doi: 10.13241/j.cnki.pmb.2018.12.019

# 丹参注射液与丹参多酚酸盐注射液对不稳定型心绞痛患者冠状动脉微循环的影响*

畅 辉[1] 宁小康[1] 韩 克[2] 王坤峰[1] 岳黎明[1△]

（1 陕西中医药大学附属医院心内科 陕西 咸阳 712000；2 西安交通大学第一附属医院心内科 陕西 西安 710061）

**摘要 目的：**比较丹参注射液与丹参多酚酸盐注射液对不稳定型心绞痛(UA)患者冠状动脉微循环的影响。**方法：**将2014年5月～2017年5月105例UA患者随机分为丹参组(n=50)与丹参多酚酸盐组(n=55)，前者在PCI术前静脉滴注丹参注射液20 mL，1次/d，连续3 d；后者静脉滴注丹参多酚酸盐注射液200 mg，1次/d，连续3 d。分别在PCI术前及术后即刻检测冠状动脉血流储备(CFR)、冠状动脉微循环阻力系数(IMR)及TIMI血流分级。**结果：**两组术后CFR、IMR及TIMI血流分级均较术前明显改善(P＜0.05)，丹参多酚酸盐组IMR明显小于丹参组(P＜0.05)，CFR、TIMI血流分级与丹参组比较无统计学意义(P＞0.05)。**结论：**丹参注射液与丹参多酚酸盐注射液均能显著改善UA患者的冠状动脉微循环，丹参多酚酸盐注射液一定程度上优于丹参注射液。

**关键词：**丹参注射液；丹参多酚酸盐注射液；不稳定型心绞痛；冠状动脉；微循环

**中图分类号：**R541.4 **文献标识码：**A **文章编号：**1673-6273(2018)12-2294-04

# Effect of Danshen Injection and Salvia Miltiorrhiza Injection on the Coronary Microcirculation in Patients with Unstable Angina Pectoris*

*CHANG Hui[1], NING Xiao-kang[1], HAN Ke[2], WANG Kun-feng[1], YUE Li-ming[1△]*

*(1 Department of Cardiology, the Affiliated Hospital of Shaanxi Traditional Chinese Medicine University, Xianyang, Shaanxi, 712000, China; 2 Department of Cardiology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, 710061, China)*

**ABSTRACT Objective:** To compare the effect of Danshen injection and Salvia miltiorrhiza injection on the coronary microcirculation in patients with unstable angina pectoris (UA). **Methods:** 105 cases of patients with UA from May 2014 to May 2017 were randomly divided into the Salvia miltiorrhiza group (n=50) and the Salvia miltiorrhiza polyphenol salt group (n=55), the Salvia miltiorrhiza group was given intravenous drip of Salvia miltiorrhiza injection 20 mL before PCI, 1 time/d, in total 3 d; and the Salvia miltiorrhiza polyphenol salt group was given intravenous drip Salvia miltiorrhiza polyphenol salt injection 200 mg,1 time/d, in total 3 d. The coronary flow reserve (CFR), coronary microcirculation resistance coefficient (IMR) and TIMI blood flow classification were measured before and immediately after PCI. **Results:** The CFR, IMR and TIMI flow grade of both groups were significantly improved compared with preoperation(P < 0.05), and the IMR of Salvia miltiorrhiza group was significantly lower than that of the Salvianolate group (P<0.05), while the CFR, TIMI flow grade of two groups showed no significant difference (P>0.05). **Conclusions:** Danshen injection and Salvia miltiorrhiza injection could significantly improve the coronary microcirculation in patients with UA, and the injection of Salvia miltiorrhiza Bunge was better than Danshen injection.

