 Animal species	造模方法 Specific methods	造模周期 Molding cycle	临床病证吻合度 Clinical disease coincidence
阿霉素诱导 Doxorubicin induced	Wistar 大鼠 Wistar rat	腹腔注射浓度 1 mg/mL 阿霉素溶液 2.5 mg/kg,1 次/周,累积剂量 15 mg/kg[37] Rats were injected intraperitoneally with a Dox solution at a concentration of 1 mg/mL at one week 2.5 mg/kg for a total dose of 15 mg/kg[37]	6 周 6 weeks	符合西医核心指标①②和间接相关指标①,吻合度 45%;符合中医主症①②,吻合度 30% In line with the core indicators ①②, indirectly related indicators ① of Western medicine, the coincidence rate was 45%; In line with the primary symptoms ①② of TCM, the coincidence rate was 30%
	SD 大鼠 SD rat	腹腔注射阿霉素溶液 1 mg/kg,2 次/周[38] Rats were injected intraperitoneally with Dox solution twice a week at 1 mg/kg[38]	6 周 6 weeks	符合西医核心指标①②③,直接相关指标①③和间接相关指标①②,吻合度 90%;符合中医主症①②④和次症①②③,吻合度 75% In line with the core indicators ①②③, directly related indicators ①③ and indirectly related indicators ①② of Western medicine, the coincidence rate was 90%; In line with the primary symptoms ①②④ and secondary symptoms ①②③ of TCM, the coincidence rate was 75%
	BALB/c 小鼠 BALB/c mice	腹腔注射阿霉素溶液,3 次/周,累积剂量 15 mg/kg[39] Mice were injected intraperitoneally with Dox solution three times a week for a total dose of 15 mg/kg[39]	2 周 2 weeks	符合西医核心指标①②,直接相关指标③和间接相关指标①,吻合度 55%;符合中医主症①②,吻合度 30% In line with the core indicators ①②, directly related indicators ③ and indirectly related indicators ① of Western medicine, the coincidence rate was 55%; In line with the primary symptoms ①② of TCM, the coincidence rate was 30%
	C57BL/6J 小鼠 C57BL/6J mice	尾静脉注射浓度 1 mg/mL 阿霉素溶液 5 mg/kg,1 次/周,累积剂量 15 mg/kg[40] Mice were injected in the tail vein with a Dox solution at a concentration of 1 mg/mL once a week for a total dose of 15 mg/kg[40]	3 周 3 weeks	符合西医核心指标①②,直接相关指标①③和间接相关指标①,吻合度 65%;符合中医主症①②,吻合度 30% In line with the core indicators ①②, directly related indicators ①③ and indirectly related indicators ① of Western medicine, the coincidence rate was 65%; In line with the primary symptoms ①② of TCM, the coincidence rate was 30%
	新西兰兔 New Zealand rabbit	耳缘静脉注射浓度 1 mg/mL 阿霉素溶液 1 mg/kg,2 次/周[41] New Zealand rabbits were injected intravenously at the ear margin with Dox solution at a concentration of 1 mg/mL twice a week at 1 mg/kg[41]	8 周 8 weeks	符合西医核心指标①②,直接相关指标①③和间接相关指标①②,吻合度 70%;符合中医主症①②③④和次症①③,吻合度 80% In line with the core indicators ①②, directly related indicators ①③ and indirectly related indicators ①② of Western medicine, the coincidence rate was 70%; In line with the primary symptoms ①②③④ and secondary symptoms ①③ of TCM, the coincidence rate was 80%
	比格犬 Beagle	左主干注射阿霉素溶液 0.7 mg/kg,1 次/周[42] Beagles were injected weekly into the left main coronary artery with Dox solution at 0.7 mg/kg[42]	5 周 5 weeks	符合西医核心指标①②,直接相关指标③和间接相关指标①,吻合度 55%;符合中医主症①②,吻合度 30% In line with the core indicators ①②, directly related indicators ③ and indirectly related indicators ① of Western medicine, the coincidence rate was 55%; In line with the primary symptoms ①② of TCM, the coincidence rate was 30%
柔红霉素诱导 Daunorubicin induced	新西兰兔 New Zealand rabbit	耳缘静脉注射浓度 4 mg/mL 柔红霉素,每周 4 mg/kg[43] Daunorubicin at a concentration of 4 mg/mL was administered intravenously at the ear margin at 4 mg/kg per week[43]	6 周 6 weeks	符合西医核心指标②和间接相关指标①,吻合度 25%;符合中医主症符合中医主症①②,吻合度 30% In line with the core indicators ②, indirectly related indicators ① of Western medicine, the coincidence rate was 25%; In line with the primary symptoms ①② of TCM, the coincidence rate was 30%
呋喃唑酮诱导 Furazolidone induced	Wistar 大鼠 Wistar rat	自主饮用 70%呋喃唑酮水溶液[44] Self-administered 70% furazolidone aqueous solution[44]	10 周 10 weeks	符合西医核心指标①②,直接相关指标①和间接相关指标①,吻合度 55%;符合中医主症①②,吻合度 30% In line with the core indicators ①②, directly related indicators ① and indirectly related indicators ① of Western medicine, the coincidence rate was 55%; In line with the primary symptoms ①② of TCM, the coincidence rate was 30%

