·综 述·

# 丹参多酚酸盐对冠状动脉粥样硬化性心脏病的临床疗效和药理机制研究进展

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**摘要：**冠状动脉粥样硬化性心脏病（coronary atherosclerotic heart disease，CAHD）临床可分为稳定型心绞痛（stable angina pectoris，SAP）、不稳定型心绞痛（unstable angina pectoris，UAP）及心肌梗死（myocardial infarction，MI），其发病机制包括内皮损伤、炎症、氧化应激、斑块破裂及血栓形成等。西药、经皮冠状动脉介入治疗及冠状动脉旁路移植术等西医疗法防治 CAHD 效果显著，但相关心血管不良事件发生率仍较高。丹参具有抑制炎症、降低心肌缺血损伤、抑制血小板聚集和活化、改善 MI 面积等作用，为治疗胸痹心痛使用率最高的中药之一，亦是 CAHD 治疗常用药。现针对 SAP、UAP 及 MI 发病机理，综述丹参多酚酸盐（salvianolate）对 CAHD 的临床疗效和药理机制研究进展，为临床提供参考。

**关键词：**丹参多酚酸盐；冠状动脉粥样硬化性心脏病；临床疗效；药理机制
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# Research progress on clinical efficacy and pharmacological mechanism of salvianolate in treating coronary atherosclerotic heart disease

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**Abstract:** Coronary atherosclerotic heart disease（CAHD） can be clinically classified as stable angina pectoris（SAP）, unstable angina pectoris（UAP）, and myocardial infarction（MI）, the pathogenesis of which includes endothelial damage, inflammation, oxidative stress, plaque rupture, and thrombosis. Western medicine, percutaneous coronary intervention and coronary artery bypass grafting are effective in the prevention and treatment of CAHD, but the incidence of cardiovascular adverse events is still high. *Salvia miltiorrhiza* can inhibit inflammation, reduce myocardial ischemic injury, inhibit platelet aggregation and activation, improve MI area, etc. It is one of the most commonly used Chinese medicines in the treatment of chest arthralgia and heartache, and is also a common drug in the treatment of CAHD. This paper reviewed the clinical efficacy and pharmacological mechanism of salvianolate for CAHD, based on the pathogenesis of SAP, UAP and MI, in order to provide reference for clinical practice.

**Key words:** salvianolate; coronary atherosclerotic heart disease; clinical efficacy; pharmacological mechanism

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冠状动脉粥样硬化性心脏病（coronary atherosclerotic heart disease，CAHD）临床可分为稳定型心绞痛（stable angina pectoris，SAP）、不稳定型心绞痛（unstable angina pectoris，UAP）及心肌梗死（myocardial infarction，MI）等[1]。目前，CAHD 西医疗法主要包括西药、经皮冠状动脉介入（percutaneous coronary intervention，PCI）治疗及冠状动脉旁路移植术[2—3]。然而，西医疗法仍存在相关心血管不良事件发生率较高、部分西药成本高的限制，如 β 受体阻滞剂可增加心力衰竭（heart failure）发生风险[4]，肾素 - 血管紧张素系统抑制剂与急性肾损伤（acute kidney injury）存在相关性[5]，PCI 术后有较高的血栓形成和出血风险[6]。故而，如何进一步降低残余风险，是目前亟待解决的问题。

中药具有不良反应少、多成分及多靶点等优点，在疾病治疗中可发挥协同作用[7]。CAHD 属中医“胸痹”“心痛”范畴，气虚血瘀为主要病机，主要治则为益气活血化瘀[8]。丹参味苦，性微寒，归心、肝经，具有活血化瘀、通经止痛、凉血消痈及清心除烦等功效[9]，因其心血管保护作用显著，丹参类制剂临床上被广泛用于 CAHD 的治疗[10]。丹参多酚酸盐（salvianolate）是提取自丹参的高度纯化水溶性成分，主要成分为丹参乙酸镁、迷迭香酸及紫精酸[11—12]，具有抗氧化、抗炎、内皮保护、抗心肌缺血及再灌注损伤等作用[13]，较传统中药丹参有效性、安全性更佳[14—15]。现对丹参多酚酸盐治疗 CAHD 的临床效果和药理机制研究进展作一综述。

