病证结合与冠心病防治策略

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摘要 病证结合是中西医结合临床的最佳模式, 具有原始创新的重要价值。冠心病是危害人类健康的重大疾病, 中医药以血瘀证为关键证候发展了冠心病病机新认识, 从定性到定量确立了冠心病病证结合量化标准及诊断新标志物, 以循证方法证实了相关药物的临床疗效与安全性, 采用现代科学技术方法深入探索了以活血化瘀中药为代表的中医药防治冠心病的作用机理, 构建了以病证结合为特色的冠心病中西医结合防治策略。病证结合血瘀证诊断标准的制定实现了中医证候的定量诊断, 涌现了大量活血化瘀药物防治冠心病的随机对照研究(randomized controlled trial, RCT)用以证实其有效性与安全性。冠心病血瘀证生物学实质与活血化瘀机理研究涉及血小板功能、炎症介质、氧化应激等多方面, 体现出中医药多靶点特征与优势。本文以冠心病血瘀证和活血化瘀为病证结合研究的切入点, 系统梳理了60年来中西医结合防治冠心病的研究历程, 并对未来的研究方向进行展望, 以期为进一步完善、优化具有中国特色的冠心病防治的中国方案提供参考。

关键词 冠心病, 血瘀证, 活血化瘀, 病证结合, 中西医结合

冠心病是全球范围内死亡率及致残率最高的疾病之一, 在中国目前约有1100万人罹患该病^[1]。近30年来冠心病西医治疗手段不断丰富, 冠心病患者的生存率得到显著提高, 但同时冠心病慢病综合管理的需求也逐步增加。随着社会老龄化的进展, 冠心病常合并糖尿病、高血压、卒中等多种慢病, 极大提高了疾病综合管理的难度^[2], 中医药防治冠心病的临床实践优势不断显现, 值得深入研究。冠心病中医药防治在20世纪60年代前长期处于以经验医学为主的医家各家争鸣状态, 未得到统一共识。中西医的碰撞出于诊疗需求,

现代医学结合中医对疾病的病理状态认识, 形成以西医疾病与中医证候结合的“病证结合模式”^[3]。以陈可冀院士为代表的中国第一代中西医结合医学家在大量临床实践中发现, 冠心病患者的诸多表现与中医血瘀证候存在相似之处, 尝试使用活血化瘀中药治疗后取得较好临床疗效^[4,5]。中国中医研究院与中国医学科学院阜外医院协作开发活血化瘀代表性方剂冠心2号, 十多家医院临床大协作同时开展基础研究, 是首先在我国开展循证医学临床研究实践的项目^[6], 从而正式开启了以“血瘀”为切入点的冠心病病证结合的系列研

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究。经过数代人的不懈努力,取得了一系列创新性成果,丰富了冠心病的防治策略,显著降低了冠心病病死率^[7,8],走出了一条具有原始创新的中西医结合研究之路。

1 走向共识: 冠心病中医病机与病证结合诊断标准

1.1 冠心病中医病机: 创新与发展

冠心病属于中医“胸痹”范畴,中医经典古籍《金匱要略》中首次提出该病名,且将胸痹的病机归纳为“阳微阴弦”(即上焦阳虚而阴寒内盛),后世沿用此法治以通阳豁痰宣痹,但临床疗效仍有很大的提高空间。随着现代医学体系对中医药传统诊疗模式的巨大冲击和不断融合,西医明确诊断结合中医辨证论治的“病证结合模式”成为最佳的中西医结合研究范式^[3]。20世纪60年代,陈可冀等学者通过大量的临床实践发现,“血瘀”可能是冠心病发病及加重的关键中医病机,应用活血化瘀中药治疗可明显减轻冠心病心绞痛患者的症状,且可明显减少硝酸酯类药物的用量^[9]。冠状动脉病变严重程度、经皮冠状动脉介入治疗(percutaneous coronary intervention, PCI)后再狭窄等情况与中医血瘀证密切相关^[10,11],尤其发现血瘀证患者存在更高的不良心血管事件(major adverse cardiovascular events, MACE)风险^[12],从而正式提出“血瘀”是冠心病中医核心病机的认识,基于以上认识,采用活血化瘀中药防治冠心病成为学界共识。后续临床中又发现,稳定性冠心病患者有的长期稳定,有的却突发急性冠脉综合征(acute coronary syndrome, ACS),单纯的血瘀并不能解释所有临床现象。因此,陈可冀院士带领团队研究发现,中医“瘀毒理论”结合冠心病现代病理的炎症、氧化应激等机制,以“毒”的内涵可以更全面概括解释冠心病突发炎症风暴继而引发病理性血栓破裂的过程,从而提出了冠心病“瘀毒致变”的中医病机新认识,即瘀为常,毒为变^[13,14],遂采用活血解毒中药防治ACS,显示出更为显著的临床效果^[15,16]。病证结合明确了血瘀、瘀毒等中医病机在冠心病发病中的关键地位,并通过现代医学方法评价其临床应用价值。中医因病机认识学上的每一次发展和创新,都会带来治疗学的改变和相应疾病防治效果的巨大进步,从另一个角度来说,冠心病的中医辨证也丰富了冠心病现代医学的

