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症状性颈动脉狭窄支架置入术后并发症：临床危险因素与蛋白质组学机制的研究进展

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摘　要

症状性颈动脉狭窄是导致缺血性脑卒中的重要病因，颈动脉支架置入术(carotid artery stenting, CAS)是其血运重建的关键手段。然而，术后30天内卒中、心肌梗死及远期支架内再狭窄等并发症仍严重影响患者预后。识别高危人群并阐明再狭窄的发生机制，是优化临床决策和改善远期结局的关键。本文系统综述了CAS术后并发症的临床危险因素及代谢综合征背景下血管再狭窄的蛋白质组学分子机制，并探讨二者之间的内在关联。临床研究显示，除年龄、高血压等传统危险因素外，主动脉弓形态与变异、颈内动脉扭曲指数、颈总动脉开口病变等解剖学特征在手术风险中发挥独立作用，复杂解剖结构可增加操作难度、诱发血管损伤和血流动力学紊乱。蛋白质组学研究揭示，代谢综合征环境下血管壁发生显著的分子重构，主要涉及细胞外基质重塑、炎症免疫应答、氧化应激及细胞骨架调控等通路，这些事件共同驱动血管平滑肌细胞增殖迁移和内膜增生。进一步分析表明，临床危险因素可通过改变局部力学微环境或放大损伤反应，启动或加剧上述分子事件，从而构成“解剖－分子”级联的病理基础。本文旨在整合临床表型与分子机制的研究进展，为深入理解再狭窄的发生发展提供理论依据，并为优化风险评估和干预策略提供新视角。

关键词

症状性颈动脉狭窄，颈动脉支架置入术，再狭窄，危险因素，解剖学，蛋白质组学，代谢综合征，分子机制

Research Progress on Clinical Risk Factors and Proteomic Mechanisms of Postoperative Complications after Symptomatic Carotid Artery Stenosis Stent Implantation

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Abstract

Symptomatic carotid artery stenosis is an important cause of ischemic stroke, and carotid artery stenting (CAS) is a key means of revascularization. However, complications such as stroke, myocardial infarction and long-term in-stent restenosis within 30 days after surgery still seriously affect the prognosis of patients. Identifying high-risk groups and elucidating the mechanism of restenosis are the keys to optimizing clinical decision-making and improving long-term outcomes. This article systematically reviews the clinical risk factors of complications after CAS and the molecular mechanism of proteomics of vascular restenosis in the context of metabolic syndrome, and explores the intrinsic relationship between the two. Clinical studies have shown that in addition to traditional risk factors such as age and hypertension, anatomical features such as aortic arch morphology and variation, internal carotid artery tortuosity index, and common carotid artery opening lesions play an independent role in surgical risks. Complex anatomical structures can increase the difficulty of operation and induce vascular injury and hemodynamic disorders. Proteomics studies have revealed that significant molecular remodeling of vascular wall occurs in the environment of metabolic syndrome, mainly involving extracellular matrix remodeling, inflammatory immune response, oxidative stress and cytoskeleton regulation. These events jointly drive the proliferation and migration of vascular smooth muscle cells and intimal hyperplasia. Further analysis shows that clinical risk factors can initiate or aggravate the above molecular events by changing the local mechanical microenvironment or amplifying the damage response, thus forming the pathological basis of the 'anatomical-molecular' cascade. This article aims to integrate the research progress of clinical phenotypes and molecular mechanisms, provide a theoretical basis for in-depth understanding of the occurrence and development of restenosis, and provide a new perspective for optimizing risk assessment and intervention strategies.

