综 述

急性感染与心肌梗死的联系*

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20 世纪早期首次认识到流感流行期间心血管死亡率上升,在之后的研究中,急性流感感染一直被怀疑是急性心肌梗死的危险因素[1]。本文总结急性感染与心肌梗死相关的证据,探讨急性感染导致心肌梗死可能的机制,讨论疫苗在预防心血管事件中可能的价值。

急性感染后心肌梗死风险增高

Smeeth 等[2]指出呼吸道感染后心肌梗死风险显著升高,且在前 3 d 内最高。研究证明流感病毒与主要心血管事件之间存在强烈的关联[3~5],并提出通过免疫接种或预防感染来减少呼吸道感染可能对减少心血管事件的发生有益[6]。最近的一项实验室研究显示,流感病毒、呼吸道合胞病毒或其他呼吸道病毒感染后的 1 周内,心肌梗死的风险增加,分别达到对照间期(感染发生之前或之后 1 年期间)心肌梗死风险的 6 倍、4 倍和 3 倍[7]。不仅上呼吸道感染能增加心肌梗死风险,Musher 等[8,9]研究指出,在因肺炎球菌肺炎住院的患者中,心肌梗死发生率为 7% ~8%。研究证实急性呼吸道感染(包括肺炎链球菌或流感嗜血杆菌)是心肌梗死的危险因素[10,11],肺炎相关的心肌梗死风险在感染发生时达到峰值,且与疾病的严重程度成正比[12],可以增加短期及长期心血管事件发生风险。目前也发现泌尿道感染[2]和社区获得性菌血症[13]可以增加心肌梗死的风险。

急性感染与心肌梗死风险之间的联系可能与感染严重程度及时间相关。多项研究表明心肌梗死风险与感染严重程度成正比[14]。在上呼吸道感染后数周内,风险恢复至基线水平[2]。在脓毒症或肺炎患者中,感染后第 1 年心肌梗死风险最高,且风险随着时间的推移而降低,但直至感染后 10 年仍超过基线风险[15]。感染较严重时,近期和远期心肌梗死风险均显著增加[16]。

急性感染导致心肌梗死的机制

急性冠脉闭塞 1 型心肌梗死是与动脉粥样斑块破裂和血栓形成相关的急性冠状动脉闭塞所引起的心肌缺血[17]。动脉粥样硬化斑块含有炎性细胞,心肌梗死发生前,脂质已经积聚在冠状动脉壁中,内弹性膜变薄,内膜和平滑肌细胞破裂,纤维蛋白沉积。同时存在泡沫状巨噬细胞、T 淋巴细胞、金属蛋白酶、肽酶和中性粒细胞胞外诱捕网[18]。而体内的感染会产生循环炎性细胞因子,包括肿瘤坏死因子 α(TNF-α)以及白细胞介素(IL)1、6 和 8[19]。细胞因子能够激活动脉粥样硬化斑块中的炎性细胞[20]。在小鼠实验中发现,感染会使炎症时间延长,巨噬细胞浸润到动脉粥样硬化斑块中,增加动脉粥样硬化负荷,同时在主动脉组织中增加内皮单核细胞粘附并激活血管炎症标志物[21]。人体尸检研究也得出相似的结果,在感染发生后出现炎症,粥样斑块中的炎性活动会增加。活化的斑块内炎性细胞会上调宿主应答蛋白,包括金属蛋白酶和肽酶,并且促进氧化暴发,导致斑块不稳定[17],从而出现薄帽粥样瘤破裂,向管腔内释放炎性细胞和纤维蛋白。Otsuka 等[19]研究显示超过 2/3 的急性冠状动脉事件与覆盖炎性纤维帽的斑块破裂有关。

另一方面,急性感染可以导致止凝血系统失衡,包括局部静脉血液的高凝状态,急性弥散性血管内凝血等,其特征是广泛的微血管血栓形成和随后消耗的血小板和凝血蛋白,最终导致出血表现[22]。这种并发症发生的关键是宿主对炎性因子的反应,导致炎症介质的过度表达。多研究表明,血小板在心肌梗死的发展中起关键作用[23~25]。研究发现,感染