## 1 SAP

SAP 症状与动脉粥样硬化斑块的发展高度相关，并易引发心肌氧的供需失衡，约占所有冠状动脉疾病的 50%[16]。SAP 发病机制主要包括内皮损伤、慢性炎症、冠状动脉狭窄及血流储备下降等[17]。

丹参乙酸镁可通过抑制 Yes 相关蛋白、具有 PDZ 结合基序转录共激活剂、炎症蛋白 c-Jun 氨基末端蛋白激酶（c-Jun *N*-terminal kinase，JNK）、核因子 κB（nuclear factor kappa-B，NF-κB）、肿瘤坏死因子（tumor necrosis factor，TNF）-α 在内皮细胞和周细胞中的表达，抑制主动脉环松弛和人脐静脉内皮细胞（human umbilical vein endothelial cells，HUVEC）排列[18]；抑制 NF-κB，促进核转录因子红系 2 相关因子（nuclear factor-erythroid 2-related factor，Nrf）2 在人微血管内皮细胞激活[19]；减少泛素 - 蛋白质连接酶、蛋白酪氨酸磷酸酶表达，保护内皮细胞凋亡[20]。丹参乙酸镁的抗炎作用体现在抑制关键通路与炎症小体，进而抑制炎症反应，发挥抗动脉粥样硬化作用，改善心功能[21—23]；促血管生成作用体现在抑制胰岛素样生长因子结合蛋白 3[24]，调节血管内皮生长因子信号传导，促进 HUVEC 生成[25]。故而，丹参多酚酸盐具有保护内皮、抑制炎症以及促进血管新生等作用。

研究显示，丹参多酚酸盐在 SAP 治疗中效果显著。王彦等[26]发现，丹参多酚酸盐对于老年 SAP 疗效高，可有效改善血脂代谢、血流动力学及心肌酶谱。徐鹏飞等[27]发现，联用美托洛尔（metoprolol）和丹参多酚酸盐的心血瘀阻型 SAP 患者的血清内皮素、高迁移率组蛋白 1 水平显著下降，症状减轻。另有研究显示，丹参多酚酸盐对 SAP 的临床改善率为 88.2%，心电图改善率为 68.8%[28]；可有效降低心绞痛（angina pectoris）的发作频率及不良反应发生率，缩短 CAHD 患者住院时间[29]。故而，丹参多酚酸盐可作为 SAP 的治疗药物选择之一。

## 2 UAP

UAP 由动脉斑块破裂和血栓形成引起，病理基础为局部血小板积聚、血栓形成、炎症及氧化应激[30—32]，治疗通常采用抗凝剂、抗血小板以及钙拮抗剂等溶栓药物，严重者倾向于手术治疗，但西药和手术的医疗费用和风险相对较高，且不良反应较多[33]。

丹参乙酸镁通过下调 CD40/NF-κB 通路，抑制血小板活化和促炎介质的产生[34]。丹参多酚酸盐

通过降低白介素（interleukin，IL）-6 和 TNF-α 含量，下调 Toll 样受体（Toll-like receptor，TLR）4 的信使 RNA 的表达和转录，减少信号转导和转录激活因子（signal transducer and activator of transcription，STAT）3 磷酸化水平，从而抑制 TLR4/IL-6/STAT3 通路，减轻炎症反应[22]。丹参乙酸镁的抗氧化作用核心环节体现在可调节 Nrf2/Kelch 样 ECH 关联蛋白 1 通路[35]；亦可激活 Nrf2/ 血红素加氧酶 -1 发挥抗氧化应激保护作用[36]；通过靶向不同信号通路，促进血液循环[37]。故而，丹参多酚酸盐能通过抑制急性炎症、抗氧化应激等机制发挥稳定易损斑块的功效。

