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基于中西医临床病证特点的动脉粥样硬化动物模型分析

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【摘要】 对常见动脉粥样硬化(AS)动物模型与中西医临床病证特点进行吻合度分析与评分,为研究 AS 疾病选择的动物模型提供参考。对常见 AS 动物模型的品种、造模方法、原理、特点进行总结,并根据 AS 中西医临床诊断标准对 15 种常见模型进行吻合度分析。现有 AS 动物模型常用的制备方法有高脂喂养型、机械损伤联合高脂喂养型、基因工程联合高脂喂养型、化学诱导结合高脂喂养型以及病证结合模型。其中,中西医临床吻合度相对较高的是球囊损伤联合高脂喂养型、ApoE$^{-/-}$联合高脂喂养型以及病证结合中的痰瘀互结型。现有的 AS 动物模型大多以西医造模方法为主,评价标准亦以西医诊断指标为主,缺少中西医病证结合的特点,很难揭示中医整体观念、辨证论治的核心。因此,构建准确、高吻合度的中西医病证结合动物模型将是深入研究 AS 机制和防治的重点。

【关键词】 动脉粥样硬化;病证结合;诊断标准;动物模型;吻合度
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Animal model analysis of atherosclerosis based on clinical symptoms in traditional Chinese medicine and Western medicine

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【Abstract】 On the basis of the clinical characteristics of atherosclerosis (AS) in traditional Chinese medicine (TCM) and Western medicine, this paper analyzes common animal models of AS. The coincidence of clinical characteristics of the models was scored in the hope of providing new ideas and a reference for those studying AS. This paper reviews the varieties, modeling method, modeling principles, and characteristics of common animal models of

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AS. Moreover, similarities among common animal models, in terms of their clinical diagnostic criteria and symptom characteristics, were assessed. High-fat feeding type, mechanical injury combined with high-fat feeding type, genetic engineering combined with high-fat feeding type, chemical induction combined with high-fat feeding type, and combined Chinese clinical syndrome and Western disease AS models are widely established. Comparative analysis showed that balloon injury combined with high fat feeding type, ApoE receptor-knockout mouse combined with high-fat diet type, and phlegm and blood stasis type models of disease and symptom combinations showed a comparatively high level of clinical agreement between Chinese and Western medicine. Presently, most animal models of AS have a high degree of relevance to Western medicine, and the evaluation criteria used for the models are predominately from a Western medicine perspective. Models that combine disease and syndrome are lacking, hindering the development of wholism concepts and treatment through the differentiation of syndromes used in TCM. Therefore, establishing an animal model with a high degree of accuracy and coincidence between TCM and Western perspectives that combines the disease and its TCM symptoms is a top priority for studying the prevention and treatment of AS.

【**Keywords**】 atherosclerosis; combination between disease and syndrome; diagnostic criteria; animal models; coincidence degree

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动脉粥样硬化(atherosclerosis,AS)是一种脂类复合物沉积于大、中动脉血管,最终形成粥样斑块,并可诱发血栓形成、斑块破裂及斑块出血等继发改变的慢性疾病,也是心脑血管疾病发生发展的重要病理基础[1-2]。近年来,AS 的全球发病率明显上升,严重威胁人们健康。目前,临床上治疗 AS 主要用调脂药、抗血小板药、溶栓药等药物或动脉支架介入术、血运重建及旁路移植等手术进行干预[3]。但药物治疗存在肝肾功能受损、横纹肌溶解症等多种不良反应,手术治疗存在血管再狭窄、血管内血栓形成、感染等并发症[4]。基于完整的中医理论,AS 以心脉痹阻为主要病机,临床表现为本虚标实、虚实夹杂,总治则为先治其标,后治其本,治标重在活血化瘀,治本重在补益心气,在各个病变时期均灵活辨证、因人而异地开具处方用药,兼具灵活性、实用性与安全性等优点[5]。因此,中西医结合防治 AS 具有重要意义。

动物模型在疾病的防治研究中扮演重要角色。目前,现代医学对 AS 病因病机的认识尚未完全,故此构建贴合临床的中西医病证结合的 AS 动物模型对中西医防治 AS 至关重要。本文基于 AS 中西医临床病证特点,总结目前常见 AS 动物模型的应用情况,比较其中西医临床症状的吻合度,以期为中西医病证结合的 AS 模型改良、动物实验研究以及新药开发提供基础,有利于更全面地认识 AS 本质。

1 动脉粥样硬化的中西医病因病机

1.1 西医病因病机

目前认为,高脂血症、高血压、糖尿病、吸烟等为 AS 的主要危险因素[6]。而 AS 现有的发病机制主要集中于脂质浸润学说、损伤-反应学说、血小板聚集与血栓形成假说及平滑肌细胞克隆学说等[7-8]。在高脂血症、剪切应力等危险因素作用下,血浆低密度脂蛋白因内皮细胞受损进入内膜,并被氧化成氧化低密度脂蛋白(Ox-LDL);同时,大量单核细胞黏附在内膜,并移入内膜成为巨噬细胞,而巨噬细胞在 Ox-LDL 的作用下转变为泡沫细胞形成最早的脂质条纹[8]。活化的巨噬细胞分泌多种生长因子和炎症因子,促进斑块生长、炎症反应[9]。部分血管平滑肌细胞亦可吞噬脂质成为泡沫细胞,部分从中膜迁移至内膜大量增殖,分泌胶原和弹力纤维形成纤维帽[9]。最终,纤维帽包绕脂质条纹形成典型斑块。