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会导致机体血小板的高反应性和活化[26,27]。这种促血栓形成、促凝血状态进一步增加了斑块破裂部位的冠状动脉血栓形成风险[22,28]。导致冠状动脉血栓形成的因素包括斑块内和循环中性粒细胞产生中性粒细胞胞外诱捕网、血小板活性增加、促凝血因子(例如组织因子)生成增加、纤维蛋白溶解功能受损以及内皮的抗凝血功能受损[29]。流感病毒和其他呼吸道病毒感染后,与血小板活化和心肌梗死风险相关的基因发生表达[29],并发心肌梗死的肺炎患者的血小板活化和血栓素合成水平更高[30],全身和斑块内炎性活动增加、高凝状态以及血小板和内皮功能障碍持续至急性感染临床消退之后[31]。在存在循环促凝血因子和活化血小板的情况下,血液循环中血小板、纤维蛋白和中性粒细胞积聚,红细胞被捕获,这些都会导致冠状动脉急性闭塞,即发生 1 型心肌梗死。

供氧-需氧失衡 2 型心肌梗死,是指氧供需失衡导致缺血的心肌缺血坏死[32]。研究表明,在应激条件下,冠状动脉阻塞和舒张灌注时间是限制心内膜下灌注和与心肌功能障碍程度相关的因素。急性感染会导致 IL-1、TNF-α 和儿茶酚胺释放,这些物质会增加核心体温、需氧量和心率。心率加快会缩短心脏舒张期的充盈时间,减少主要发生于心动周期中舒张期的冠状动脉灌注[33]。这其中细胞因子也起到抑制心排血量的作用,感染产生的毒素也可以引起冠状血管收缩和心肌收缩力的丧失[34]。在老年人中,慢性斑块造成的冠状动脉狭窄和毒素介导的血管收缩均可能加重心脏代谢不匹配。尤其在呼吸道感染(肺炎等)中,由于通气-灌注缺陷,血氧水平可能下降,从而进一步减少心肌供氧[35]。如果发生感染性休克,会对冠状动脉供血有显著的不良影响。这些因素共同造成需氧量和供氧量的不匹配,导致需氧量增加性心肌缺血,出现 2 型心肌梗死。

心肌细胞病变 Brown 等[36]发现死于肺炎球菌肺炎的 9 例患者中,2 例发生心肌细胞破裂,中性粒细胞浸润相对很少。肺炎链球菌感染导致的菌血症时期,心肌细胞的病变包括心肌细胞的空泡化和丧失,而无炎性细胞积聚。这些变化可能与肌钙蛋白水平升高、心律失常和心电图异常相关。心肌细胞破裂导致心脏局部微小病变的形成可能导致传导途径中断,肺炎球菌溶血素引起的心肌细胞死亡以及毒素释放导致的微血管收缩性丧失可以导致心功能不全[37]。Headley 等[38]发现,感染结核分枝杆菌后的小鼠具有明显的心律失常、心脏肥大、心脏纤维化。抗生素治疗后心肌细胞形成胶原沉积,伴有大量免疫细胞浸润,提示微小细胞形成后细菌死亡导致心肌重塑,这种心肌变化也见于心肌梗死后。这种疤痕已被证明可导致心脏电生理和功能的永久性变化[39,40]。心肌损伤病灶未累及冠状动脉,但当发生心肌梗死时,病灶会加重心肌损伤,并且可能引起心律失常以及新发心力衰竭或心力衰竭恶化[41~43]。最后,细胞因子风暴具有广泛的效应(包括抑制线粒体对氧的利用),它会导致脓毒症患者发生急性心力衰竭,甚至发生在无心脏危险因素或冠状动脉异常的年轻人[44,45]。

