

# 缺血伴非阻塞下冠脉疾病患者发生不良心血管事件的危险因素分析

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## 摘要

冠状动脉粥样硬化性心脏病是人类死亡的最主要原因之一, 也是对公众健康威胁最大的疾病。目前对冠心病的诊断、治疗及预防等工作, 往往局限于与阻塞性冠脉疾病(狭窄>50%), 非阻塞性冠脉疾病表现出的胸疼等症状, 既往被认为与心脏无关, 是良性病变, 未引起公众关注。但近几年来研究提示缺血伴非阻塞性冠脉疾病并非良性, 因管理的缺乏性, 导致发生不良心血管事件。此文探讨缺血伴非阻塞性冠脉疾病患者发生不良心血管事件的危险因素。

## 关键词

冠状动脉粥样硬化性心脏病, 非阻塞性冠脉疾病, 不良心血管事件

# Analysis of Risk Factors for Adverse Cardiovascular Events in Ischemia Patients with Non-Obstructive Coronary Arteries

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## Abstract

Coronary atherogenic heart disease is one of the most leading causes of human death and represents the greatest threat to public health. At present, the diagnosis, treatment and prevention of coronary heart disease are often limited to obstructive coronary disease (stenosis > 50%), chest pain shown by non-obstructive coronary disease, which was considered to be unrelated to the heart, are benign, and have not attracted public attention. However, in recent years, studies have suggested that ischemia with non-obstructive coronary disease is not benign, due to the lack of management, leading to adverse cardiovascular events. This article explores the risk factors for adverse cardiovascular events in patients with ischemia and non-obstructive coronary disease.

## Keywords

Coronary Atherosclerotic Heart Disease, Non-Obstructive Coronary Artery Disease, Adverse Cardiovascular Events

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## 1. 前言

根据 2017 年全球疾病负担显示, 冠状动脉粥样硬化性疾病(coronary artery disease, CAD)占据国内居民死亡原因的第二位[1], 冠脉疾病的诊断金标准为: 冠状动脉造影检查。据报道, 由于心绞痛和心肌缺血证据而接受冠状动脉造影检查的患者, 有 60%~70%的患者无阻塞性冠状动脉疾病[2] [3] [4]。此类患者临床上被定义为缺血伴非阻塞性冠状动脉疾病(ischemia with non-obstructive coronary arteries, INOCA), ACC 公布了 INOCA 的统一定义如下: 1) 持续(数周或更长)的症状提示缺血性心脏病; 2) 心电图或其他心脏成像测试(如超声心动图、磁共振成像、核成像或光谱学)中心肌缺血的客观证据; 3) 根据心外膜冠状动脉狭窄的定义, 冠状动脉造影无血流限制性阻塞  $\geq 50\%$ 或部分流量储备  $< 0.8$  [4]。临床上, 对冠脉疾病患者的治疗及预防方案仅限于阻塞性冠脉疾病患者, 缺血伴非阻塞性冠脉疾病往往被认为是良性病变, 系列研究表明, 缺血伴非阻塞性冠状动脉疾病(INOCA)是更严重病变的前兆, 以及随后出现的动脉粥样硬化血栓并发症和相关临床症状[5]。

目前对 INOCA 患者的预后等相关研究少, 迄今为止, 尚未制定针对这一人群的最佳管理策略[6]。对此类患者的管理仍是难题。INOCA 患者存在典型的症状和体征, 但这些症状经常误诊为非心源性, 患者未能得到个体化治疗及健康宣教, 导致此类患者不良心血管事件发病率增加、生活质量下降、医疗保健费用的增加。国内外相关研究多以单个因素为中心进行 INOCA 患者远期预后研究。INOCA 患者 5 年内发生不良心血管事件(不良心血管事件定义为心源性死亡、急性心肌梗死、恶性心律失常和再次冠脉紧急血运重建)中, 关于多个危险因素影响作用大小比较的研究较少。

缺血伴非阻塞性冠脉疾病拟机制如下: ① 冠状动脉微循环功能障碍: 微循环异常原因中内皮功能障碍患者约占非阻塞性 CAD 患者的三分之二, 并显示出聚集性心血管事件的风险增加[7] [8] [9] [10]。② 冠状动脉痉挛[11]; ③ 氧化应激[12]: 氧化应激可导致血管收缩和内皮损伤, 导致冠状动脉微血管功能障碍和冠状动脉血管痉挛, 进而导致 INOCA。