1.2 中医病因病机

AS 并无明确统一的中医学病名,但可根据其胸闷胸痛、心悸、气促、眩晕、一过性黑蒙及记忆力减退等临床症状,将其归属于“胸痹”“真心痛”“中风”“眩晕”等范畴[10]。中医认为 AS 与饮食失调、五志所伤、年高体衰、气血亏耗等病因相关[11]。AS 病机可分为虚实两个方面,“虚”为正虚,指气血阴阳亏虚,“实”为邪实,指瘀血、痰浊、湿热等[12]。脏腑功能失调易形成痰浊、血瘀、气滞、热毒,而痰瘀互结,凝结成块,阻滞脉络,最终形成动脉粥样硬化斑块[13]。其中脾胃受损,运化无权,水谷精微变为浊脂,入血则使血脂升高,浊脂累及而成血中之痰浊[14]。脉络瘀闭,则使气血阴阳更虚,脉络受损愈加严重,如此往复,因虚致实,因实致虚,虚实错杂,不断推进斑块形成。

2 动脉粥样硬化诊断标准

2.1 西医诊断标准

西医主要通过观察症状体征、实验室检查及影像学检查等方式,结合患者病史等做出临床诊断。本文参照《动脉粥样硬化中西医防治专家共识(2021)》[15]、2018 年出版的《内科学》[16] 及文献[17-19]的标准,拟定以下 AS 西医诊断标准,参考模型评价新方法[20],认为影像学指标、血清学指标是重点评估内容且可信度高,应作为主要指标,各赋分 40%,其中 CT 血管造影赋分 20%,磁共振显像血管造影和多普勒超声各赋分 10%;血脂指标中 LDL-C 赋分 30%,炎症因子赋分 10%;心电图检查、超声心动图检查、放射性核素心脏检查、负荷试验等检查应作为次要指标,各赋分 4%,共计 100%。见表 1。

2.2 中医诊断标准

中医诊断标椎依据 2017 年中国中医药出版社发行的《中医内科学》[21]、《动脉粥样硬化中西医防治专家共识(2021)》[15] 及文献[22-24]的标准来制定,中医临床诊断动脉粥样硬化具体表现的主症为:①形体变化;②面色/皮色色暗少华;③胸痛胸闷,心悸头晕;④肢体麻木;⑤身困乏力。次症为各证型不同症状,包括:①多痰;②情绪变化;③睡眠状态;④饮食变化;⑤二便变化为各证型不同症状。在判断与中医临床诊断标准吻合度时,符合主症一项赋值 15%,符合次症一项赋值 5%,总分值为 100%。依据中医诊断标准可以将动脉粥样硬化的中医辨证分型分为五类:痰瘀互结证、痰热互结证、气阴两虚证、气滞血瘀证、气虚血瘀证[15]。见表 2。

3 动脉粥样硬化模型分析

3.1 模型动物的选择

目前 AS 动物模型已成功在大鼠、小鼠、家兔、小型猪等动物中复制。其中鼠类和家兔类为 AS 模型常用的研究对象。鼠类因其病变过程与人体类

表 1 动脉粥样硬化西医诊断标准

Table 1 Diagnostic criteria of western medicine for atherosclerosis (AS)

指标 Indicators			临床表现 Clinical features
主要指标(80%) Key indicators (80%)	影像学指标(40%) Imaging indices (40%)		①CT 血管造影(CTA)(20%):血管狭窄性或扩张性病变 ①CT angiography (CTA) (20%): Stenosis or dilatation of blood vessels
			②磁共振显像血管造影(MRA)(10%):血管狭窄性或扩张性病变 ②Magnetic resonance imaging angiography (MRA) (10%): Stenosis or dilatation of blood vessels
			③多普勒超声(10%):血流情况和血管病变 ③Doppler ultrasound (10%): Blood flow and vascular disease
	血清学指标(40%) Serum markers (40%)	血脂指标(30%) Lipid indices (30%)	④低密度脂蛋白胆固醇(LDL-C)增高(15%) ④Increased low-density lipoprotein cholesterol (LDL-C) (15%)
			⑤血清总胆固醇(TC)增高(5%) ⑤Increased serum total cholesterol (TC) (5%)
			⑥甘油三酯(TG)增高(5%) ⑥Increased triglyceride level (5%)
			⑦高密度脂蛋白胆固醇(TG)(HDL-C)降低(5%) ⑦Decreased high-density lipoprotein cholesterol (HDL-C) (5%)
		炎症因子(10%) Inflammatory cytokines (10%)	⑧白细胞介素 6(IL-6)、白细胞介素 1(IL-1)、肿瘤坏死因子(TNF-α)、C 反应蛋白(CRP)等 ⑧Interleukin-6 (IL-6), interleukin-1 (IL-1), tumor necrosis factor receptor-α (TNF-α), C-reactive protein (CRP), et al.
次要指标(20%) Secondary indicators (20%)			①心电图检查 ①Electrocardiogram
			②超声心动图 ②Echocardiographic
			③放射性核素心脏检查 ③Radionuclide cardiac
			④负荷试验 ④Stress test
			⑤血管内超声显像 ⑤Intravascular ultrasound imaging

表 2 动脉粥样硬化中医辨证分型
Table 2 Traditional Chinese medicine syndrome differentiation of AS