分型策略,为病证结合的定量研究提供了理论基础。病证结合的代表性成果见图1。

1.2 冠心病病证结合诊断标准: 从主观判断到客观量化

从定性诊断到定量诊断,以血瘀证为切入点,围绕冠心病病证结合诊断标准的制定,截至目前已发布7篇有指导意义的标准或专家共识,可大致分为以下三个阶段:(i) 1982~2000年,血瘀证的中医诊断标准确立。主要基于回顾性或横断面研究数据及专家共识确定血瘀证各诊断依据的占比;(ii) 2001~2015年血瘀证诊断标准开始广泛结合临床常用理化检查,描述更精确;(iii) 2016年正式发布冠心病血瘀证量化诊断标准。舌质紫暗及瘀斑、面色唇色紫黑、脉涩及脉结代、体表肿块及肌肤甲错、疼痛性质、出血倾向及离经之血是中医血瘀证诊断的主体内容,也是各版血瘀证诊断标准的共同点。在对现代辅助检查结果的纳入上各版本情况不一,2011年至今通过循证医学的方法对冠脉病变程度、凝血功能、血流动力学指标补充入血瘀证诊断,丰富了临床血瘀证诊断的应用范围。具体见表1。

2 循证评价: 以活血化瘀方药的临床研究为例

病证结合的临床研究通过引入循证医学和转化医学,实现了药效的客观评价^[30,31],也证实中医药的临床应用可丰富冠心病的现代综合管理方案。病证结合冠心病的临床研究始于对活血化瘀中药的临床评价,中医药领域第一个随机对照研究(randomized clinical trial, RCT)于1982年在《中华心血管病杂志》发表,该研究首次以多中心、双盲的方法评价了活血化瘀复方精制冠心片(丹参、赤芍、川芎、红花、降香)防治冠心病的效果^[6],显示其可显著改善冠心病的症状及心电图的变化结果,明显减少硝酸甘油的使用。

随后的40年来,临床研究涵盖多种治法方剂(活血化瘀、益气活血、活血解毒等)、不同剂型(水煎剂、中成药、喷雾剂、注射剂等)、冠心病不同类型或阶段(稳定型冠心病、不稳定性心绞痛、PCI术后再狭窄、缺血再灌注后无复流等)。众多RCT显示不同配伍的活血化瘀方剂可有效防治冠心病^[32,33],提示活血化瘀本身存在生物学机制的一致性,胸痹皆瘀。研究显

图 1 1949年后冠心病病证结合研究代表性成果^[6-9,17-25](网络版彩图)

Figure 1 Representative research results of coronary artery disease of combination of disease and syndrome after 1949^[6-9,17-25] (color online)