Keywords

Symptomatic Carotid Artery Stenosis, Carotid Artery Stenting, Restenosis, Risk Factors, Anatomy, Proteomics, Metabolic Syndrome, Molecular Mechanism

1. 前言

脑卒中是我国成人致死、致残的首位病因，给家庭和社会带来沉重的疾病负担[1]。颈动脉狭窄是缺血性脑卒中的重要病因之一，尤其是症状性颈动脉狭窄患者，其 6 个月内再发卒中风险显著升高，及时恢复血运重建对改善预后至关重要[2]。颈动脉支架置入术(carotid artery stenting, CAS)作为症状性狭窄的重要治疗手段，具有微创、恢复快等优势，已广泛应用于临床。然而，CAS 术后 30 天内发生的卒中、心

肌梗死以及远期支架内再狭窄等并发症，仍严重制约着患者的临床获益[3]-[5]。因此，精准识别高危患者、深入理解并发症的发生机制，成为优化治疗策略和改善远期预后的关键。

早期研究多聚焦于传统心血管危险因素，如年龄、高血压、糖尿病、高脂血症等，这些因素通过长期影响血管结构和功能，增加围术期风险[6]-[8]。然而，随着影像学技术的快速发展，个体化的解剖学特征在手术风险评估中的作用日益凸显。主动脉弓分型与变异、血管扭曲程度、病变位置等解剖参数，直接影响器械输送的难易程度、支架贴壁的顺应性以及血管壁的局部应力分布，从而与术后并发症的发生密切相关[9]-[11]。系统评估这些解剖学危险因素，有助于更精准地进行术前风险分层。

与此同时，再狭窄的发生机制极为复杂，单纯依靠临床危险因素难以全面解释其病理本质。代谢综合征(metabolic syndrome, MetS)作为多种心血管危险因素的聚集状态，已被证实可加速动脉粥样硬化进程并促进介入术后再狭窄[12]。在代谢紊乱环境下，血管壁局部发生一系列分子事件，包括细胞外基质重塑、炎症免疫应答激活、氧化应激失衡及血管平滑肌细胞表型转换等[13]。蛋白质组学技术的发展，为系统性揭示这些分子事件及其调控网络提供了强有力的工具，使从整体水平理解再狭窄的分子机制成为可能。

值得注意的是，临床危险因素与分子机制之间并非相互独立。如血管扭曲、主动脉弓变异等异常解剖可能通过改变局部血流动力学环境，将力学信号转化为生物学信号，从而启动或放大特定分子通路[14] [15]；而年龄增长所致的血管衰老，则从分子层面改变了血管壁的生物学特性，削弱了其维持结构完整性和修复病理性损伤的内在能力[16]。阐明二者之间的内在关联，有助于构建从“临床表型”到“分子事件”的完整认知框架。本文旨在系统综述症状性颈动脉狭窄患者 CAS 术后并发症的临床危险因素(特别是解剖学特征)及代谢综合征背景下再狭窄的蛋白质组学分子机制，并探讨临床因素与分子事件之间的潜在联系，以期为深入理解再狭窄的发生发展提供理论依据，并为优化围术期风险评估和干预策略提供新思路。

2. CAS 术后并发症的临床危险因素研究进展

颈动脉支架置入术(CAS)术后并发症的发生是多因素共同作用的结果。早期研究多聚焦于传统心血管危险因素，而近年来随着影像学技术的进步，个体化解剖学特征在手术风险中的作用日益受到重视。系统识别和评估这些危险因素，对于术前风险分层、手术策略制定以及术后管理具有重要临床意义。

2.1. 传统人口学特征与合并症

在众多人口学特征中，年龄是研究最为深入且证据最为充分的危险因素之一。随着年龄增长，血管壁发生一系列退行性改变：弹性蛋白降解、胶原交联增加导致血管顺应性下降[17]；内皮祖细胞数量减少、功能减退，使内皮修复能力减弱[18]；动脉粥样硬化负荷加重，斑块易损性增加[19]。这些变化使得老年患者在 CAS 术中更易因导管操作诱发斑块脱落、血管痉挛或血栓形成。多项大型随机对照试验的荟萃分析证实，在接受颈动脉支架植入术(CAS)的患者中，高龄(≥70 岁)与术后 30 天内卒中及死亡风险显著升高相关。例如，Carotid Stenting Trialists Collaboration (CSTC)的个体患者数据荟萃分析显示，70 岁及以上患者的 30 天卒中/死亡风险超过 12%，远低于 70 岁以下患者(<6%) [20]。