辨证分型 Syndrome differentiation	主症 Main syndrome	次症 Secondary syndrome	舌脉 Pulse and tongue
痰瘀互结证 Phlegm turbidity and blood stasis syndrome	①形体肥胖 ①Physical obesity ②面色晦暗 ②Dim complexion ③胸闷、心悸、头晕 ③Oppression in the chest, palpitations, dizziness ④肢体麻木、痿废 ④Numbness and flaccidity of limbs ⑤身困乏力 ⑤Physical fatigue	①多痰 ①Phlegm ②心烦易怒 ②Irritability ③少寐 ③Restlessness at night ④大便干结 ④Constipation ⑤局部肿块、局部刺痛 ⑤Local lump, local tingling	舌紫暗或有斑点,苔腻或少津,脉弦涩或弦滑 Tongue is purple and dark or spotted, the moss is greasy or less fluid, the pulse is stringy and slippery or unsmooth and stringy
痰热互结证 Phlegm-heat accumulation syndrome	①形体肥胖 ①Physical obesity ②面色晦暗 ②Dim complexion ③胸闷胀痛、头晕 ③Chest tightness, pain and dizziness ④肢体麻木、疼痛,间歇性跛行、肢端溃疡、坏疽,甚至趾(指)节脱落等 ④Limb numbness, pain, intermittent claudication, acromegaly ulcer and gangrene or joint shedding ⑤身困乏力 ⑤Physical fatigue	①夜寐鼾声阵作或夜寐不安 ①Snoring at night or restlessness at night ②口干或口臭 ②Dry mouth or fetid mouth odor ③大便干结或黏滞不爽 ③Constipation or sticky ④小便黄或黄浊 ④Yellow urine ⑤烦躁易怒 ⑤Irritability	舌质红、苔黄燥或黄腻,脉滑数;或舌质绛红,苔少,脉细数 Tongue is red, the moss is yellow and greasy or yellow and dry, pulse slip number, tongue is crimson, the moss is less and the pulse is thin
气阴两虚证 Qi and yin deficiency syndrome	①形体消瘦 ①Thin body ②面色少华 ②Bad complexion ③胸痛隐隐、眩晕 ③Chest pain, dizziness ④肢体麻木 ④Limb numbness ⑤神疲乏力 ⑤Mental fatigue	①口干少饮 ①Dry mouth ②大便无力或干结 ②Constipation ③自汗盗汗 ③Spontaneous sweating and night sweats ④失眠多梦 ④Insomnia and dreams ⑤遇劳加重 ⑤Aggravated by exertion	舌质红或淡,苔少,脉细弱 Tongue is red or light red, the moss is less, the pulse is thin
气滞血瘀证 Qi-stagnancy and blood stasis syndrome	①形体消瘦 ①Thin body ②面色紫暗 ②Purple complexion ③局部胀闷,走窜疼痛 ③Local bloating, unfixed pain ④肢体麻木或偏瘫 ④Numbness or hemiplegia of limbs ⑤神疲乏力 ⑤Mental fatigue	①皮肤青筋暴露 ①Exposure of skin blue veins ②情志抑郁 ②Emotional depression ③急躁易怒 ③Impatience and irritability ④刺痛、拒按 ④Stinging, tenderness ⑤肿块坚硬,局部青紫肿胀 ⑤Hard lump, local bruising and swelling	舌质紫暗或见瘀斑,脉涩 Tongue is purple or have ecchymosis, the pulse is stringy

似、价格低廉、饲养成本低、喂养方便、易于繁殖等特性,常被用于 AS 实验研究[25]。其中,小鼠由于体型过小,较难进行临床性检查评估,故常通过基因工程法构建 ApoE$^{-/-}$小鼠和 LDL-R$^{-/-}$小鼠以缩短模型构建周期、提高成功率,多适用于 AS 炎症和免疫因子的作用机制研究;以 SD 大鼠为代表的大鼠对外科手术操作的耐受力强,且其抗感染能力强,故常被用于球囊损伤术、结扎术等手术造模法[26]。家兔对高脂饮食极为敏感,故选择家兔作为研究对象具有复制简单、建模时间短、成功率高、损伤条件可控性好、易于评判的优点,通常适用于疾病预防治疗等研究[27]。然而家兔 AS 病变大多只表现为早期脂质条纹,难以形成稳定的纤维斑块,同时也存在造模周期长、死亡率较高等缺点[28]。目前,用于构建 AS 模型的动物种属各有其优缺点和适用范围,故此,应根据实验目的和条件选择合适的动物模型

作为研究对象。

3.2 动脉粥样硬化动物模型与临床特点的吻合度

AS 模型常用的制备方法有高脂喂养型、结扎型、机械损伤联合高脂喂养型、基因工程联合高脂喂养型、化学诱导联合联合高脂喂养型及病证结合模型。具体造模方法、造模原理、特点、吻合度及应用情况如表 3 所示。

3.3 观测指标

观测 AS 动物模型的指标有如下几类:①表观指标和行为学变化:包括动物精神状态、饮食量、体重等情况;②血清生化指标检测:ELISA 等方法测定 TC、TG、HDL、LDL、ox-LDL、白介素-10(IL-10)等;③病理形态学检查:肉眼观察、HE 染色、油红 O 染色、电镜法等方法检测血管内膜中膜厚度比值、斑块面积等;④影像学指标:小动物超声、彩色多普勒、冠状动脉血管造影等方法观察动脉的外形、走行,管壁的厚度,内膜有无增厚及斑块,管腔有无狭窄闭塞,颈总动脉内血流情况等[24,62-63]。

表 3 常见动脉粥样硬化动物模型与中西医临床病证特点吻合度分析

Table 3 Consistency between common animal model of AS and clinical symptoms in traditional Chinese medicine and western medicine