示, 同一活血化瘀药物可应用于不同冠心病疾病阶段, 如服用血府逐瘀相关制剂^[34-36]及芎苈胶囊^[17,18,37]不仅可明显改善稳定性心绞痛及不稳定性心绞痛的临床症状及心电图结果, 同时被证实可抑制PCI术后的血管再狭窄。复方丹参滴丸^[38-40]、速效救心丸^[41]、愈心痛胶囊^[42,43]等可有效缓解心绞痛症状, 减少硝酸甘油使用, 稳定ACS患者的临床症状。通心络胶囊^[44-46]保护心肌梗死后再灌注的心肌及微血管, 维持左室射血分数, 减少坏死心肌面积, 安全性良好。因此活血化瘀治疗贯穿冠心病始终, 有重要的临床应用价值。

冠心病病程漫长, 病机多变, 在血瘀的基础上对合

并气虚、痰浊、瘀毒病机的不断探索, 不仅丰富了冠心病病证结合研究的科学内涵, 对拓展冠心病的中医治法也提供了理论基础。气虚血瘀是冠心病患者最为常见的证型之一, 临床治以益气活血, 其中抗心梗合剂^[47]以益气养阴活血法治疗急性心肌梗死可提高患者抗休克耐力, 减少心律失常发生。心悅胶囊联合复方丹参片^[48]、参术冠心病方^[49]均通过益气活血改善心肌梗死血运重建后心肌灌注情况, 具有良好的心肌保护效果。芳香温通、化痰活血用以治疗心绞痛急性发作, 宽胸气雾剂^[50,51]、丹萎片^[52]可明显改善冠心病患者心绞痛症状, 抑制炎症反应、促进斑块稳定。愈梗通瘀汤

表 1 血瘀证相关诊断标准简要情况

Table 1 Overview of diagnostic criteria for syndromes of blood stasis

名称	年份	量化诊断	实验室检查项目	影像学项目	共性内容
血瘀证诊断试行标准 ^[21]	1983	否	无	(1) 头颅血管造影; (2) 头颅CT	
血瘀证诊断标准 ^[26]	1987	定量积分	(1) 血液流变学功能; (2) 微循环功能; (3) 凝血及纤溶功能; (4) 血小板功能; (5) 血流动力学功能	血管造影	(1) 舌质紫黯或舌体瘀斑、瘀点; (2) 面部、唇、齿龈及眼紫黑; (3) 肌肤甲错; (4) 脉涩, 或结、代、或无脉; (5) 固定性疼痛;
国际瘀血诊断标准试行方案 ^[27]	1987	定性诊断	(1) 血液流变学功能; (2) 微循环功能; (3) 血小板功能; (4) 血液黏度	(1) 血管造影; (2) 心肌闪烁显像; (3) 骨盆腰椎X线异常	(6) 痛经伴色黑有血块或闭经; (7) 脏器肿大、新生物、病理性肿块;
血瘀证中西医结合诊疗共识 ^[28]	2011	否	(1) 血液流变学功能; (2) 血小板功能	血管造影	(8) 出血倾向、离经之血, 出血后引起的瘀血(包括外伤后出血)
实用血瘀证诊断标准 ^[24]	2016	定性诊断	(1) 血液流变学功能; (2) 微循环功能; (3) 凝血及纤溶功能	(1) 血管造影; (2) 提示血栓、梗死、栓塞的证据	
冠心病血瘀证诊断标准 ^[25]	2016	定量积分	凝血及纤溶功能	(1) 血管造影; (2) 心脏超声	
国际血瘀证诊断指南 ^[29]	2021	定性诊断	(1) 血液流变学功能; (2) 微循环功能; (3) 凝血及纤溶功能; (4) 血小板功能	(1) 血管造影; (2) 提示血栓、梗死、栓塞的证据; (3) 胸部CT	

用于急性心肌梗死患者改善血流动力学紊乱、修复损伤心肌、缩小梗死面积从而减少心肌梗死并发症的出现, 显著改善心功能^[53]。由活血解毒中药组成的清心解瘀方可降低稳定性冠心病患者心源性死亡、非致命性心肌梗死及卒中的发生率, 并可降低稳定性冠心病患者心血管复合终点结局的发生率, 安全性良好^[7], 并从细胞焦亡、炎症反应、肠道菌群等层面解释该方的作用机制^[54-56]。