**Key words:** Salvia injection; Salvia miltiorrhiza injection; Unstable angina pectoris; Coronary artery; Microcirculation

**Chinese Library Classification(CLC): R541.4 Document code: A**

**Article ID:1673-6273(2018)12-2294-04**

## 前言

不稳定型心绞痛(Unstable angina，UA)是由冠状动脉粥样硬化导致的心肌供血不足、缺血缺氧而引发心绞痛的一种心血管系统急危重症，其临床表现介于劳累性稳定型心绞痛与急性心肌梗死和猝死之间，主要包括初发心绞痛、恶化劳力性心绞痛、静息心绞痛伴心电图缺血改变和心肌梗死后早期心绞痛，特征是心绞痛症状进行性增加，新发作的休息或夜间性心绞痛或出现心绞痛持续时间延长[1]。经皮冠状动脉介入术(Percutaneous coronary intervention，PCI)是治疗UA的重要手段[2]。

近年多项研究表明冠状动脉微循环密切影响着PCI的远期疗效与预后[3]，术前使用一些具有血管扩张、改善微循环功效的药物进行预处理对改善冠状动脉微循环有积极作用[4,5]。现代研究表明丹参具有扩张血管、抗凝、促进微循环、抗氧化、保护心肌等多重作用[6]。丹参注射液与丹参多酚酸盐注射液均是以丹参为核心成分的中药制剂，而后者中丹参乙酸镁含量高于80%[7]，理论上药物效应更强[8]。本研究比较了丹参注射液与丹参多酚酸盐注射液对UA患者冠状动脉微循环的影响，结果报

* 基金项目：国家中医药管理局国家中医临床研究基地业务建设科研专项(JDZX2015252)

作者简介：畅辉(1973-)，男，本科，副主任医师，研究方向：心血管方向，E-mail: changhui_1973@papmedline.top

△ 通讯作者：岳黎明(1975-)，男，本科，副主任医师，研究方向：心血管方向，E-mail: yueliming_1975@papmedline.top

(收稿日期：2017-11-11 接受日期：2017-11-30)

道如下。

## 1 资料与方法

### 1.1 一般资料

入选 2014 年 5 月～2017 年 5 月 105 例 UA 患者，所有患者均根据《2007 中国不稳定性心绞痛和非 ST 段抬高心肌梗死诊断与治疗指南》[9] 相关诊断标准及经冠状动脉造影确诊为 UA，并具有 PCI 手术指征。排除急性心肌梗死、严重主动脉狭窄、II 度以上房室传导阻滞、严重窦性心动过缓及严重脑血管疾病患者。随机分为丹参组(n=50)与丹参多酚酸盐组(n=55)，两组一般资料比较无统计学意义(P＞0.05)。见表 1。

**表 1 两组一般资料比较**

Table 1 Comparison of the general information between two groups

| Items | Salvia group(n=50) | Salvia miltiorrhiza group(n=55) | P |
|---|---|---|---|
| Male [n (%)] | 31(62.0) | 37(67.3) | 0.572 |
| Age (years) | 59.67± 5.02 | 61.38± 4.09 | 0.057 |
| Smoking[n(%)] | 22(44.0) | 24(43.6) | 0.273 |
| Hypertension[n(%)] | 16(32.0) | 13(23.6) | 0.338 |
| Hyperlipidemia [n(%)] | 14(28.0) | 17(30.9) | 0.744 |
| Diabetes[n(%)] | 7(14.0) | 5(9.1) | 0.429 |
| Left anterior descending lesion[n(%)] | 24(62.0) | 27(67.3) | 0.683 |
| Left circumflex lesion[n(%)] | 17(34.0) | 14(25.5) | |
| Right coronary artery[n(%)] | 9(18.0) | 14(25.5) | |
| Average number of stents | 1.67± 0.88 | 1.73± 0.79 | 0.714 |
| Total stent length(mm) | 37.21± 15.35 | 43.58± 17.07 | 0.092 |