续表 3

模型方式 Moulding methods	实验动物 Animal species	造模方法 Specific methods	造模周期 Molding cycle	临床病证吻合度 Clinical disease coincidence
	SD 大鼠 SD rat	自主饮用 70%呋喃唑酮水溶液[45] Self-administered 70% furazolidone aqueous solution[45]	10 周 10 weeks	符合西医核心指标①②,直接相关指标③和间接相关指标①,吻合度 55%;符合中医主症①②,吻合度 30% In line with the core indicators ① ②, directly related indicators ③ and indirectly related indicators ① of Western medicine, the coincidence rate was 55%; In line with the primary symptoms ① ② of TCM, the coincidence rate was 30%
免疫诱导 Immunological induced	BALB/c 小鼠 BALB/c mice	第 0 天和第 7 天皮下注射浓度 2 mg/mL 猪心肌肌球蛋白乳化液,累积剂量 0.2 mg[46] Mice were subcutaneously injected with porcine myocardial myocardin emulsion at a concentration of 2 mg/mL at day 0 and day 7 for a total dose of 0.2 mg[46]	8 周 8 weeks	符合西医核心指标①②和间接相关指标①,吻合度 45%;符合中医主症①②,吻合度 30% In line with the core indicators ① ②, indirectly related indicators ① of Western medicine, the coincidence rate was 45%; In line with the primary symptoms ①② of TCM, the coincidence rate was 30%
	Lewis 大鼠 Lewis rat	第 0 天和第 7 天皮下注射浓度 5 mg/mL 猪心肌肌球蛋白乳化液[47] Rats were subcutaneously injected with porcine myocardial myocardin emulsion at a concentration of 5 mg/mL at day 0 and day 7[47]	4 周 4 weeks	符合西医核心指标①②,直接相关指标①和间接相关指标①,吻合度 55%;符合中医主症①②,吻合度 30% In line with the core indicators ① ②, directly related indicators ① and indirectly related indicators ① of Western medicine, the coincidence rate was 90%; In line with the primary symptoms ① ② of TCM, the coincidence rate was 30%
病毒感染 Viral infections	BALB/c 小鼠 BALB/c mice	腹腔注射柯萨奇病毒 B3 型(CVB3),每月每次 100 L[48] Intraperitoneal injection of CVB3 at 100 L per month[48]	24 周 24 weeks	符合西医核心指标②,直接相关指标①和间接相关指标①,吻合度 35%;符合中医主症①②,吻合度 30% In line with the core indicators ②, directly related indicators ① and indirectly related indicators ① of Western medicine, the coincidence rate was 35%; In line with the primary symptoms ① ② of TCM, the coincidence rate was 30%
	杂种犬 Canine	希氏束消融制备Ⅲ度房室传导阻滞模型后植入永久起搏器,快速心室起搏,起搏频率每分钟 250 次[49] After the complete atrioventricular block model was prepared by radio frequency catheter ablation to His bundle, a permanent pacemaker was implanted and rapid ventricular pacing was performed at a pacing rate of 250 bpm[49]	3 周 3 weeks	符合西医核心指标①②和间接相关指标①②,吻合度 50%;符合中医主症①②④和次症①②③,吻合度 75% In line with the core indicators ① ②, indirectly related indicators ①② of Western medicine, the coincidence rate was 50%; In line with the primary symptoms ①②④ and secondary symptoms ①②③ of TCM, the coincidence rate was 75%
快速起搏诱导 Rapid pacing induced	约克夏猪 Yorkshire pig	快速心房起搏,起搏频率每分钟 240 次[50] Rapid atrial pacing was performed at a pacing rate of 240 bpm[50]	3 周 3 weeks	符合西医核心指标①和间接相关指标①,吻合度 25%;符合中医主症①②,吻合度 30% In line with the core indicators ①, indirectly related indicators ① of Western medicine, the coincidence rate was 25%; In line with the primary symptoms ①② of TCM, the coincidence rate was 25%
	绵羊 Sheep	快速心室起搏,起搏频率每分钟 230 次[51] Rapid ventricular pacing was performed at a pacing rate of 230 bpm[51]	(2 ± 1)周 (2 ± 1) weeks	符合西医核心指标①②和间接相关指标①,吻合度 45%;符合中医主症①②,吻合度 30% In line with the core indicators ① ②, indirectly related indicators ① of Western medicine, the coincidence rate was 45%; In line with the primary symptoms ①② of TCM, the coincidence rate was 30%