模型类型 Model type		动物名称 Animal name	造模方法及原理 Preparation method and principle	模型优缺点 Model advantages and disadvantages	与临床病症特点的吻合度 Consistency with clinical disease characteristics
高脂喂养型 High-fat feeding model		新西兰兔 New Zealand rabbit	高脂饲料饲喂 12 周,诱发高脂血症[29-30] Rabbit was fed with HFD for 12 weeks to induce hyperlipidemia[29-30]	优点:操作简单,成本较低,较符合人类饮食的特点,病理改变与人早期相似 缺点:动物成模率较低,造模周期也较长,无法形成稳定的 AS 斑块 Advantages: Simple operation, low price Disadvantages: Difficult surgical, longer mold-making period, failure to form stable plaques	西医(1)符合主要指标:①③④⑤⑥⑦⑧,吻合度 70% 中医(2)符合主症①⑤,吻合度 30% Western medicine primary index: ①③④⑤⑥⑦⑧, 70% match TCM primary evidence: ①⑤, 30% match
结扎型 Ligated model		SD 大鼠 Sprague-Dawley rat	冠状动脉左前降支结扎,阻断血流引起管腔内剪切力改变[31-32] Ligate coronary artery left anterior descending branch to block blood flow and change shear forces in luminal[31-32]	优点:可重复性和可行性高 缺点:需精良的设备,手术操作技术难度大、要求高 Advantages: High repeatability and high feasibility Disadvantages: Sophisticated equipment, difficult and demanding surgical operation	符合西医诊断主要指标:①③⑤⑥⑧;次要指标:①②,吻合度 58% 符合中医诊断主症①②⑤;吻合度 45% Western medicine primary index: ① ③ ⑤ ⑥ ⑧; secondary index: 58% match TCM primary evidence: ①②⑤, 45% match
机械损伤联合高脂喂养型 Mechanical injury combined with high-fat feeding type	球囊损伤型联合高脂喂养型 Balloon injury combined with HFD model	新西兰大白兔 New Zealand rabbit	右髂动脉球囊损伤术联合高脂饲料饲养 12 周,高脂血症的基础上损伤内膜[33] Rabbits underwent right iliac artery balloon injury combined with HFD for 12 weeks[33]	优点:造模周期短,成功率高,血流变及凝血指标有明显改变 Advantages: Longer mold-making period, high success rate, significantly change of blood flow change and coagulation indexes	符合西医诊断主要指标:①③④⑤⑥⑦⑧;次要指标:⑤,吻合度 75% 符合中医诊断主症:①②⑤,吻合度 45% Western medicine primary index: ①③④⑤⑥⑦; secondary index, 75% match TCM primary evidence: ①②⑤, 45% match
		SD 大鼠 Sprague-Dawley rat	主动脉球囊损伤联合高脂饮食饲喂 6 周[34] Rats underwent aorta balloon injury technique combined with HFD for 6 weeks[34]		
		中国实验小型猪 China experimental miniature pig	冠状动脉血管内皮损伤联合高脂饮食饲喂 8 周[35] Pigs underwent coronary vascular endothelial injury combined with HFD for 8 weeks[35]		
		西藏小型猪 Tibet mini-pig	饲喂高脂饲料 2 周,行颈外动脉穿刺术造成左侧颈总动脉球囊损伤[36] Pigs underwent left common carotid artery balloon combined with HFD for 2 weeks[36]		