高血压、糖尿病、冠心病及高脂血症等合并症同样在术后并发症中扮演重要角色。高血压长期作用于血管壁，导致血管重塑和内皮功能障碍[21] [22]；糖尿病通过晚期糖基化终产物(AGEs)积累、氧化应激增强等途径加速动脉粥样硬化进程，并影响内皮修复质量[23] [24]；冠心病患者常合并全身性动脉粥样硬化，心脑血管事件风险同步升高[25]。值得注意的是，这些合并症往往相互聚集，形成代谢综合征，其对血管系统的损害具有协同放大效应。然而，单纯依赖这些传统因素进行风险预测，其敏感性和特异性仍显不足，提示可能存在未被充分认识的独立危险因素。

2.2. 解剖学危险因素

解剖学特征对 CAS 手术难度和并发症风险的影响，近年来受到广泛关注。主动脉弓的解剖形态直接影响 CAS 术中导丝、导管通过弓上血管的难度[26]。根据无名动脉、左颈总动脉及左锁骨下动脉与主动脉弓顶点的相对位置关系，主动脉弓分为 I、II、III 型。III 型主动脉弓因头臂动脉开口位置较低，导管需经锐角转折方能超选进入目标血管，显著增加了操作难度。在此类解剖结构中，反复的导管操作易导致血管壁损伤、不稳定斑块脱落或气栓形成，从而提高围术期神经并发症的风险[10] [27] [28]。Faggioli 等[27]的研究显示，主动脉弓异常可使 CAS 术后神经系统并发症风险增加约 2 倍(OR = 2.01, P = 0.026)，提示 III 型主动脉弓及某些弓上变异是 CAS 术后卒中及 TIA 的独立危险因素。

血管扭曲程度是另一关键解剖参数。颈总动脉(CCA)及颈内动脉(ICA)的走行并非完全平直，扭曲的血管可能导致术后并发症风险的升高。研究表明，颈内动脉迂曲在介入术中可能导致机械应力分布不均，使支架在迂曲段内拉伸、塌陷，增加操作次数和再通时间。这种技术困难进一步引发血管内皮损伤风险上升，导致术后卒中发生率升高。

病变位置与性质同样影响手术预后。颈总动脉开口处病变因靠近主动脉弓，器械输送路径长且需跨越弯曲区域，常面临导丝支撑力不足、支架定位困难等问题，这可能是导致患者术后残余狭窄或支架移位风险升高的原因[27]。同一血管存在多处狭窄所产生的串联病变，其病变部位较多，需要更长的手术时间、更多的造影剂及更复杂的器械操作，理论上将增加围术期风险。此外，溃疡形成、富含脂质的坏死核心(LRNC)、斑块内出血(IPH)和纤维帽破裂，显著增加了斑块的不稳定性。这些特征不仅与自发性缺血事件密切相关，也使得在血管内操作(如颈动脉支架置入术)过程中，器械通过时更易导致斑块表面碎片脱落，从而增加远端栓塞的风险。

因此，CAS 术后并发症的危险因素谱已从传统的临床指标拓展至精细化解剖学参数。年龄作为基础性因素不可干预，而解剖学特征的识别可为手术策略的个体化调整提供依据。然而，这些因素如何通过影响血管壁生物学行为最终导致并发症的发生，仍需从分子层面深入探讨。

3. 代谢综合征背景下血管再狭窄的蛋白质组学分子机制

颈动脉支架置入术(CAS)后血管再狭窄的发生机制极为复杂，涉及血管损伤后一系列细胞与分子事件的级联反应。单纯依靠临床危险因素难以完全解释其病理本质，而蛋白质组学技术的发展为系统性揭示再狭窄的分子网络提供了有力工具。特别是在代谢综合征(MetS)背景下，全身性代谢紊乱与局部血管损伤反应相互交织，形成独特的蛋白质表达谱，深入理解这些分子事件对于阐明再狭窄机制具有重要意义。