研究表明，丹参多酚酸盐可降低人体血清中可溶性 Fas、可溶性 Fas 配体以及纤维蛋白原等含量，延长部分凝血活酶时间，增加 UAP 患者斑块稳定性，保护心肌细胞，改善凝血状态[38]。研究显示，丹参多酚酸盐联合尼可地尔（nicorandil）可有效降低体内血清趋化因子、IL-4、γ- 干扰素及降钙素原水平，同时增加血清脂肪因子表达，改善老年 UAP 的疗效[39]。夏杨等[40]发现，丹参多酚酸盐联合二丁酰环磷腺苷钙（calcium dibutyryladenosine cyclophosphate）治疗 UAP 能显著降低血清妊娠相关血浆蛋白 α 等水平，提高疗效。丹参多酚酸盐可降低 UAP 的心绞痛发作频率、严重程度，缩短持续时间，并且减少硝酸甘油（nitroglycerin）使用量[41]。

**3 急性 MI**（acute myocardial infarction，AMI）

AMI 机制与急性氧化损伤，急性动脉粥样硬化血栓形成和斑块破坏有关[42]。MI 常规疗法包括抗血小板聚集、降脂、稳定斑块及 PCI 治疗，但前述方法并不能提高生存率或减少新病例的发生[43]，且 PCI 术后会增加肾病发生风险[44]。

动物试验显示，丹参多酚酸盐可作用于Ⅴ型胶原、肌球蛋白 -β、和丝氨酸 / 苏氨酸 - 蛋白激酶靶点，保护 MI 大鼠的心肌组织[45]。丹参多酚酸盐可通过调节转化生长因子 -β/Smads 蛋白信号传导，抑制心肌纤维化[46]；通过调节三联基序 / 谷胱甘肽过氧化物酶 1 途径，抑制缺血 - 再灌注诱导的细胞凋亡和氧化应激，保护心肌[47]；激活 Nrf2 信号通路，抑制铁死亡[48]；调节 NF-κB/JNK/p38 丝裂原活化蛋白激酶信号通路，减少血栓形成[49]，改善 MI；调节哺乳动物雷帕霉素靶蛋白 1 活化，抑制巨噬细胞中的糖酵解，进而抑制心肌缺血再灌注损伤心脏中的 M1 巨噬细胞极化[50]；调节还原型辅酶Ⅱ氧化酶 4 表达，保护肾功能[51]；拮抗嘌呤能受体 2，阻止人血小板活化和抑制磷酸二酯酶[52]。综上，丹参多酚酸盐能抑制血小板聚集、抑制心肌纤维化以及改善缺血再灌注损伤等。

同时，有学者进一步证实了丹参多酚酸盐能降低 AMI 急性期血栓事件发生率，改善远期预后。PCI 围手术期的 AMI 患者采用丹参多酚酸盐后，血浆中肾上腺髓质素 2 水平改善，促进心功能恢复，提高心肌灌注量[53]。Shen 等[54]提出，丹参多酚酸盐改善急性 ST 段抬高型 MI 患者的冠状动脉微循环，减少心肌梗塞面积。研究表明，丹参多酚酸盐可降低 PCI 相关重度心肌损伤和 MI 发生率[55]。丹参多酚酸盐可降低 PCI 术后肾损伤发生率，保护肾功能[56]。

**4 结语与展望**

丹参多酚酸盐具有多种生物活性，可起到抗炎、抗氧化、降低心肌缺血损伤、抑制血小板聚集和活化以及改善 MI 面积等作用，这为丹参多酚酸盐在心血管疾病治疗中的应用提供了理论基础。但目前仍缺乏丹参多酚酸盐多中心、大样本量临床对照研究数据，以及与其他药物的联合治疗研究数据，具体作用机制尚需深入探讨，未来需加强此类探索，以期为丹参多酚酸盐在心血管疾病治疗中的应用提供更严密的依据。

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