4　讨论

现代医学对 DCM 的治疗研究取得了一定成果,目前治疗原则主要包括改善心肌损害、控制心衰和心律失常、预防猝死和栓塞以及提高患者生活质量及生存率等[24]。虽 DCM 发病率较低,但由于 DCM 病因复杂多样,机制尚未被完全阐明,现有干预措施对患者的预后改善有限,10 年存活率甚至不足 25%,给患者的生活和经济带来严峻考验[52]。因此,探索 DCM 的内在机制和潜在治疗靶点是亟需解

决的重点问题。动物模型在疾病发病机制解析、预防、药物筛选与治疗评价、诊断标志物的发现等方面有巨大贡献,是生物医学的基础和重要组成部分[11]。模型临床吻合度是评估模型与临床模拟效果一致性的重要方法,对确立成熟、理想的 DCM 动物模型,以及对未来 DCM 的深入研究具有重要意义。

本研究通过梳理文献,依据动物模型评价新方法[11],总结现有 DCM 动物模型构建特征,并评价模型中西医临床吻合度。研究结果表明,啮齿类动物是构建 DCM 模型最主要的实验动物,以小鼠和大鼠最为常见。文献显示[36],小鼠与人的基因同源性高达 90%,具有环境适应性强、饲养成本低、繁殖周期短、可遗传操纵等诸多优势,是人类心血管研究中应用最为普遍的动物模型,其中最常见的小鼠品种是 C57BL/6J 小鼠和 BALB/c 小鼠,均属遗传背景稳定的近交系小鼠;大鼠作为疾病动物模型在人类心血管研究中的应用仅次于小鼠,目前 Wistar 大鼠、SD 大鼠、Lewis 大鼠等品种已被成功用于构建 DCM 模型。斑马鱼模型也被广泛应用于人类心脏研究。斑马鱼基因组包含大量 DCM 变异体的同源基因,与人类基因同源性高,且主要细胞类型和信号通路高度保守,具有饲养成本低、发育周期短、繁殖能力强等优势。果蝇的遗传背景简单、基因编辑技术成熟、具有开放的循环系统,在 DCM 研究中具有独特优势。此外,兔、犬、羊、猴和猪等中、大型动物亦可用于 DCM 等心血管疾病的研究,其电生理状态、解剖结构与人类更为接近。然而,由于存在成本高、技术复杂、操作难度大、重复性较差等局限性,中、大型动物在 DCM 的研究中应用相对较少。