3.1. 再狭窄的病理生理基础

研究表明，支架植入扩张过程中在支架单元之间区域产生的高周向应力，引发急性动脉损伤，血管内皮剥脱，随即触发血管损伤修复反应[29]。这一过程可主要概括为三个相互重叠的阶段：炎症反应期、细胞增殖迁移期和细胞外基质(ECM)重塑期。内皮细胞损伤，表面基质蛋白暴露与血小板结合，并使其发生黏附聚集并释放多种生长因子和趋化因子，募集炎症细胞浸润，促进局部微血栓形成[30]；此外，中膜的血管平滑肌细胞(VSMC)在局部微环境信号刺激下，从收缩表型向合成表型转换，获得迁移和增殖能力，穿过内弹力膜迁移至内膜；这些合成型 VSMC 大量分泌胶原、蛋白多糖等 ECM 成分，与增殖的 VSMC 共同构成新生内膜，最终导致管腔狭窄[31]。在这一系列事件中，VSMC 的表型转换、迁移增殖以及 ECM 的合成降解平衡，受控于复杂的分子调控网络。

3.2. 蛋白质组学揭示的关键分子通路

基于蛋白质组学的研究发现，MetS 环境下再狭窄血管组织发生显著的蛋白质表达谱改变，涉及多个

生物学过程，其中以 ECM 重塑、细胞骨架调控、炎症免疫应答及氧化应激等通路最为突出。

ECM 重塑相关分子在再狭窄组织中呈现广泛变化。基质金属蛋白酶(MMPs)是 ECM 降解的核心酶类，其中 MMP-2 在再狭窄血管中表达显著上调[32]。研究表明，MMP-2 在调节血管平滑肌细胞(VSMC)迁移中起关键作用。MMP-2 缺失会导致动脉平滑肌细胞迁移和侵袭能力下降，并通过降解构成血管基底膜的胶原和层粘连蛋白等细胞外基质(ECM)成分，促进 VSMC 向内膜的迁移，从而参与新生内膜形成[33]-[36]。MMP-2 缺失会导致动脉平滑肌细胞迁移和侵袭能力下降，并通过降解细胞外基质(ECM)成分(包括构成血管基底膜的胶原和层粘连蛋白)，促进 VSMC 向内膜的迁移，从而参与新生内膜的形成。与此同时，在 TGF-β 信号通路的调控下，COL1A1 和 COL3A1 等多种胶原蛋白基因的表达同步上调，可促进 ECM 合成与沉积，促进基质硬度增加[37]。这种 ECM 降解与合成的失衡，一方面导致血管壁结构的重塑，另一方面为新迁移至内膜的 VSMC 提供附着点。ECM-受体相互作用通路的激活，进一步提示细胞与微环境之间的信号交流在再狭窄中的关键作用。

此外，细胞骨架调控与黏附相关蛋白的显著变化，反映了 VSMC 功能状态的改变[38]。肌动蛋白细胞骨架的动态调控是平滑肌细胞表型转换的关键。Tang & Gerlach [39]指出，以 c-Abl 为核心的激酶信号通过调控肌动蛋白结合蛋白网络(如 N-WASP、cofilin)及 vimentin 磷酸化，驱动细胞获得迁移能力。Xu [40]等则进一步揭示，肌动蛋白本身的可逆氧化修饰及上游 Rho GTPases 的氧化激活，直接影响肌动蛋白聚合状态，从而在血管疾病中促进平滑肌由收缩型转化为具有更强迁移和增殖能力的合成/迁移型。黏附斑复合物的动态组装与组成蛋白的可塑性变化，使其能够作为细胞响应 ECM 物理特性及力学信号的整合平台，双向信号传导调控细胞功能[41]。此外，整合素家族成员作为跨膜受体，能够感知细胞外基质的力学与化学信号，并通过双向信号传导机制将这些信号传入胞内。通过招募并激活黏着斑激酶等胞内激酶，整合素启动下游信号级联反应，进而调控细胞骨架重组、基因表达及细胞的关键生物学行为，如增殖、存活、迁移与分化[42]。这些分子事件共同构成了 VSMC 功能重塑的分子基础。