接种疫苗与药物治疗

Smeeth 小组[2]研究显示无论是接种流感疫苗还是肺炎球菌疫苗,甚至破伤风疫苗均能显著降低感染后的急性心血管病发病风险,尤其是 AMI 的风险。一项荟萃分析指出,接种流感疫苗可降低冠心病患者复合心血管事件的风险[46]。另一项 MATA 分析表明,接种肺炎球菌多糖疫苗的 65 岁及以上人群,心肌梗死风险降低约 17%,该分析同时指出该疫苗可能具有心脏保护作用[47]。有研究表示,对于 65 岁及以上的人群,接种肺炎球菌疫苗可能产生获益[48]。

Roberto 等[49]研究显示,接受糖皮质激素和抑制血管紧张素药物的患者患肺炎后心肌梗死的风险低于未接受这些药物治疗的患者。但是对于是否积极应用此类药物,仍缺乏大样本研究支持。

我国的冠心病和 AMI 的发病率和死亡率还在呈现逐渐上升趋势,基于上述研究成果,对于心血管疾病患病人群,我们是否应该提倡积极使用预防呼吸道病原体的疫苗?对于有心血管疾病危险因素但无明确用药指征人群,在急性感染期,是否应该预防性使用他汀类药物和血小板活化抑制药物以减少心脑血管疾病发病的风险?这些仍是值得进行临床研究的问题。急性感染后其他心血管事件(例如心力衰竭、心律失常和卒中)的风险也会增加,相关机制仍需进一步确定。如果能明确急性感染和心血管系统之间的相互作用,有助于我们降低急性感染后的心肌梗死和其他心血管事件风险。

参 考 文 献

1 Warren-Gash C, Blackburn R, Whitaker H, et al. Laboratory-confirmed respiratory infections as triggers for acute myocardial infarction and stroke: a self-controlled case series analysis of national linked datasets from Scotland[J]. Eur Respir J, 2018, 51(3): 1701794.

2 Smeeth L, Thomas SL, Hall AJ, et al. Risk of myocardial infarction and stroke after acute infection or vaccination[J]. New Engl J Med, 2004, 351(25): 2611-2618.