续表3

模型类型 Model type		动物名称 Animal name	造模方法及原理 Preparation method and principle	模型优缺点 Model advantages and disadvantages	与临床病症特点的吻合度 Consistency with clinical disease characteristics
基因敲除联合高脂喂养型 Genetic engineering combined with high-fat feeding type	气体干燥型联合高脂喂养模型 Airdrying combined with HFD model	日本大耳白兔 Japanese white rabbit	干燥气体联合高脂饲料喂养 8 周,损伤内膜激活组织型纤溶酶原激活剂、前列环素[37] Rabbts were underwent airdrying methods combined with HFD for 8 weeks, to damage inner membrane activates tissue plasminogen activator, prostacyclin[37]	优点:造模时间短,重复性好,操作简便 缺点:不稳定 Advantages: Shorter mold-making period, high repeatability and simple operation Disadvantages: Instability	符合西医诊断主要指标:①③④⑤⑥⑦,吻合度 60% 符合中医诊断主症:②,吻合度 30% Western medicine primary index: ①③④⑤⑥⑦, 60% match TCM primary evidence: ②, 30% match
	ApoE 基因敲除型联合高脂喂养模型 ApoE receptor knockout mouse combined with HFD model	$ApoE^{-/-}$ 小鼠 $ApoE^{-/-}$ mice	高脂饲料饲喂 12 周,$ApoE^{-/-}$ 小鼠清除血浆脂蛋白的能力严重受损,血浆胆固醇水平升高[38-42] Mice were fed with HFD for 12 weeks, and $ApoE^{-/-}$ mice have a severely impaired ability to clear plasma lipoproteins, with elevated plasma cholesterol levels[38-42]	优点:AS 模型成功概率高 缺点:脂质代谢与人体不同,体型小、可获得的血液样本少,形成的 AS 病变不具有厚纤维帽 Advantages: High success rate Disadvantages: Different lipid metabolism, small size, few available blood samples and lack of fiber cap	符合西医诊断主要指标:①③④⑤⑥⑦⑧,吻合度 70% 符合中医诊断主症:①②⑤;次症:④,吻合度 50% Western medicine primary index: ①③④⑤⑥⑦⑧, 70% match TCM primary evidence: ①②⑤; secondary evidence: ④, 50% match
	LDL-R 基因敲除型联合高脂喂养模型 LDL receptor knockout mouse combined with HFD model	$LDL\text{-}R^{-/-}$ 小鼠 $LDL\text{-}R^{-/-}$ mice	高脂饲料喂养 12 周,$LDL\text{-}R^{-/-}$ 小鼠血浆中脂蛋白增多,血胆固醇水平升高[43-44] $LDL\text{-}R^{-/-}$ mice were fed with HFD for 12 weeks, with increased lipoprotein in plasma and increased blood cholesterol levels[43-44]	优点:在脂代谢实验研究中更稳定 缺点:造模成功率相对较低,病变进展需要饲料调控,形成的 AS 病变不具有厚纤维帽 Advantages: More stable in the experimental studies of lipid metabolism Disadvantages: Low success rate, feed regulation requirement and lack of fiber cap	符合西医诊断主要指标:①③④⑤⑥⑦⑧,吻合度 70% Western medicine primary index: ①③④⑤⑥⑦⑧, 70% match
	$ApoE^{-/-}$ 与 $LDL\text{-}R^{-/-}$ 双敲除模型 ApoE receptor and LDL receptor knockout mouse combined with HFD model	双纯合 $ApoE^{-/-}$ 和 $LDL\text{-}R^{-/-}$ 小鼠 $ApoE^{-/-}$ $LDL\text{-}R^{-/-}$ mice	高脂饮食喂养 22 周,ApoE 和 LDL-R 双敲除使其清除血浆脂蛋白的能力严重受损,脂蛋白增多加速[45-46] $ApoE^{-/-}$ $LDL\text{-}R^{-/-}$ mice were fed with HFD for 22 weeks, and mice have a severely impaired ability to clear plasma lipoproteins and the lipoproteins were accelerated[45-46]	优点:AS 的严重程度增加,能自发性形成斑块破裂和心肌梗死 缺点:易发生严重管腔闭塞,导致过早死亡 Advantages: Increases severity, spontaneous formation plaque rupture and myocardial infarction Disadvantages: Prone to severe lumen occlusion and premature death	符合西医诊断主要指标:①③④⑤⑧,吻合度 60% Western medicine primary index: ①③④⑤⑧, 60% match
	AAV-PCSK9 联合高脂喂养模型 AAV-PCSK9 mouse combined with HFD model	AAV-PCSK9 小鼠 AAV-PCSK9 mice	高脂饲料喂养+尾静脉注射 $AAV\text{-}PCSK9^{DY}$ 3 个月,增强肝 LDL 受体的降解[47] Mice were injected with $AAV\text{-}PCSK9^{DY}$ and fed with Western diet for 3 months, to enhancet the degradation of the hepatic LDL receptor[47]	优点:不依赖转基因动物,造模迅速 缺点:病变进展需要饲料调控;缺乏复杂病变的证据 Advantages: Do not rely on transgenic animals, shorter mold-making period Disadvantages: Feed regulation requirement, lack of evidence of complex lesions	符合西医诊断主要指标:①③⑤⑥⑧,吻合度 50% Western medicine primary index: ①③⑤⑥⑧, 50% match
	维生素 D3 联合高脂喂养联合模型 Fed with HFD combined with vitamin D3 solution intraperitoneal injection model	Wistar 大鼠或 SD 大鼠 Wistar rats or Sprague-Dawley rat	高脂饲料喂养,同时在前 3 d 腹腔注射维生素 D3 溶液(6×10^5 U/kg),加速斑块内钙沉积,稳定斑块[48-49] Rat were fed with HFD combined with vitamin D3 solution intraperitoneal injection (6×10^5 U/kg), accelerating calcium deposition in the plaque and stabilizing the plaque[48-49]	优点:经济,省时省力,病变过程较稳定,易形成后期粥样斑块、钙沉积病变 缺点:维生素 D 剂量难以把握 Advantages: Low price, timesaving, stable lesion process, easy to form later plaque and calcium deposition lesions Disadvantages: Unpredictable dose	符合西医诊断主要指标:①③④⑤⑥⑦⑧,吻合度 70% 符合中医诊断主症:②,吻合度 15% Western medicine primary index: ①③④⑤⑥⑦⑧, 70% match TCM primary evidence: ②, 15% match