在肥胖、2 型糖尿病等代谢综合征状态下，免疫相关通路被显著激活，表现为慢性低度炎症反应，涉及多种炎症因子(如 TNF-α)、JNK、IKK、NF-κB 等信号通路以及免疫细胞在代谢组织中的浸润与活化[43]。补体活化可释放过敏毒素，如 C3a 和 C5a，这些分子通过与其 G 蛋白偶联受体结合，发挥强烈的趋化作用，引导中性粒细胞、单核细胞和巨噬细胞向活化部位浸润。此外，补体激活的终末阶段可形成膜攻击复合物(MAC)，该复合物插入细胞膜并形成裂孔，直接导致血管壁细胞及其他靶细胞的损伤或裂解[44]。研究表明，在动脉粥样硬化斑块中可见主要组织相容性复合体 II 类分子(如 HLA-DP、HLA-DR)在巨噬细胞上的表达上调，反映了局部抗原呈递和免疫应答的激活，这提示再狭窄中存在类似的免疫炎症机制[45]。

研究表明，代谢综合征不仅涉及传统的心血管危险因素，其病理核心还在于由活性氧过量生成所诱导的氧化应激状态，加剧炎症反应，促进动脉粥样硬化斑块的形成与不稳定化，显著提升心血管事件风险[46]。氧化应激产生的活性氧(ROS)可经由 NF-κB 通路介导炎症基因表达，导致内皮功能障碍细胞功能障碍，加速动脉粥样硬化，继发再狭窄可能[47]。

3.3. 代谢综合征对再狭窄分子事件的放大效应

MetS 并非单一危险因素，而是以胰岛素抵抗为核心，集簇性存在高血压、高血糖、血脂异常和中心性肥胖等多种代谢异常的综合状态[48]。这些代谢异常通过多种机制协同放大上述分子事件。

高血糖条件下可加速晚期糖基化终产物(AGEs)的形成与积累；AGEs 与其受体 RAGE 结合后可激活多种炎症信号通路，并促进细胞外基质(ECM)蛋白的交联，从而导致血管壁僵硬度增加和顺应性下降[49]。氧化型低密度脂蛋白(ox-LDL)是连接脂代谢紊乱与血管炎症的关键分子，由渗入血管内膜下的低密度脂

蛋白经氧化修饰形成[50]。ox-LDL 可被巨噬细胞上的清道夫受体(如 CD36)识别并内吞，引发溶酶体损伤和线粒体功能障碍，进而激活 NLRP3 炎症小体，促使成熟 IL-1β 的释放，放大局部炎症反应[51] [52]。同时，ox-LDL 可直接作用于内皮细胞，通过结合 LOX-1 受体损害一氧化氮的生物利用度并上调黏附分子表达，破坏内皮屏障功能，形成加速动脉粥样硬化进展的恶性循环[50] [52]。脂肪组织功能障碍导致脂肪因子失衡，如瘦素抵抗、脂联素水平下降，进一步加剧胰岛素抵抗和血管炎症。更为重要的是，这些代谢异常并非孤立作用，而是相互协同。例如，高血糖可通过激活多元醇通路、蛋白激酶 C(PKC)通路等促进活性氧(ROS)的生成，而 ROS 的积累又可进一步加重胰岛素抵抗[53]。这种恶性循环使得 MetS 环境下血管壁处于持续激活的促炎、促氧化、促增殖状态，对支架植入后的机械损伤产生过度或失调的修复反应，从而显著增加再狭窄风险。

蛋白质组学研究揭示，MetS 背景下血管再狭窄涉及 ECM 重塑、细胞骨架调控、炎症免疫应答及氧化应激等多重分子通路的协同变化。这些通路相互交织，形成复杂的调控网络，共同驱动 VSMC 的异常增殖迁移和 ECM 过度沉积。理解这些分子事件及其相互作用，有助于从本质上认识再狭窄的病理过程，也为识别潜在干预靶点提供了理论依据。