最新研究 INOCA 患者五年内发生不良心血管事件的危险因素如下:

① 斑块位置: 近端血管供应心肌的大部分, 斑块破裂和血栓闭塞倾向于聚集在冠状动脉近三分之一处。多数认为发生不良心血管事件与冠脉狭窄的严重程度相关, 但部分不良心血管事件与非阻塞冠脉疾病相关。早期血管造影研究结果表明, 位于近端的动脉粥样硬化斑块因急性冠状动脉事件而发生侵蚀或破裂的风险较高[13], 在一项 2065 位 INOCA 患者参与的随访研究中, 当 INOCA 患者按近端受累进一步分层时, 无近端受累和近端受累的 INOCA 患者的 5 年内发生不良心血管事件发生率分别为 1.3% 和 2.2%。与无近端受累的患者相比, 近端受累患者的不良心血管事件发生率更高( $P = 0.033$ ), 因此 INOCA 患者近端冠状动脉受累与不良心血管事件发生风险增加相关, 与冠状动脉斑块的程度无关[14]。冠脉斑块位置可为 INOCA 患者发生 MACE 的预测提供额外的价值。

② 低密度脂蛋白胆固醇(LDL-C)变异性: LDL-C 变异性是指根据每位患者连续测量 LDL-C 的平均值计算个体内平均值(LDL-C-mean)。连续 LDL-C 测量的标准偏差(LDL-C-sd)为 LDL-C 变异性。可能由于脂质流出机制的变异性(即损害斑块稳定的胆固醇依赖性机制)而导致血管壁的不稳定。一项 2012 名非阻塞性 CAD 患者在 5 年随访中, 用 LDL-C 变异系数(LDL-C-cv)校正平均值。由于缺乏现有的 LDL-C 变异性指数的截止点, 我们根据每个 LDL-C 变异性指数的中位数将受试者分为高、低两组, 共观察到 99 例(4.92%)死亡病例和 154 例(7.65%)复合终点病例。LDL-C 变异性越高, 在长期随访中全因死亡率或复合终点越高[15]。结果表明, 即使在调整了可能的混杂因素(包括该人群的 LDL-C 平均水平)后, 访问 LDL-C 变异性是全因死亡率或复合终点的强大且独立的预测因子。

③ D-二聚体: D-二聚体是交联纤维蛋白的降解产物, 被广泛认为是血栓形成的标志物。D-二聚体升高对健康人和 CAD 患者的不良心血管事件具有预测价值[16] [17], 研究表明, D-二聚体水平升高与微血管血栓形成[18]、炎症[19]和内皮损伤[20]有关, 在充分调整了其他潜在的临床危险因素, 包括年龄、性别、高血压、糖尿病、吸烟、饮酒和血小板后, 高 d-二聚体(>500 ng/ml)患者发生冠脉微循环障碍的风险是低 d-二聚体患者的 1.86 倍(95% CI: 1.09~3.19) ( $P < 0.05$ ) [21]。冠脉微循环功能障碍增加 INOCA 患者 5 年内发生不良心血管事件发生率。

④ 高敏感性 C-反应蛋白: hs-CRP 水平较高的患者中, BMI 较高, 糖尿病患者比例较高, 总胆固醇、甘油三酯、葡萄糖和胰岛素水平较高。Hs-CRP 是异常冠状动脉血管反应性的独立预测因子。在未使用降脂治疗的患者中, hs-CRP 较高的患者心外膜和微血管内皮功能较差。这种关系似乎与其他心血管危险因素和潜在混杂因素无关[22]。

## 2. 结语

尽管最初有人提出, INOCA 可能构成良好心血管预后良好, 近年来, 有充分证据表明, INOCA 患者的心血管发病率和死亡率有所增加。与无 CAD 的预后相比, INOCA 的存在会导致不良预后[23]。基于证据的 INOCA 患者个性化管理指南仍然缺失[4]。目前国内外研究均以单个因素为中心进行研究, 但关于多个危险因素在不良心血管事件为终点的 INOCA 患者中的影响作用大小比较的研究较少。未来需要在 INOCA 患者 5 年内发生不良心血管事件的危险因素影响作用进行统计分析, 构建危险因素预测模型, 进行分层。能够以上述危险分层预测不良心血管事件发生率, 让患者及家属理解疾病危险, 通过饮食、运动、药物等干预措施, 减少不良心血管事件发生, 改善 INOCA 患者预后及生活质量。