目前虽已有大量活血化瘀中药防治冠心病的RCT发表, 但多数研究样本量小、随机化方法和结局指标选择不太恰当, 因此研究水平及证据级别有限, 但近年来亦有高水平的临床研究发表引起广泛关注。一项纳入3505例患者的多中心随机双盲研究显示, 芪参益气滴丸对心血管复合终点、非致命性心肌梗死及卒中发生率与阿司匹林无统计学差异, 芪参益气滴丸可能具有类似阿司匹林的心肌梗死二级预防效果^[8]。MUST研究^[19]纳入97个中心的2674例患者, 进行24个月干预后MACE事件及心绞痛症状发生率均有统计学差异, 麝香保心丸的活血化瘀治疗可作为冠心病患者的长期治疗手段。QUEST研究^[7]多中心纳入1500例患者, 经6个月随机双盲干预, 发现试验组心源性死亡、非致命性心肌梗死和缺血性卒中组成的复合终点事件

发生率显著降低, 提示清心解瘀方对稳定性冠心病的临床防治具有重要价值。

3 机制研究: 血瘀证的生物学实质与活血化瘀现代机理的有益探索

冠心病病证结合研究不仅初步明确了冠心病血瘀证的生物学实质^[57], 同时对活血化瘀中药的现代作用机理进行了有益的探索, 取得了一定的进展。目前冠心病血瘀证相关生物标志物众多, 单一的指标变化无法充分显示冠心病血瘀证生物学实质的复杂性^[58]。随着多组学技术的快速发展和对冠心病不同分型及阶段病理状态间交互机制的深入认识, 目前的认知告诉我们冠心病血瘀证的生物学实质是多维度而非线性的。活血化瘀的现代理解也包括两个层次, “活血”为改善生理功能, “化瘀”为消除病理变化。从目前的研究结果来看, 活血化瘀中药可调节血小板功能^[59,60], 抑制炎症反应^[61], 抑制氧化应激^[62], 改善血流动力学^[63], 改善脂代谢异常^[64], 调控表观遗传^[65,66]等。近3年来研究热点聚焦为线粒体, 外泌体, 非编码RNA, 如微小核糖核酸(microRNA, miRNA)及长非编码(long non-coding RNA, lncRNA)、细胞自噬、肠道菌群等^[67-69]。

3.1 血瘀证、活血化瘀与血小板功能

冠心病血瘀证及活血化瘀机理研究中最为核心的就是围绕血小板功能的探索。血小板功能可影响凝血进程, 维持血管壁完整性, 调节血液流变学, 控制炎症因子释放, 调节单核-吞噬细胞系统等^[70], 与血瘀证密切相关^[71]。冠心病血瘀证患者血浆代谢组学分析发现, 其存在明显的血小板聚集, 花生四烯酸、亚油酸表达显著增高, 血小板膜糖蛋白CD62P, GP II b/IIIa, CD40L活化^[72], 血小板微粒(platelet microparticle)、内皮细胞微粒(endothelial microparticle, EMP)等表达增加^[73]。冠心病血瘀证患者血小板的吞噬乳胶颗粒数量减少、吞噬功能降低, 免疫清除功能降低^[74], 致血小板活化、黏附及聚集性增强。冠心病血瘀证血小板蛋白质组学的研究引起广泛关注^[60]。