DCM 造模方法主要包括基因编辑、药物诱导、免疫诱导、病毒感染、快速起搏诱导等。其中,基因编辑是最常用的 DCM 造模方法,因其在 DCM 病因、发病机制、疾病发展等进程中与人 DCM 相似,故能够构建出较为理想的 DCM 动物模型。基因编辑涉及的修复途径主要为 CRISPR-Cas9 系统、Cre-LoxP 重组酶系统及 TALEN 核酸酶系统,实验动物主要包括小鼠、大鼠、斑马鱼、果蝇、猪等[36],目前已构建 *LMNA*[53]、*NEXN*[54]、*TBX*5[55] 基因敲入小鼠模型,*SORBS2*[56]、*JARID2*[57]、*FLNC*[58]、*BAG*3[59]、*NEXN*[60]、*SRF*[61]、*ORAI*1[62]、*ORAI*3[63]、*CAP*2[64]、*NMRK*2[65] 基因敲除小鼠模型,*BAG*3[66]、*FLNC*[67] 基因敲低和 *NEXN* 基因敲除[68] 斑马鱼模型,*STIM* 和 *ORAI* 基因敲低果蝇模型[69] 以及 *RBM*20 基因突变猪模型[70] 等。药物诱导、免疫诱导与病毒感染动物模型实验动物以小鼠和大鼠为主,快速起搏诱导法多适于犬、猪和羊等大型动物。研究结果显示,以阿霉素诱导制备 DCM 动物模型最为常见,造模周期 2 ~ 8 周,此模型成本低、操作简单、稳定性强、成模率高、重复性强,其中以 SD 大鼠 DCM 动物模型的中西医临床吻合度最高。阿霉素属蒽环类药物,能激活氧化应激,促进心肌细胞凋亡、结缔组织增生,导致心肌纤维化,具有不可逆的心脏毒性[71-73]。阿霉素诱导的心脏毒性主要分为急、慢性 2 种,单次、大剂量阿霉素用于建立急性心脏毒性模型,虽成模周期短,但动物死亡率相对高[74];慢性心脏毒性模型建立则是通过小剂量、重复多次给药直至累积剂量,具有成模率高、稳定性好、重复性强等优势[75]。同时,研究表明,阿霉素具有多器官毒性,不同累积量会导致成模率和死亡率有较大差异,阿霉素低于 10 mg/kg 时不易成模,超过 20 mg/kg 则死亡率显著升高,实验剂量需进行严格把控[76]。尾静脉注射方式可有效避免腹腔黏连、腹膜炎、血性腹水等后果,且药物吸收率高,相比腹腔注射能更好地模拟临床给药方式。此外,呋喃唑酮可抑制儿茶酚胺清除,显著升高交感活性,导致心肌细胞极度兴奋、变性、坏死,具有强烈的心脏毒性;免疫诱导则是通过外源性抗原诱发自身免疫反应,介导心肌损伤;萨奇病毒 B3 型反复感染能够诱发代谢紊乱、炎症反应和免疫反应,进而造成心肌损伤;快速起搏诱导是通过持续性心动过速导致心肌细胞收缩功能和储备能力降低、心肌血流减少、超微结构破坏及心肌细胞凋亡,最终致使心脏重构[1,36]。

DCM 中医辨证分型标准尚未确立,本研究通过文献总结得到心肺气虚证、气阴两亏证、心肾阳虚证、气虚血瘀证、阳虚水泛证、痰饮阻肺证、阴竭阳脱证 7 种证型,依据动物模型评价新方法[11],提取主症和次症,评价模型中医临床吻合度。中医吻合度较高的模型有阿霉素诱导新西兰兔模型、快速起搏诱导杂种犬模型、阿霉素诱导 SD 大鼠模型;西医吻合度较高的造模方法有阿霉素诱导 SD 大鼠、阿霉素诱导新西兰兔、阿霉素诱导 BALB/c 小鼠、阿霉素诱导比格犬、呋喃唑酮诱导 SD 大鼠、免疫诱导 Lewis 大鼠等。然而,DCM 动物模型与中医诊断标准吻合度整体水平偏低,溯源发现,目前同一类型 DCM 动物模型所选实验动物、实验用药及其单次或

累积剂量、给药方式、造模周期等均有差异,尚无统一规范,一定程度上影响了各类模型临床吻合度的一致性。目前,DCM 动物模型成模标准多以西医理论为基础,而中医证候模型辨证标准及四诊信息采集标准尚未规范统一,不同文献记录的表征信息缺乏中医特色及特异性,导致 DCM 动物模型中西医临床吻合度水平参差不齐,同一模型中医临床吻合度普遍较低。

综上,DCM 造模方法主要包括基因编辑、药物诱导、免疫诱导、病毒感染、快速起搏诱导等,实验动物以小鼠和大鼠为主。基因编辑是最常用的 DCM 造模方法,其次是阿霉素诱导造模。值得注意的是,同种 DCM 动物模型造模方法未达统一,中西医临床吻合度水平参差不齐,中医临床吻合度整体偏低,提示造模过程中在注重西医病理机制和临床特征的同时,应兼顾中医病因病机、中医表观特征观察以及证候相关理化指标等,加强疾病与证候的关联性,优化造模因素和统一操作流程,建立更完善的符合中西医临床特点的 DCM 病证结合模型,规范动物模型评价体系,促进科学探索疾病病理机制和有效拓展治疗策略。

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