## 参考文献

- [1] Zhou, M., *et al.* (2019) Mortality, Morbidity, and Risk Factors in China and Its Provinces, 1990-2017: A Systematic Analysis for the Global Burden of Disease Study 2017. *Lancet*, **394**, 1145-1158. [https://doi.org/10.1016/S0140-6736\(19\)30427-1](https://doi.org/10.1016/S0140-6736(19)30427-1)

- [2] Patel, M.R., Peterson, E.D., Dai, D., Brennan, J.M., Redberg, R.F., Anderson, H.V., *et al.* (2010) Low Diagnostic Yield of Elective Coronary Angiography. *The New England Journal of Medicine*, **362**, 886-895. <https://doi.org/10.1056/NEJMoa0907272>
- [3] Kunadian, V., Chieffo, A., Camici, P.G., Berry, C., Escaned, J., Maas, A., *et al.* (2020) An EAPCI Expert Consensus Document on Ischaemia with Non-Obstructive Coronary Arteries in Collaboration with European Society of Cardiology Working Group on Coronary Pathophysiology and Microcirculation Endorsed by Coronary Vasomotor Disorders International Study Group. *European Heart Journal*, **41**, 3504-3520. <https://doi.org/10.1093/eurheartj/ehaa503>
- [4] Bairey Merz, C.N., Pepine, C.J., Walsh, M.N. and Fleg, J.L. (2017) Ischemia and No Obstructive Coronary Artery Disease (INOCA): Developing Evidence-Based Therapies and Research Agenda for the Next Decade. *Circulation*, **135**, 1075-1092. <https://doi.org/10.1161/CIRCULATIONAHA.116.024534>
- [5] Oxner, A., Elbaz-Greene Ahmadi, A., Argulian, E., Leipsic, J., Newby, D.E. and Narula, J. (2019) From Subclinical Atherosclerosis to Plaque Progression and Acute Coronary Events: JACC State-of-the-Art Review. *Journal of the American College of Cardiology*, **74**, 1608-1617. <https://doi.org/10.1016/j.jacc.2019.08.012>
- [6] Qui, F., Masih, S., Zivkovic, N., Alnasser, S., *et al.* (2017) Variations in Use of Optimal Medical Therapy in Patients with Nonobstructive Coronary Artery Disease: A Population-Based Study. *Journal of the American Heart Association*, **6**, e007526. <https://doi.org/10.1161/JAHA.117.007526>
- [7] Halcox, J., Schenke, W.H., Zalos, G., *et al.* (2002) Prognostic Value of Coronary Vascular Endothelial Dysfunction. *Circulation*, **106**, 653-658. <https://doi.org/10.1161/01.CIR.0000025404.78001.D8>
- [8] Bugiardini, R., Manfredi, O., Pizzi, C., *et al.* (2004) Endothelial Function Predicts Future Development of Coronary Artery Disease: A Study of Women with Chest Pain and Normal Coronary Angiograms. *Circulation*, **109**, 2518-2523. <https://doi.org/10.1161/01.CIR.0000128208.22378.E3>
- [9] Suwaidi, J.A., Hamasaki, S., Higano, S.T., *et al.* (2000) Long-Term Follow-Up of Patients with Mild Coronary Artery Disease and Endothelial Dysfunction. *Circulation*, **101**, 948-954. <https://doi.org/10.1161/01.CIR.101.9.948>
- [10] Von Mering, G.O., Arant, C.B., Wessel, T.R., *et al.* (2004) Abnormal Coronary Vasomotion as a Prognostic Indicator of Cardiovascular Events in Women: Results from the National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE). *Circulation*, **109**, 722-725. <https://doi.org/10.1161/01.CIR.0000115525.92645.16>
- [11] Matta, A., Bouisset, F., Lhermusier, T., Campelo-Parada, F., Elbaz, M., Carrié, D. and Roncalli, J. (2020) Coronary Artery Spasm: New Insights. *Journal of Interventional Cardiology*, **2020**, Article ID: 5894586. <https://doi.org/10.1155/2020/5894586>
- [12] Pahimi, N., Rasool, A.H.G., Sanip, Z., Boki, N.A., Yusof, Z. and Isa, W.Y.H.W. (2022) An Evaluation of the Role of Oxidative Stress in Non-Obstructive Coronary Artery Disease. *Journal of Cardiovascular Development and Disease*, **9**, Article 51. <https://doi.org/10.3390/jcdd9020051>