血小板功能大致分为活化、黏附、聚集和炎症四部分, 多种活血化瘀中药具有其中一种或多种调节作用^[75]。现代研究中通过对血小板活化机制的分类, 将抗血小板药物分为环氧化酶(cyclooxygenase, COX)抑制剂、二磷酸腺苷(adenosine diphosphate, ADP)受体拮抗剂、血小板膜糖受体 II b/IIIa(glycoprotein, GP II b/IIIa)抑制剂及磷酸二酯酶(phosphodiesterases, PDEs)抑制剂, 中医药多种药物在通路上与现有抗血小板药物存在机制互补, 尤其在GP II b/IIIa受体抑制等西药转化的瓶颈上^[76]。不同活血化瘀药物调节血小板功能机制可大致分为花生四烯酸(arachidonic acid, AA)通路、前列环素(prostaglandin I₂, PGI-2)/环磷腺苷(adenosine cyclophosphate, cAMP)通路、P2Y₁₂/cAMP通路、血小板活化因子(platelet-activating factor, PAF)通路、Ca²⁺相关通路以及多种血小板膜糖蛋白相关通路(CD62p, GP II b/IIIa)等^[72,77]。研究发现, 活血化瘀中药复方: 复方丹参滴丸^[78]、大黄蛰虫丸^[79]、血府逐瘀汤^[80]、补阳还五汤^[81]、桃红四物汤^[82]、冠心 II 号方^[83]、芍药胶囊^[84]、通心络胶囊^[46]、活血化瘀中药注射液: 丹红注射液^[76]、血塞通注射液^[85]、活血化瘀单药或其有效单体: 川芎^[86,87]、鸡血藤^[88]、丹参^[89](丹参多酚酸盐^[90]、丹参酮 II A^[91])、赤芍^[92]、三七(三七皂苷^[93])、虎杖^[94]、红花^[95](红花黄色素^[96])、蒲黄^[97]、银杏^[98]等可抑制血小板活化, 有良好的抗血小板作用, 其具体机制见图2。

3.2 血瘀证、活血化瘀与炎症介质

炎症反应在冠心病的发生发展过程中扮演了极为重要的角色, 不仅促进动脉粥样硬化的形成, 同时可诱发急性斑块破裂血栓形成。炎症反应涉及靶点众多、受累细胞组织广泛, 目前相关药物研发仍存显著局限。在丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)抑制剂、PLA2抑制剂、烟酰胺腺嘌呤二核苷酸磷酸(nicotinamide adenine dinucleotide phosphate, NADPH)氧化酶抑制剂、肿瘤坏死因子(tumor necrosis factor, TNF- α)受体的研发折戟沉沙后^[99~101], 秋水仙碱治疗冠心病临床试验^[102]的成功提示植物来源的抗炎成分可能存在巨大潜力。血瘀、痰热的程度可以提示患者炎症反应程度的差异^[103~105], 活血化瘀解毒治疗存在较为明确的抗炎效应^[106], 具有进一步的研究价值。川芎-赤芍配伍^[107]、红花及丹参注射液^[108,109]等联合冠心病二级预防药物较单纯西药治疗可显著降低稳定性冠心病患者的血清超敏C反应蛋白(hypersensitive C-reactive protein, hs-CRP)、TNF- α 水平, 同时改善血脂异常。

活血、解毒中药改善炎症反应的机制近年来逐步得到初步阐明。丹参酮诱导中性粒细胞凋亡, 促进中性粒细胞反向迁移^[110], 通过调控Toll样受体4(Toll-like receptors 4, TLR4)-髓细胞分化初级反应蛋白88(myeloid differentiation primary response protein 88, MyD88)复合物及TLR4-TNF受体相关因子6(TNF receptor associated factor 6, TRAF6)-核因子- κ B(nuclear factor- κ B, NF- κ B)信号通路发挥抗炎效应^[111], 二氢丹参酮 I 通过雷帕霉素的机制靶点(mechanistic target of rapamycin, mTOR)-转录因子EB(transcription factor EB, TFEB)-NF- κ B信号通路改善心肌炎症^[112]。黄连小檗碱的抗炎作用可通过腺苷酸活化蛋白激酶(AMP-activated protein kinase, AMPK)通路^[113]和沉默信息调节因子T1(silent information regulator T1, SIRT1)/衔接蛋白p66Shc^[114]等发挥心血管保护效应。丹参酮 II A不仅可以降低CRP、TNF- α 、白介素6(interleukin-6, IL-6)等常见炎症指标, 同时可抑制血管紧张素 II(angiotensin II, Ang II)介导的Ca²⁺内流以调节NF- κ B通路, 抑制基质金属蛋白酶(matrix metalloproteinases, MMPs)以稳定斑块延缓血管重塑等^[115,116]。

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活血、行气活血、活血解毒等诸多治法, 同时围绕其危险因素的防治, 如高血压^[123]、高脂血症^[124]及糖尿病^[125]等皆有相应临床证据, 不断促进精准诊疗的实现. 虽然目前糖尿病及血脂异常的中医药治疗已进入西医防治指南^[126,127], 但多数中医药的应用场景较为模糊, 对中医药与西药联合应用的具体策略、获益与风险、应用周期等研究尚未有共识^[128], 因此冠心病病证结合策略仍需不断探索, 定位关键优势环节仍是一大挑战.