3 Pearce DC, McCaw JM, McVernon J, et al. Influenza as a trigger for cardiovascular disease: An investigation of serotype, subtype and geographic location[J]. Environ Res, 2017, 15(6): 688-696.
4 Vejpongsa P, Kitkungvan D, Madjid M, et al. Outcomes of acute myocardial infarction in patients with influenza and other viral respiratory infections[J]. Am J Med, 2019, 132(10): 1173-1181.
5 López-Fernández Laura, López-Messa Juan, Andrés-de Llano Jesús, et al. Relationship between seasonal influenza rates and hospitalization and mortality rates due to acute cardiovascular diseases in a Spanish region[J]. Med Clin (Barc), 2019, 153: 133-140.
6 Wu HH, Chang YY, Kuo SC, et al. Influenza vaccination and secondary prevention of cardiovascular disease among Taiwanese elders-A propensity score-matched follow-up study[J]. PloS one, 2019, 14(7): e0219172.
7 Cuervo G, Viasus D, Carratalà J. Acute myocardial infarction after laboratory-confirmed influenza infection[J]. New Engl J Med, 2018, 378(26): 2540.
8 Musher DM, Alexandraki I, Graviss EA, et al. Bacteremic and nonbacteremic pneumococcal pneumonia. A prospective study[J]. Medicine, 2000, 79(4): 210-221.
9 Musher DM, Rueda AM, Kaka AS, et al. The association between pneumococcal pneumonia and acute cardiac events[J]. Clin Infect Dis, 2007, 45(2): 158-165.
10 Corrales-Medina VF, Serpa J, Rueda AM, et al. Acute bacterial pneumonia is associated with the occurrence of acute coronary syndromes[J]. Medicine, 2009, 88(3): 154-159.
11 Violi F, Cangemi R, Falcone M, et al. Cardiovascular complications and short-term mortality risk in community-acquired pneumonia[J]. Clin Infect Dis, 2017, 64(11): 1486-1493.
12 Corrales-Medina VF, Alvarez KN, Weissfeld LA, et al. Association between hospitalization for pneumonia and subsequent risk of cardiovascular disease[J]. JAMA, 2015, 313(3): 264-274.
13 Dalager-Pedersen M, Søgaard M, Schønheyder HC, et al. Risk for myocardial infarction and stroke after community-acquired bacteremia: a 20-year population-based cohort study[J]. Circulation, 2014, 129(13): 1387-1396.
14 Coutsoumbas GV, Di Pasquale G. Influenza infection and risk of myocardial infarction: the protective effect of influenza vaccination. One more reason to vaccinate[J]. G Ital Cardiol, 2018, 19(11): 620-627.
15 Bergh C, Fall K, Udumyan R, et al. Severe infections and subsequent delayed cardiovascular disease[J]. Eur J Prev Cardiol, 2017, 24(18): 1958-1966.
16 Jafarzadeh SR, Thomas BS, Warren DK, et al. Longitudinal study of the effects of bacteremia and sepsis on 5-year risk of cardiovascular events[J]. Clin Infect Dis, 2016, 63(4): 495-500.
17 Libby P. Mechanisms of acute coronary syndromes and their implications for therapy[J]. New Engl J Med, 2013, 368(21): 2004-2013.
18 Musher DM, Abers MS, Corrales-Medina VF. Acute infection and myocardial infarction[J]. New Engl J Med, 2019, 380(2): 171-176.
19 Otsuka F, Joner M, Prati F, et al. Clinical classification of plaque morphology in coronary disease[J]. Nature reviews. Cardiology, 2014, 11(7): 379-389.
20 Beristain-Covarrubias N, Perez-Toledo M, Thomas MR, et al. Understanding infection-induced thrombosis: lessons learned from animal models[J]. Front Immunol, 2019, 10(2569).
21 Kaynar AM, Yende S, Zhu L, et al. Effects of intra-abdominal sepsis on atherosclerosis in mice[J]. Critical care, 2014, 18(5): 469.
22 Semeraro N, Ammollo CT, Semeraro F, et al. Sepsis, thrombosis and organ dysfunction[J]. Thromb. Res, 2012, 129(3): 290-295.
23 Campbell RA, Schwertz H, Hottz ED, et al. Human megakaryocytes possess intrinsic antiviral immunity through regulated induction of IFITM3[J]. Blood, 2019, 133(19): 2013-2026.
24 Guan XR, Li X, Xin XM, et al. Influenza virus infection and risk of acute myocardial infarction[J]. Inflammation, 2008, 31(4): 266-272.
25 Rubinfeld GD, Smilowitz NR, Berger JS, et al. Association of thrombocytopenia, revascularization, and in-hospital outcomes in patients with acute myocardial infarction[J]. Am J Med, 2019, 132(8): 942-948. e5.
26 Lichenstein R, Magder LS, King RE, et al. The relationship between influenza outbreaks and acute ischemic heart disease in Maryland residents over a 7-year period[J]. J Infect Dis, 2012, 206(6): 821-827.
27 Headley CA, Gerberick A, Mehta S, et al. Nontuberculous mycobacterium M. avium infection predisposes aged mice to cardiac abnormalities and inflammation[J]. Aging cell, 2019, 18(3): e12926.