### 1.2 治疗方法

两组入院后即刻顿服阿司匹林(拜尔医药保健有限公司 国药准字 J20130078)300 mg，之后维持每天 100 mg 至长期；顿服氯吡格雷(赛诺菲制药有限公司，国药准字 J20130007)300 mg，之后维持每天 75 mg 至 PCI 术后 1 年以上；皮下注射依诺肝素(杭州九源基因工程有限公司，国药准字 H20064067)1 mg/kg 至术后 5 d，每隔 12 h 一次。在此基础上术前丹参组静脉滴注丹参注射液(西安汉丰药业有限责任公司，国药准字 Z61021674)20 mL，1 次 /d，连续 3 d；丹参多酚酸盐组静脉滴注丹参多酚酸盐注射液 (上海绿谷制药有限公司，国药准字 Z20050248)200 mg，1 次 /d，连续 3 d。两组均接受 PCI 治疗，Seldinger 法经桡动脉经冠状动脉造影。

### 1.3 观察指标

分别在 PCI 术前及术后即刻检测以下冠状动脉微循环指标：① 冠状动脉血流储备(Coronary flow reserve，CFR)：采用多普勒导丝测定，仪器为美国 GEVolusonE8 彩色多普勒超声诊断仪，CFR 为最大冠脉舒张期血流峰速与静息时舒张期血流峰速的比值，正常范围为 2~2.5。② 冠状动脉微循环阻力系数(Microcirculation resistance index，IMR)：采用多普勒导丝测定，IMR 为远端冠状动脉压力除以平均传导时间的倒数，正常范围为 IMR＜25[10]。③ TIMI 血流分级[11,12]：经冠状动脉造影评估，无灌注为 0 级；渗透而无灌注为 1 级；部分灌注为 2 级；完全灌注为 3 级。

### 1.4 统计学方法

采用 SPSS19.0 统计学软件，计量数据采用($\bar{x}$± s)表示，组间比较采用 t 检验；计数资料采用%表示，采取 $x^2$ 检验，以 P＜0.05 为差异具有统计学意义。

## 2 结果

两组术后 CFR、IMR 及 TIMI 血流分级均较治疗前明显改善(P＜0.05)，丹参多酚酸盐组 IMR 明显小于丹参组(P＜0.05)，CFR、TIMI 血流分级与丹参组比较无统计学意义(P＞0.05)。见表 2、3。

**表 2 两组治疗前后 CFR、IMR 比较($\bar{x}$± s)**

Table 2 Comparison of the CFR, IMR between two groups before and after treatment ($\bar{x}$± s)

| Group | CFR | | IMR | |
|---|---|---|---|---|
| | Preoperative | Postoperative | Preoperative | Postoperative |
| Salvia group(n=50) | 1.91± 0.58 | 2.13± 0.55* | 25.25± 2.61 | 23.96± 2.68* |
| Salvia miltiorrhiza group(n=55) | 1.87± 0.62 | 2.38± 0.81* | 25.61± 2.73 | 22.47± 2.79* |
| P | 0.351 | 0.069 | 0.492 | 0.006 |

Note: Compared with before treatment, *P<0.05.

表 3 两组治疗前后 TIMI 血流分级的比较[n(%)]

Table 3 Comparison of the TIMI blood flow between two groups before and after treatment [n(%)]

| Group | Preoperative | | Postoperative | |
|---|---|---|---|---|
| | Level0～2 | Level 3 | Level0～2 | Level 3 |
| Salvia group(n=50) | 11(22.0) | 39(78.0) | 6(12.0) | 44(88.0) |
| Salvia miltiorrhiza group(n=55) | 14(25.5) | 41(74.5) | 2(3.6) | 53(96.4) |
| P | 0.624 | | 0.106 | |

## 3 讨论

目前研究认为冠状动脉微循环障碍会导致心肌缺血,其中 CFR 降低是其发病机制之一[13]。由于 UA 具有独特的病理生理机制及临床预后,如果不能恰当及时的治疗,患者可能发展为急性心肌梗死[14]。PCI 在 UA 治疗领域有着举足轻重的地位,但即便手术技巧及器械操作高超,仍不能完全避免对心肌的损伤[15,16]。PCI 过程中涉及的一些如球囊扩张等环节可能导致斑块碎片、微血栓等堵塞远端微血管,伤害心肌细胞及血管内皮细胞,并刺激一些炎性因子的释放[17],从而引起微循环功能障碍。研究表明 PCI 可加重稳定型心绞痛患者的冠状动脉微循环阻力,增加 PCI 相关性心肌梗死的危险[18]。冠脉微循环障碍是冠心病远期预后及心血管事件的独立预测指标[19]。