续表3

模型类型 Model type		动物名称 Animal name	造模方法及原理 Preparation method and principle	模型优缺点 Model advantages and disadvantages	与临床病症特点的吻合度 Consistency with clinical disease characteristics
化学诱导联合高脂喂养型 Chemical induction combined with high-fat feeding model	静脉注射脂多糖联合高脂喂养模型 Intravenous treatment with lipopolysaccharide combined with HFD model model	新西兰白兔 New Zealand rabbit	高脂饲料喂养,每周 1 次耳缘静脉注射不同剂量 LPS(100、200、1000、2000 ng/kg),持续 8 周,引起严重全身炎症反应,损伤内皮细胞[50] Rabbits were fed with HFD and different doses of LPS (100、200、1000、2000 ng/kg) were injected once a week for 8 weeks, to cause a severe systemic inflammatory response and damage the endothelial cells[50]	优点:适合 AS 中炎症信号通路的研究 缺点:注射后易引起兔的感染性休克甚至死亡 Advantages: Suitable for studying the inflammatory signaling pathways in AS Disadvantages: Easily cause of septic shock and death	符合西医诊断主要指标:①③④⑤⑥⑦⑧,吻合度 70% 符合中医诊断主症:①,吻合度 15% Western medicine primary index: ①③④⑤⑥⑦⑧, 70% match TCM primary evidence: ①, 15% match
	静脉注射牛血清白蛋白法联合高脂喂养模型 Intravenous treatment with bovine serum album combined with HFD model model	日本大耳白兔 Japanese white rabbit	耳缘静脉注射牛血清白蛋白(250 mg/kg),皮下注射卵清白蛋白(2.5 mg/kg),诱导免疫反应,联合高脂饲料饲喂 8 周[51-52] Bovine serum albumin (250 mg/kg) was injected at the ear margin and ovalbumin (2.5 mg/kg) was injected subcutaneously to induce immune response combined with HFD for 8 weeks[51-52]	优点:时间短、成活率高、模型稳定、可控性好 缺点:单纯免疫损伤造模周期长,常联合高脂喂养 Advantages: Shorter mold-making period, high success rate, stable models and well controllable Disadvantages: Longer mold-making period	符合西医诊断主要指标:③④⑤⑥⑦⑧,吻合度 50% 符合中医诊断主症:①,吻合度 15% Western medicine primary index: ③④⑤⑥⑦⑧, 50% match TCM primary evidence: ①, 15% match
	痰淤互结证 AS 模型 Phlegm and blood stasis syndrome AS model	中国实验小型猪 China experimental miniature pig	高脂饲料喂养 2 周,用介入法行冠状动脉血管内皮损伤,诱导脾失健运,聚湿生痰,血液黏度增加,瘀血阻络[35] Fed with HFD for 2 weeks, pigs underwent coronary vascular endothelial injury, to induce the dysfunction of spleen in transportation, the accumulation of dampness and phlegm stasis and blood stasis[35]	优点:模型符合传统中医病因病机理论,成模率高,对中西医临床特点均有较好的表现力 Advantages: Accordance with the theory of etiology and pathogenesis of TCM, high success rate, good performance on the clinical characteristics of traditional Chinese and Western medicine	符合西医诊断主要指标:①③④⑤⑥⑦⑧,吻合度 70% 符合中医诊断主症:①③⑤,次症:①④,吻合度 55% Western medicine primary index: ①③④⑤⑥⑦⑧, 70% match TCM primary evidence: ①③⑤, secondary evidence: ①④, 55% match
	肝郁证 AS 模型 Liver depression syndrome AS model	ApoE$^{-/-}$小鼠 ApoE$^{-/-}$ mice	CUMS 方法:孤立后群居 6 h、湿润环境 6 h、快速灯光交换加白噪音 2 h、倾斜鼠笼 6 h、整晚照明 12 h、夹尾 15 min、禁水 24 h、禁食 24 h,8 种方法随机安排,模拟肝郁证,肝失条达则气滞血瘀[53] CUMS method: Live in groups after isolation for 6 h, live in wet environment for 6 h, rapid light exchange and white noise for 2 h, tilted rat cage for 1 h, lighting all night for 12 h, tail clipped for 15 min, water prohibition for 24 h, fasting for 24 h, 8 methods were randomly arranged to simulate liver depression syndrome, and loss of liver function causes Qi stagnation and blood stasis[53]	优点:成模率高,对中西医临床特点均有较好的表现力 缺点:造模过程较为复杂 Advantages: High success rate, good performance on the clinical characteristics of traditional Chinese and Western medicine Disadvantages: Complicated method	符合西医诊断主要指标:①③④⑤⑥⑦⑧,吻合度 70% 符合中医诊断主症:①②⑤;次症:②⑤,吻合度 55% Western medicine primary index: ①③④⑤⑥⑦⑧, 70% match TCM primary evidence: ①②⑤; secondary evidence: ②⑤, 55% match
	脾虚痰浊证 AS 模型 Spleen deficiency and phlegm syndromes AS model	ApoE$^{-/-}$小鼠 ApoE$^{-/-}$ mice	高脂饲料喂养 12 周,过食肥甘,脾失健运,聚湿生痰[54] Mice were fed with HFD for 12 weeks, excessive HFD caused dysfunction of spleen in transportation, the accumulation of dampness and phlegm stasis[54]	优点:模型易复制,对中西医临床特点均有较好的表现力 Advantages: High repeatability, good performance on the clinical characteristics of TCM and Western medicine	符合西医诊断主要指标:③④⑤⑥⑦⑧,吻合度 50% 符合中医诊断主症:①②⑤;次症:⑤,吻合度 50% Western medicine primary index: ③④⑤⑥⑦⑧, 50% match TCM primary evidence: ①②⑤; secondary evidence: ⑤, 50% match