28 Rose JJ, Voora D, Cyr DD, et al. Gene expression profiles link respiratory viral infection, platelet response to aspirin, and acute myocardial infarction[J]. PloS one, 2015, 10(7): e0132259.
29 Mangold A, Alias S, Scherz T, et al. Coronary neutrophil extracellular trap burden and deoxyribonuclease activity in ST-elevation acute coronary syndrome are predictors of ST-segment resolution and infarct size[J]. Circ Res, 2015, 116(7): 1182-1192.
30 Cangemi R, Casciaro M, Rossi E, et al. Platelet activation is associated with myocardial infarction in patients with pneumonia[J]. J Am Coll Cardiol, 2014, 64(18): 1917-1925.
31 Yende S, D'Angelo G, Mayr F, et al. Elevated hemostasis markers after pneumonia increases one-year risk of all-cause and cardiovascular deaths[J]. PloS one, 2011, 6(8): e22847.
32 DeFilippis AP, Chapman AR, Mills NL, et al. Assessment and treatment of patients with Type 2 myocardial infarction and acute nonischemic myocardial Injury[J]. Circulation, 2019, 140(20): 1661-1678.
33 Smit M, Coetzee AR, Lochner A. The Pathophysiology of myocardial ischemia and perioperative myocardial infarction[J]. J Cardiothor Vasc An, 2020, 34(9): 2501-2512.
34 Buja LM, Zehr B, Lelenwa L, et al. Clinicopathological complexity in the application of the universal definition of myocardial infarction[J]. Cardiovasc Pathol, 2020, 44(10): 7153.
35 Quinton LJ, Walkey AJ, Mizgerd JP. Integrative physiology of pneumonia[J]. Physiol Rev, 2018, 98(3): 1417-1464.
36 Brown AO, Mann B, Gao G, et al. Streptococcus pneumoniae translocates into the myocardium and forms unique microlesions that disrupt cardiac function[J]. PLoS pathogens, 2014, 10(9): e1004383.
37 Corrales-Medina VF, Suh KN, Rose G, et al. Cardiac complications in patients with community-acquired pneumonia: a systematic review and meta-analysis of observational studies[J]. PLoS medicine, 2011, 8(6): e1001048.
38 Headley CA, Gerberick A, Mehta S, et al. Nontuberculous mycobacterium M. avium infection predisposes aged mice to cardiac abnormalities and inflammation[J]. Aging cell, 2019, 18(3): e12926.
39 Arenal A, Hernández J, Pérez-David E, et al. Do the spatial characteristics of myocardial scar tissue determine the risk of ventricular arrhythmias[J]? Cardiovasc Res, 2012, 94(2): 324-332.
40 Wu KC. Assessing risk for ventricular tachyarrhythmias and sudden cardiac death: is there a role for cardiac MRI[J]? Circ-Cardiovasc Imag, 2012, 5(1): 2-5.
41 Corrales-Medina VF, Musher DM, Wells GA, et al. Cardiac complications in patients with community-acquired pneumonia: incidence timing risk factors and association with short-term mortality[J]. Circulation, 2012, 125(6): 773-781.
42 Corrales-Medina VF, Musher DM, Shachkina S, et al. Acute pneumonia and the cardiovascular system[J]. Lancet, 2013, 381(9865): 496-505.
43 Feldman C, Anderson R. Community-acquired pneumonia: pathogenesis of acute cardiac events and potential adjunctive therapies[J]. Chest, 2015, 148(2): 523-532.
44 Drosatos K, Lymperopoulos A, Kennel PJ, et al. Pathophysiology of sepsis-related cardiac dysfunction: driven by inflammation energy mismanagement or both[J]? Current heart failure reports, 2015, 12(2): 130-140.
45 De Angelis E, Pecoraro M, Rusciano MR, et al. Cross-talk between neurohormonal pathways and the immune system in heart failure: a review of the literature[J]. Int J Mo Sci, 2019, 20(7): 186-188.
46 Caldeira D, Rodrigues B, David C, et al. The association of influenza infection and vaccine with myocardial infarction: systematic review and meta-analysis of self-controlled case series[J]. Expert Rev Vaccines, 2019, 18(11): 1211-1217.
47 Ren S, Newby D, Li SC, et al. Effect of the adult pneumococcal polysaccharide vaccine on cardiovascular disease: a systematic review and meta-analysis[J]. Open heart, 2015, 2(1): e000247.
48 Kaplan A, Arsenault P, Aw B, et al. Vaccine strategies for prevention of community-acquired pneumonia in Canada: Who would benefit most from pneumococcal immunization[J]? Can Fam Physician, 2019, 65(9): 625-633.
49 Cangemi R, Falcone M, Taliani G, et al. Corticosteroid Use and Incident Myocardial Infarction in Adults Hospitalized for Community-acquired Pneumonia[J]. Ann Am Thorac Soc, 2019, 16(1): 91-98.

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