如颈内动脉扭曲、主动脉弓变异等临床解剖学危险因素与再狭窄分子事件之间通过局部力学微环境的改变实现因果关联。影像学结合计算流体力学研究证实，血管扭曲程度与局部壁面剪切力、振荡剪切指数等参数密切相关，扭曲节段远端常出现低剪切力区，这些力学异常与内皮功能障碍及局部炎症反应高度一致[54] [55]。力学信号向分子事件的转化依赖于整合素–黏着斑激酶通路、YAP/TAZ 核转位及 NF-κB 信号通路的激活，进而上调基质金属蛋白酶(MMP-2、MMP-9)表达、促进炎症因子(如 IL-6、TNF-α)释放，并诱导血管平滑肌细胞表型转换[14] [40] [55]。近年来，将影像解剖参数与局部组织蛋白质组学直接关联的研究为上述机制提供了人体内的直接证据。在低剪切力区域的动脉组织中，MMP-2、COL1A1、IL-6 等蛋白表达显著升高，且 NF-κB 依赖的炎症通路被特异性激活，伴随巨噬细胞浸润增加和细胞外基质降解酶活性升高[55] [56]。上述发现共同构建了“解剖–力学–分子”级联的病理基础，揭示了解剖学危险因素通过改变局部力学微环境，系统性地激活细胞外基质重塑、炎症免疫应答及平滑肌表型转换等再狭窄核心分子通路的内在机制。

4. 小结

上述各因素之间并非孤立发挥作用，而是相互叠加、协同放大。从分子层面看，这种多因素交互体现为信号通路的交叉对话。例如，机械应力激活整合素/FAK 通路可增强 NF-κB 的转录活性，而氧化应激同样激活 NF-κB，二者汇合于同一炎症放大器；炎症因子可诱导 MMP 表达，而 MMP 降解 ECM 产生的片段又可作为 DAMPs 进一步激活炎症反应。这些正反馈循环使得初始的局部损伤被不断放大，最终演变为显著的内膜增生。本综述通过总结临床危险因素及基于蛋白组学的再狭窄风险分子机制研究发现，临床危险因素与分子机制之间存在清晰的因果链条：年龄通过分子衰老改变血管的基线状态和解剖储备；血管扭曲通过力学转导将异常血流转化为促增殖信号；解剖变异和开口病变通过机械损伤触发局部炎症免疫应答。这些机制相互交织，共同驱动再狭窄的发生发展。理解这一关联，有助于将临床观察与基础机制相统一，为靶向干预提供理论依据。

5. 局限与展望

尽管临床危险因素与蛋白质组学机制的研究取得了重要进展，但目前仍面临诸多挑战。首先，临床研究多为单中心回顾性设计，样本量有限，解剖参数的测量标准尚未统一，难以对多因素症状性颈动脉狭窄患者进行风险分层预测。其次，蛋白质组学数据多来源于动物模型，与人体再狭窄组织存在种属差

异，且多为横断面研究，难以揭示分子事件的动态演变过程；此外，关键分子的功能验证尚不充分，仍需进一步实验证实。

未来研究应开展大样本多中心前瞻性队列研究，统一解剖参数测量标准，验证危险因素及预测模型的稳健性，其次可整合影像组学、蛋白质组学与代谢组学等多维数据，构建多模态风险预测模型。例如可基于拟行 CAS 的症状性颈动脉狭窄患者开展一项多中心前瞻性队列研究，通过留取患者的血液样本行蛋白组学研究，动态检测 MMP-2、IL-6 等再狭窄相关分子水平，并对患者解剖学数据、分子数据与远期再狭窄结局进行关联分析以进行相关验证。通过上述具体研究设计，可将本文理论框架转化为可检验的科学假说，推动临床危险因素与分子机制研究的深度融合。

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