- [13] Wang, J.C., Normand, S.L., Mauri, L. and Kuntz, R.E. (2004) Coronary Artery Spatial Distribution of Acute Myocardial Infarction Occlusions. *Circulation*, **110**, 278-284. <https://doi.org/10.1161/01.CIR.0000135468.67850.F4>
- [14] Donghee, H., Chen, B., Gransar, H., *et al.* (2021) Prognostic Significance of Plaque Location in Non-Obstructive Coronary Artery Disease: From the CONFIRM Registry. *European Heart Journal—Cardiovascular Imaging*, **23**, 1240-1247.
- [15] J., Gu, Yin, Z.F., Pan, J.A., Zhang, J.F. and Wang, C.Q. (2019) Visit-to-Visit Variability in Low-Density Lipoprotein Cholesterol is Associated with Adverse Events in Non-Obstructive Coronary Artery Disease. *The Anatolian Journal of Cardiology*, **22**, 117-124. <https://doi.org/10.14744/AnatolJCardiol.2019.26428>
- [16] Ariëns, R.A., de Lange, M., Snieder, H., Boothby, M., Spector, T.D. and Grant, P.J. (2002) Activation Markers of Coagulation and Fibrinolysis in Twins: Heritability of Theprethrombotic State. *Lancet*, **359**, 667-671. [https://doi.org/10.1016/S0140-6736\(02\)07813-3](https://doi.org/10.1016/S0140-6736(02)07813-3)
- [17] Ridker, P.M., Hennekens, C.H., Cerskus, A. and Stampfer, M.J. (1994) Plasma Concentration of Cross-Linked Fibrin Degradation Product (D-Dimer) and the Risk of Future Myocardial Infarction among Apparently Healthy Men. *Circulation*, **90**, 2236-2240. <https://doi.org/10.1161/01.CIR.90.5.2236>
- [18] Townsend, L., Fogarty, H., Dyer, A., Martin-Loeches, I., Bannan, C., Nadarajan, P., *et al.* (2021) Prolonged Elevation of D-Dimer Levels in Convalescent COVID-19 Patients is Independent of the Acute Phase Response. *Journal of Thrombosis and Haemostasis*, **19**, 1064-1070. <https://doi.org/10.1111/jth.15267>
- [19] Bruinstroop, E., van de Ree, M.A. and Huisman, M.V. (2009) The Use of D-Dimer in Specific Clinical Conditions: A Narrative Review. *European Journal of Internal Medicine*, **20**, 441-446. <https://doi.org/10.1016/j.ejim.2008.12.004>
- [20] Hileman, C.O., Longenecker, C.T., Carman, T.L., Milne, G.L., Labbato, D.E., Storer, N.J., *et al.* (2012) Elevated D-Dimer Is Independently Associated with Endothelial Dysfunction: A Cross-Sectional Study in HIV-Infected Adults on Antiretroviral Therapy. *Antiviral Therapy*, **17**, 1345-1349. <https://doi.org/10.3851/IMP2297>
- [21] Lin, Y., Hu, X.M., Wang, W.M., Yu, B.Y., Zhou, L.P., Zhou, Y.L., Li G. and Dong, H.J. (2022) D-Dimer Is Asso-

ciated with Coronary Microvascular Dysfunction in Patients with Non-Obstructive Coronary Artery Disease and Preserved Ejection Fraction. *Frontiers Cardiovascular Medicine*, **9**, Article ID: 937952.

- [22] Jaskanwal, D.S., Prasad, M., Zhang, M., Lennon, R.J., Herrmann, J., Lerman, L.O. and Lerman, A. (2017) High-Sensitivity C-Reactive Protein Is an Independent Marker of Abnormal Coronary Vasoreactivity in Patients with Non-Obstructive Coronary Artery Disease. *American Heart Journal*, **190**, 1-11. <https://doi.org/10.1016/j.ahj.2017.02.035>
- [23] Finck, T., Hardenberg, J., Will, A., Hendrich, E., Haller, B., Martinoff, S., Hausleiter, J. and Hadamitzky, M. (2019) 10-Year Follow-Up after Coronary Computed Tomography Angiography in Patients with Suspected Coronary Artery Disease. *JACC: Cardiovascular Imaging*, **12**, 1330-1338. <https://doi.org/10.1016/j.jcmg.2018.07.020>