PCI 术前预先用药可一定程度减轻或改善术后冠脉微循环障碍,如西药常使用尼可地尔、替罗非班、腺苷及抗痉挛药物等[20,21]。丹参注射液与丹参多酚酸盐注射液是临床常用于治疗冠心病 UA 的中药制剂,多项研究表明[22,23]二者在改善心绞痛症状及抑制血管炎、抑制血栓形成及保护血管内皮等方面具有突出的效果,其中丹参多酚酸盐注射液的疗效相对更好[24,25]。丹参具有改善微循环、改善缺血再灌注损伤、钙通道阻滞、抗栓、抗炎等作用,这为其改善冠脉微循环提供了理论基础[26,27]。

目前,一般根据冠状动脉循环阻力或心肌灌注间接反映微血管循环功能 [28]。CFR 是通过检测血流速度来评估血流量,CFR＜2 时对心肌缺血具有较高的敏感度和特异度,但其变化除了与微循环功能有关外,也与心外膜动脉狭窄程度有关[29]。IMR 被认为是目前评价冠状动脉微循环功能最敏感、最准确的指标,理论上不受心外膜动脉狭窄的影响。TIMI 血流分级也可间接反映冠状动脉微循环状态 [30]。本研究结合 CFR、IMR 及 TIMI 血流分级三项指标,能够较为准确地评价丹参注射液与丹参多酚酸盐注射液对冠状动脉微循环的影响。结果显示两组术后 CFR、IMR 及 TIMI 血流分级均较术前明显改善,而丹参多酚酸盐组的 IMR 改善情况明显优于丹参组(P＜0.05),说明丹参多酚酸盐对改善 UA 患者的冠状动脉微循环显示出更佳的疗效,这也与理论上认为的丹参多酚酸盐药效更强相符合。综上所述,对于需行 PCI 治疗的 UA 患者在术前预先用药有利于改善冠状动脉微循环,改善预后。丹参注射液与丹参多酚酸盐注射液均能显著改善 UA 患者的冠状动脉微循环,丹参多酚酸盐注射液一定程度上优于丹参注射液。

### 参 考 文 献(References)


[1] Alexandre M, Benjo M D F, El H G E, et al. High dose statin loading prior to percutaneous coronary intervention decreases cardiovascular events: A meta-analysis of randomized controlled trials[J]. Catheterization & Cardiovascular Interventions Official Journal of the Society for Cardiac Angiography & Interventions, 2015, 85(1): 53-60

[2] Wu J R, Liu S, Zhang X M, et al. Danshen Injection as Adjuvant Treatment for Unstable Angina Pectoris: A Systematic Review and Meta-analysis [J]. Chinese Journal of Integrative Medicine, 2017, 23 (4): 1-6

[3] Huang X F, Wang J M, Chen Q, et al. Meta-analysis on effect of compound Danshen injection in treating neonatal hypoxic-ischemic encephalopathy [J]. China Journal of Chinese Materia Medica, 2015, 40 (1): 141-148

[4] Tong C X, Xing X F, Qiao S H, et al. Effect of Low Molecular Weight Heparin Calcium Combined Compound Danshen Injection on Perinatal Outcomes of Nephrotic Syndrome Patients with Early Onset Severe Pre-eclampsia [J]. Zhongguo Zhong xi yi jie he za zhi, 2015, 35 (8): 957-961

[5] Gorsky V A, Agapov M A, Khoreva M V, et al. The effect of lornoxicam on TLR2 and TLR4 messenger RNA expression and tumor necrosis factor-α, interleukin-6, and interleukin-8 secretion in patients with systemic complications of acute pancreatitis [J]. Pancreas, 2015, 44(5): 824-830