续表3

模型类型 Model type		动物名称 Animal name	造模方法及原理 Preparation method and principle	模型优缺点 Model advantages and disadvantages	与临床病症特点的吻合度 Consistency with clinical disease characteristics
病证结合型 Models of AS combining Chinese clinical syndrome and western disease	气滞血瘀证 AS 模型 Qi stagnation and blood stasis syndrome AS model	Wistar 大鼠 Wistar rats	脂肪乳灌胃 3 周后,尾静脉注射小牛血清蛋白 468.75 mg/kg,冰水中 20 min,寒凝血脉,瘀滞脉道,造模 8 周[55] After 3 weeks of fat milk gavage, calf serum protein 468.75 mg/kg was injected into the tail vein, in ice water for 20 min, lasting 8 weeks, which caused cold pathogen obstruction[55]	优点:模型符合传统中医病因病机理论 Advantages: Accordance with the theory of etiology and pathogenesis of TCM	符合西医诊断主要指标:③④⑤⑥⑦,吻合度 40% 符合中医诊断主症:①②⑤;次症:④,吻合度 50% Western medicine primary index: ③④⑤⑥⑦, 40% match TCM primary evidence: ①②⑤; secondary evidence: ④, 50% match
	痰湿血瘀毒损证 AS 模型 Phlegm-dampness and blood stasis syndrome AS model	$ApoE^{-/-}$ 小鼠 $ApoE^{-/-}$ mice	高脂饲料喂养 14 周,肥甘厚味,伤及脾胃,脾失健运,而致痰湿内阻,气机不畅,血瘀内停,日久郁热成毒[56] Mice were fed with HFD for 14 weeks, which caused dysfunction of spleen in transportation, the accumulation of dampness and phlegm stasis, as well as Qi stagnation, blood stasis and noxious heat	优点:模型较符合传统中医病因病机理论 Advantages: Accordance with the theory of etiology and pathogenesis of TCM	符合西医诊断主要指标:①②④⑤⑥⑦,吻合度 70% 符合中医诊断主症:②⑤;次症:②③④⑤,吻合度 50% Western medicine primary index: ①②④⑤⑥⑦ secondary index: 70% match TCM primary evidence: ②⑤; secondary evidence: ②③④⑤, 50% match
	秽浊痰阻证 AS 模型 Obscene phlegm obstruction evidence syndrome AS model	$ApoE^{-/-}$ 小鼠 $ApoE^{-/-}$ mice	干寒环境和高脂饲料同时联合干预,肥甘生痰,津伤炼痰,寒凝血脉,则血运不畅[57] Mice were intervened by dry-cold environment and HFD, which can cause phlegm and stagnation of blood[57]	优点:内外环境、饮食等诸多因素联合诱导模型 Advantages: Combination internal and external environment with diet	符合西医诊断主要指标:①②④⑤⑥⑦⑧,吻合度 70% 符合中医诊断主症:②⑤;次症:②③④⑤,吻合度 50% Western medicine primary index: ①②④⑤⑥⑦⑧, 70% match TCM primary evidence: ②⑤, secondary evidence: ②③④⑤, 50% match
	湿热证 AS 模型 Damp-heat syndrome AS model	SD 大鼠 Sprague-Dawley rat	高脂高糖饲料喂养+维生素 D3+LPS 内毒素,共 6 周,模拟外感湿热邪毒,内伤饮食肥甘[58] Rats were fed with HFD, and damp-heat syndrome was induced by intraperitoneal injection of vitamin D3 + tail vein injection of LPS endotoxin for 6 weeks, imitating exogenous damp-heat and pathogenic poison and affected by improper diet[58]	优点:以脾为中心,内外合邪,病机上符合中医理论 Advantages: Accordance with the theory of pathogenesis of TCM	符合西医诊断主要指标:①②④⑤⑥⑦,吻合度 60% 符合中医诊断主症:⑤;次症:②④⑤,吻合度 30% Western medicine primary index: ①②④⑤⑥⑦, 60% match TCM primary evidence: ⑤, secondary evidence: ②④⑤, 30% match
	气虚血瘀证 AS 模型 Qi-deficiency and blood-stasis syndrome AS model	Wistar 大鼠 Wistar rats	灌胃脂肪乳+疲劳跑步双因素联合结扎冠脉[59] Rats were fed with fat milk diet, and underwent exercise fatigue combine ligation of coronary artery[59]	优点:灌胃饲养和结扎提高成模的均匀性 Advantages: High uniformity of mold	符合西医诊断次要指标:②,吻合度 5% 符合中医诊断主症:②③⑤;次症:②⑤,吻合度 55% Western medicine secondary index: ②, 5% match TCM primary evidence: ②③⑤, secondary evidence: ②⑤, 55% match
	心脾阳虚证 AS 模型 Heart and spleen yang deficiency syndrome AS model	Wistar 大鼠 Wistar rats	皮下多点注射脑垂体后叶素、BAT 切除术、隔日寒冷环境刺激联合高脂饲料,寒伤中阳[60] Rats were applied incising BAT, high fatty diet and cold stimulation every other day, and subcutaneous injection with pitutrin, with cold evil being apt to attack yang[60]	优点:病机上符合中医理论 Advantages: Accordance with the theory of pathogenesis of TCM	符合西医诊断次要指标:②, 吻合度 5% 符合中医诊断主症:①②⑤;次症:②④⑤, 吻合度 60% Western medicine secondary index: ②, 5% match TCM primary evidence: ①②⑤, secondary evidence: ②④⑤, 60% match

续表3

模型类型 Model type	动物名称 Animal name	造模方法及原理 Preparation method and principle	模型优缺点 Model advantages and disadvantages	与临床病症特点的吻合度 Consistency with clinical disease characteristics
寒凝血瘀证 AS 模型 Cold coagulation and blood stasis AS model	SD 大鼠 Sprague-Dawley rat	股静脉注射垂体后叶素 6 U/kg,引起冠状动脉较长时间强烈痉挛,急性心肌缺血,模拟寒邪致病特点射[61] 6 U/kg pituitrin was injected at femoral vein, causing intense spasm of the coronary artery for a long time and acute myocardial ischemia, imitating the characteristics of pathogenic cold causing diseases[61]	优点:病机上符合中医理论,且符合临床急性心绞痛寒邪直入心脉的发病特点 Advantages: Accordance with the theory of pathogenesis of TCM and the acute angina pectoris induced by pathogenic cold of clinical character	符合西医诊断次要指标:④,吻合度 4% 符合中医诊断主症:②;次症:④⑤,吻合度 25% Western medicine secondary index: ④, 4% match TCM primary evidence: ②, secondary evidence: ④⑤, 25% match

注:(1):西医诊断见表 1;(2):中医诊断见表 2。本文根据 AS 西医诊断标准及中医辨证分型,根据文献[20]的研究对其中西医诊断标准进行赋值,结合文献中动物模型的一般表现及检测指标计算其吻合度,同时将模型吻合度分为高中低三项,临床吻合度≥70%为高,50%~70%为中,≤50%为低。

Note. (1), See Table 1 for Western medical diagnosis. (2), See Table 2 for Chinese medicine diagnosis. According to the diagnostic criteria of Western medicine and TCM syndrome differentiation of AS and based on the literature[20], this paper assign values to the diagnostic criteria of TCM and Western medicine. Then, combined with the usual manifestations and detection indexes of animal models in the literature, the coincidence degree is calculated and is classified into high, medium and low levels. Calculated value ≥70% means high consistency, calculated value between 50% and 70% means medium consistency, and calculated value ≤50% means low consistency.