5 总结与展望

病证结合优化了现代中医药防治冠心病的研究模式, 并成功确立了以血瘀证与活血化瘀为主体的中西医结合治疗学发展方向^[129], 活血化瘀防治心血管疾病的理论创新与新药研究, 是我国中西医结合领域60余年来研究最活跃、成果最突出的标志性成就之一, 取得了一系列的创新性研究成果, 在“血瘀证”病证结合诊断标准的制定、“活血化瘀”现代内涵的阐释、系列活血化瘀中药新药的研发、临床疗效评价及作用机制探究等方面获得了丰厚成果, 推动了传统中医药的标准化和国际化进程, 形成了高质量的临床转化应用证据^[30], 为冠心病的中医药防治做出了突出贡献. 2011

年, 屠呦呦先生^[130]在*Nature Medicine*发表的文章中专门提及活血化瘀中药防治冠心病是来自中医药的智慧.

病证结合中医药防治冠心病的临床转化研究需要不断进步, 我们期望在以下方向能够开展深入的研究. 一是血瘀对早期血管衰老的识别、监测及早期干预具有重要意义, 需要积极发挥中医药“治未病”的优势, 开展“因瘀致衰”^[131]及活血化瘀防治早期血管衰老的机制研究; 二是随着代谢异常与心血管损害之间因果关系的不断明确, 代谢性心血管病的理念^[132,133]不断得到学界公认, 心血管代谢风险的综合评估也越来越受到关注, 研究糖脂代谢异常加重“血瘀”促进冠心病发展的机制对于阐明血瘀证生物实质, 丰富活血化瘀的治疗内涵, 拓展活血化瘀的应用范围意义重大; 三是大数据技术与人工智能的快速发展为冠心病的中西医结合诊疗方案或临床指南的优化研究提供了技术支撑^[134], 如何利用人工智能技术加速冠心病临床指南的制订流程, 提高效率, 创新其传播与实施模式, 乃至改变指南的未来发展, 已引起国内外学者的广泛关注^[135]; 四是关注冠心病防治的老药新用研究, 利用网络药理学等技术^[136], 预测老药新用的临床亮点开展系统化研究, 对于缩短药物研发时间尽快服务于临床具有现实意义.

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Combination of disease and syndrome in coronary artery disease: prevention and treatment strategies

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The combination of disease and syndrome might be the optimal pattern for integration of Chinese and western medicine with highly innovative value. Coronary artery disease (CAD) is a major disease that endangers health. Traditional Chinese medicine (TCM) has developed a new understanding of the pathogenesis of CAD by taking blood stasis as the key syndrome (Zheng). Quantitative criteria and new diagnostic markers of CAD were established, from qualitative to quantitative aspects. Through evidence-based methods and biotechnological methods, the clinical efficacy, safety and the mechanism of TCM against CAD were confirmed. Represented by activating blood circulation and resolving blood stasis, the strategy combining Chinese and Western medicine was established for the prevention and treatment of CAD, featuring disease-syndrome combination. Several blood stasis criteria enabled the quantitative scoring of the degree of blood stasis. Innumerable randomized controlled trials (RCTs) using activating blood circulation as the interventions confirmed the efficacy and safety of this therapy. The mechanisms of activating blood circulation involve platelet function, inflammatory mediators, and oxidative stress, and numerous relevant targets need further elaboration. Here, we review the research progress of integration of Chinese and western medicine in the prevention and treatment of CAD over the past 60 years, starting from activating blood circulation as the entry point of the disease-syndrome combination research, providing an outlook on the future research direction and reference for further optimizing the Chinese solution for the prevention and treatment of CAD with Chinese characteristics.

coronary artery disease, syndrome of blood stasis, activating blood circulation, combination of disease and syndrome, integration of Chinese and western medicine

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