[6] Zhang Y X, Cui X Y, Lu Y L, et al. Effect of Danshen injection and Xinkeshu tablets on the metabolism of CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 in rabbits by cocktail probe substrates method[J]. Journal of Chinese Pharmaceutical Sciences, 2015, 50(10): 881-887

[7] Zhang X G, Wu P, Tong Y, et al. Clinical effect of Danshen injection iontophoresis combined with Lumbrokinase in early retinal vein occlusion patients[J]. Guoji Yanke Zazhi, 2015, 15(1): 101-103

[8] Zhou W, Gastroenterology D O. Saccharomyces boulardii powder combined with mesalazine for treatment of active ulcerative colitis: Curative effect and impact on fecal calprotectin and serum inflammatory factors [J]. World Chinese Journal of Digestology, 2017, 25(22): 2065

[9] Cao S, Zhao W, Bu H, et al. Ligustrazine for the Treatment of Unstable Angina: A Meta-Analysis of 16 Randomized Controlled Trials[J]. Evidence-Based Complementray and Alternative Medicine, 2016, 13 (9963): 8617062

[10] Liu L P. Danshen injection combined with somatostatin for treatment of mild or moderate acute pancreatitis: Curative effect and impact on serum amylase levels [J]. World Chinese Journal of Digestology, 2015, 23(8): 1350

[11] Zhang G, Yang T, Jing Z, et al. Hybrid de novo, genome assembly of the Chinese herbal plant danshen ( Salvia miltiorrhiza, Bunge)[J]. Gi-

gaScience, 2015, 4(1): 62

[12] Kim H G, Oh M S. Protective Effect of Lycii Radicis Cortex against 6-Hydroxydopamine-Induced Dopaminergic Neuronal Cell Death[J]. Journal of Food Biochemistry, 2015, 39(3): 281-288

[13] Wang G, Qu F Z, Li L, et al. Necroptosis: a potential, promising target and switch in acute pancreatitis [J]. Apoptosis An International Journal on Programmed Cell Death, 2016, 21(2): 121-129

[14] Wang C, Zhao R, Li B, et al. An in vivo and in vitro study: High-dosage Danshen injection induces peripheral vascular endothelial cells injury [J]. Human & Experimental Toxicology, 2015, 3(4): 17445-17458

[15] Peng W B, Zeng Q H, Li D P, et al. Multiple on-line HPLC coupled with biochemical detection methods to evaluate bioactive compounds in Danshen injection [J]. Biomedical Chromatography, 2016, 30(11): 1854-1860

[16] Cacciapaglia R, Mandolini L, Reinhoudt D N, et al. Alkaline earth metal ion catalysis of alcoholysis of crown ether aryl acetates. Effect of the base-solvent system[J]. Journal of Physical Organic Chemistry, 2017, 5(9): 669-670

[17] Liu Z, Xu S, Huang X, et al. Cryptotanshinone, an orally bioactive herbal compound from Danshen, attenuates atherosclerosis in Apolipoprotein E-Deficient Mice: role of LOX-1[J]. British Journal of Pharmacology, 2015, 172(23): 5661-5675

[18] Yin Q, Lu H, Bai Y, et al. A metabolite of Danshen formulae attenuates cardiac fibrosis induced by isoprenaline, via a NOX2/ROS/p38 pathway [J]. British Journal of Pharmacology, 2015, 172 (23): 5573-5585

[19] Wang L, Zhang X, Chan J Y, et al. A Novel Danshensu Derivative Prevents Cardiac Dysfunction and Improves the Chemotherapeutic Efficacy of Doxorubicin in Breast Cancer Cells[J]. Journal of Cellular Biochemistry, 2016, 117(1): 94-105

[20] Li D, Shao F, Lu S. Identification and characterization of mRNA-like noncoding RNAs in Salvia miltiorrhiza [J]. Planta, 2015, 241 (5): 1131-1143

[21] Li S, Shan L, Zhang Z, et al. Pharmacokinetic and Metabolic Studies of ADTM: A Novel Danshensu Derivative Confers Cardioprotection by HPLC-UV and LC-MS/MS [J]. Journal of Chromatographic Science, 2015, 53(6): 872-878