4 讨论和结论

目前,构建 AS 动物模型的方法尚不成熟,仍需通过建立适宜的动物模型为 AS 的机制研究及临床治疗提供参考。现有的 AS 动物模型复制方法,主要包括高脂喂养型、机械损伤联合高脂喂养型、基因工程联合高脂喂养型、化学诱导联合高脂喂养型及病证结合模型,共 5 大类型。上述 5 种采用不同方法构建的 AS 动物模型,中西医的吻合度有所不同。本研究分析发现,几乎所有 AS 模型的构建都需要联合高脂喂养模型。其中单纯高脂喂养模型、机械损伤联合高脂喂养模型、$ApoE^{-/-}$基因敲除联合高脂喂养模型、LDL-R 基因敲除型联合高脂喂养模型、维生素 D 联合高脂喂养联合模型、静脉注射脂多糖联合高脂喂养模型等与临床病证吻合度较高(≥70%),但作用机制存在差异且都有各自的优缺点。此外,上述模型虽然多具备很高的西医临床吻合度,但也存在其中医证候临床模拟效果普遍不佳(吻合度≤50%)。其中机械损伤联合高脂喂养模型与 $ApoE^{-/-}$基因敲除联合高脂喂养模型与人类 AS 模型最接近,具有一定的使用价值,但前者存在手术过程较为复杂的缺点,后者存在造模成本较高、小鼠体型小可获得的血液样本少,形成的 AS 病变不具有厚纤维帽等不足。

AS 病证结合模型中,痰瘀互结证与肝郁证 AS 模型与中西医临床病证特点的吻合度最高(西医吻合度≥70%,中医吻合度≥55%),除了能较好呈现动脉内膜中膜厚度比、管腔狭窄程度、血脂四项、炎症因子、心电图异常等西医诊断指标,痰瘀互结证能利用体表心电图计算心肌缺血程度进而模拟中医胸闷、胸痛等,通过体重指数和饮食情况评价痰多体胖等,通过无创血流动力学反映脉象,最后数码图片分析舌象变化,四诊评分方法独特创新,而肝郁证表现出眯眼嗜睡、行动迟缓、毛发稀疏缺少光泽、贴边等肝郁征象,利用肝郁气滞、血行不畅的中医病机,在呈现中医证候方面有较好表现力。同时,痰瘀互结型基于中医脾失健运,聚湿生痰以及离经之血便是瘀的病机进行复制,符合 AS 中医痰浊瘀阻脉络的证型病机和表现,也是 AS 临床常见的证候类型。此外,气虚血瘀证采用灌胃脂肪乳+疲劳跑步双因素联合结扎冠脉,造模原理较符合中西医病因病机,中医吻合度良好(55%),但西医吻合度较低,应完善对血脂四项、炎症因子等指标的检测。心脾阳虚证模拟内外寒邪,损伤心脾之阳,造模符合中医理论且中医证候表现力最好(60%),但西医证候只进行了心电图检查,吻合度仅为 5%。寒凝血瘀证利用垂体后叶素单一因素造模,中西医吻合度均较低。

本文通过对比不同文献中 AS 动物模型,发现该疾病模型的构建仍在不断发展,大部分模型难以完全模拟人类发病情况,疾病深层机制尚未明确。同时,目前尚未缺乏动脉粥样硬化血虚血瘀证、心肾阴虚证等中西病证结合模型的构建。目前构建 AS 模型的评价标准多以西医病机为标准,与中医证型吻合度为中等或偏低,总体西医吻合度较中医吻合度高,该现状不利于中医药治疗和预防该病发展的研究。同时我们发现,由于 AS 中医诊断标准的主症为“胸闷”“胸痛”“头晕”“肢体麻木”等,这些

指征难以在动物模型上得到有效观测,故基于中西医临床病证特点建立的 AS 动物模型的中医吻合度普遍不高。未来构建该模型可以从以下 4 方面进行改进:①通过“以方测证”法,逆向验证中医证候模型的建立;②将难以评估的中医证候用西医诊断技术量化,如舌象和舌下络脉可通过舌象仪直接分析,或采集数码图片结合比色卡进行分析,“胸痛”症状可以用体表心电图进行评分;③建议某些中医病证结合模型(如寒凝血瘀证)的构建采用联合造模的方法;④建议采用联合西医致病因素和中医患病因素,如造模过程中增加冰水刺激,基于寒凝血脉原理诱导淤血新生,在高脂高糖饲料喂养+维生素 D3+LPS 内毒素的基础上,增加湿热环境的构建,进一步诱导湿热证 AS 模型,同时加强相关指征的检测,以提高中医临床吻合度。

近年来,以动脉粥样硬化为主的心血管事件在全球的发病率和死亡率不断升高。构建与临床有高吻合度的 AS 动物模型是深入研究该疾病的基础。本文基于动脉粥样硬化的中西医临床表现和中西医临床诊断指标,总结目前常见 AS 动物模型的评价指标,并通过对比与中西医临床诊断指标的吻合度予以相应评分,以期为日后 AS 动物模型的制备、AS 病机的深入研究、AS 治疗药物的开发提供参考。

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