[22] Zhang D, Duan X, Deng S, et al. Fingerprint analysis, multi-component quantitation, and antioxidant activity for the quality evaluation of Salvia miltiorrhiza var. alba by high-performance liquid chromatography and chemometrics [J]. Journal of Separation Science, 2015, 38 (19): 3337-3344

[23] Xiaorong Hu, Weibing Dong, Rui Liu. Effects of the Addition of Selenium on Trace Element Concentrations in Danshen (Salvia miltiorrhiza)[J]. Analytical Letters, 2015, 48(3): 513-525

[24] Gurses K M, Kocyigit D, Yalcin M U, et al. Enhanced Platelet Toll-like Receptor 2 and 4 Expression in Acute Coronary Syndrome and Stable Angina Pectoris[J]. American Journal of Cardiology, 2015, 116(11): 1666-1671

[25] Mygind N D, Michelsen M M, Pena A, et al. Coronary microvascular function and myocardial fibrosis in women with angina pectoris and no obstructive coronary artery disease: the iPOWER study[J]. Journal of Cardiovascular Magnetic Resonance, 2017, 18(1): 76

[26] Blum A. New oral nitric oxide-dependent medications for patients with coronary artery disease who have persistent angina pectoris[J]. Coronary Artery Disease, 2015, 26(8): 639-641

[27] Kume T, Akasaka T, Kaji S, et al. Relation between Angina Pectoris and Coronary Flow Reserve in Patients with Aortic Stenosis and Normal Coronary Artery [J]. Analytica Chimica Acta, 2016, 912 (2): 165-168

[28] Yildiz B S, Bilgin M, Zungur M, et al. Manual Thrombus Aspiration and the Improved Survival of Patients With Unstable Angina Pectoris Treated With Percutaneous Coronary Intervention (30 Months Follow-Up)[J]. Medicine, 2016, 95(8): e2919

[29] Prasad M, Wan A W, Sukmawan R, et al. Extracorporeal shockwave myocardial therapy is efficacious in improving symptoms in patients with refractory angina pectoris--a multicenter study [J]. Coronary Artery Disease, 2015, 26(3): 194-200

[30] Maag R, Foy A, Maag R, et al. Post prandial angina pectoris: an uncommon presentation of severe coronary artery disease [J]. Journal of the American College of Cardiology, 2017, 69(11): 2437

(上接第 2252 页)

[29] Habeeballah H, Alsuhaymi N, Stebbing MJ, et al. Central leptin and resistin combined elicit enhanced central effects on renal sympathetic nerve activity[J]. Exp Physiol, 2016, 101(7): 791-800

[30] Horvath TL, Diano S, van den Pol AN. Synaptic interaction between hypocretin (orexin) and neuropeptide Y cells in the rodent and primate hypothalamus: a novel circuit implicated in metabolic and endocrine regulations[J]. J Neurosci, 1999, 19(3): 1072-1087

[31] Kotagale NR, Upadhya M, Hadole PN, et al. Involvement of hypothalamic neuropeptide Y in pentazocine induced suppression of food intake in rats[J]. Neuropeptides, 2014, 48(3): 133-141

[32] Murakami M, Ohba T, Kushikata T, et al. Involvement of the orexin system in sympathetic nerve regulation [J]. Biochem Biophys Res Commun, 2015, 460(4): 1076-1081

[33] Rorabaugh JM, Stratford JM, Zahniser NR, et al. A relationship between reduced nucleus accumbens shell and enhanced lateral hypothalamic orexin neuronal activation in long-term fructose bingeing behavior[J]. PLoS One, 2014, 9(4): e95019

[34] Inui A. Transgenic approach to the study of body weight regulation [J]. Pharmacol Rev, 2000, 52(1): 35-61

[35] Wieland HA, Engel W, Eberlein W, et al. Subtype selectivity of the novel nonpeptide neuropeptide Y Y1 receptor antagonist BIBO3304 and its effect on feeding in rodents [J]. Br J Pharmacol, 1998, 125: 549-555