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心肌梗死后交感神经激活致室性心律失常机制的研究进展

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[摘 要] 心肌梗死后室性心律失常是在临床病例中导致此种心脏病患者猝死的主要原因之一。因此，为降低猝死率，缺血诱导心律失常的病理机制引起广泛关注。交感神经过度激活促使神经对心肌活动支配的不均一性，导致心脏电传导紊乱，是心律失常发生和维持的重要机制，抑制交感神经过度激活可有效防止室性心律失常的发生。

[关键词] 心肌梗死；室性心律失常；交感神经激活

Research progress on the mechanism of ventricular arrhythmia caused by sympathetic nerve activation after myocardial infarction

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Abstract Ventricular arrhythmia after myocardial infarction is one of the main causes of sudden death in patients with this heart disease in clinical cases. Therefore, in-depth researches on the mechanism of ischemia-induced arrhythmia in order to reduce the rate of sudden death have attracted widespread attention. Excessive activation of sympathetic nerves leads to uneven innervation of the myocardium and further results in cardiac electrical conduction disorder, which present an important mechanism for the occurrence and maintenance of arrhythmia. Additionally, targetd intervention performed in them can effectively prevent the occurrence of ventricular arrhythmia.

Keywords myocardial infarction; ventricular arrhythmia; sympathetic nerve activation

心肌梗死(myocardial infarction，MI)时心脏猝死的大多数病例归因于急性冠脉闭塞引发的持续性室性心律失常(ventricular arrhythmia，VA)[1]。室性心动过速、心室颤动等恶性心律失常极易引起MI患者出现血流动力学不稳定[2]，因其病情危急且严重影响患者生命健康，受到医学界高度重视。但目前临床仍无特效药物及措施进行有效防治，因此有必要深入探究VA的发生机制，为VA的预防提供指导[3]。近年来，交感神经过度激活被认为是MI后VA发生的重要机制之

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一，本文就MI后交感神经过度激活导致VA发生机制的研究进展作一综述。

1 MI 后自主神经功能异常对 VA 的影响

自主神经对心肌缺血时心脏电生理的影响研究较多[4-6]，交感神经刺激诱导心电复极改变及纤颤阈值降低，促进室颤发生；而心室中副交感神经刺激能延长心室动作电位时程(action potential duration，APD)和有效不应期(effective refractory period，ERP)，增加电生理稳定性。

尽管有数据[5]表明自主神经功能异常在VA发生中至关重要，但尚未在个体中建立直接的时间关系。近期在大鼠模型[1]中发现：结扎冠脉后立即出现迷走神经活动减少的现象，并且在整个观察期内保持较低水平；而交感神经逐渐激活，并一直保持上升趋势直到记录结束。该实验表明：MI后先出现迷走神经戒断，随后交感神经逐渐激活，可能分别与早期和延迟期心律失常发生有关。此外，用交感神经节前神经元的中枢抑制剂可乐定预处理的MI大鼠，延迟期VA发生率较低，但早期心律失常不受影响[2]。

2 MI 后交感神经过度激活机制及其对 VA 的影响

2.1 神经重构

MI后梗死区心肌发生去神经化，周边未坏死区神经轴突以非正常排列的“芽生”方式修复，称为心脏神经重构。研究[7]发现：MI可导致局部神经生长因子(nerve growth factor，NGF)立即释放，随后生长相关蛋白43(growth associated protein 43，GAP43)表达上调，NGF和GAP43逆行转运至左侧星状神经节(left stellate ganglion，LSG)，LSG神经发芽信号导致整个心脏神经密度增加。有研究[8]证实：加入NGF功能阻断抗体可消除神经发芽作用。在MI慢性期[9]，局部心脏神经重构增加心室电不稳定性，并增强交感神经重建的空间异质性。梗死部位NGF和GAP43表达持续快速上调被认为是MI后交感神经过度增生的基础，这种交感神经不均一性增生是导致心律失常猝死的常见原因。β受体阻断剂和血管紧张素转换酶抑制剂的治疗方法强调了在控制VA时抑制神经重构的重要性[9]，由此可显著降低MI后猝死的发生率。因此，对MI后神经重构的干预可为VA治疗提供新机会。

2.2 下丘脑室旁核中炎性因子作用

MI后恶性心律失常是由交感神经过度激活导致的致死性并发症之一。研究[10]表明：下丘脑室旁核(paraventricular nucleus，PVN)内炎性因子参与心血管交感神经的调节。

2.2.1 巨噬细胞诱导型 C 型凝集素受体

PVN是大脑皮层下调节心血管活动的高级中枢[11-12]。研究[13]发现：源于PVN的巨噬细胞诱导型C型凝集素(macrophage-inducible C-type lectin，Mincle)受体在交感神经兴奋以及MI后VA中具有直接作用。先天免疫在保护宿主免受病原体侵袭以及包括MI在内多种疾病病理过程中具有重要意义[14]，Mincle可以通过识别Sin3A相关蛋白130 kD(Sin3A-associated protein 130，SAP130)激活[15]；激活Mincle受体后，下游酪氨酸蛋白激酶被磷酸化，合成促炎细胞因子，引发免疫炎症反应。有研究[13]表明：MI后24 h，PVN内Mincle表达显著增加，并伴有交感神经过度激活。在PVN局部应用干扰Mincle表达的双链沉默核糖核酸(silencing ribonucleic acid，siRNA)沉默*Mincle*基因，可减少交感神经激活。程序电刺激后，与用Mincle siRNA处理的大鼠相比，MI大鼠心律失常评分明显增高，说明抑制Mincle可减少MI后VA。SAP130是Mincle的内源性配体，可诱导高水平NOD样受体家族3(NOD-like receptors，NLRP3)和成熟白细胞介素-1β(Interleukin-1β，IL-1β)合成。PVN靶向注射NLRP3 siRNA或IL-1β拮抗剂gevokizumab可减轻交感神经亢进。总之，抑制PVN内小胶质细胞中Mincle可通过减弱交感神经亢进和心室敏感性来预防VA，部分原因是抑制NLRP3/IL-1β轴。干预Mincle信号通路可能成为预防MI后VA的新靶点。

2.2.2 小胶质细胞嘌呤能离子通道型受体 7

小胶质细胞嘌呤能离子通道型受体7(purinergic ligand-gated ion channel 7 receptor，P2X7R)是细胞外三磷酸腺苷离子型P2X受体之一，在肿瘤坏死因子-α(tumor necrosis factor-α，TNF-α)和IL-1成熟和释放中起关键作用。研究[16]发现：上调小胶质细胞P2X7R可提高PVN中TNF-α、IL-1水平和心率变异性。该结果表明：PVN中小胶质细胞P2X7R可以增强急性心肌缺血大鼠交感神经活动，增加VA发生率。在巨噬细胞中，P2X7R通过P2X7/NLRP3途径调节IL-1β，促进梗死后炎症的发生[17]。P2X7R拮抗剂A-740003可改善由NLRP3/IL-1β引起的心脏重构，干预P2X7信号通路可能是改善MI后交感神经过度激活的一种新方法。

2.3 内皮素 -B 受体缺乏

实验研究[18]表明：在急性缺血早期阶段内皮素-B受体(endothelin-B receptor，ETB)可能发挥保护作用。研究[19]发现：ETB缺陷型大鼠心率变异性指数及血清去甲肾上腺素水平升高，表明ETB缺乏可引起交感神经过度激活，诱导心电复极改变、促进功能性折返形成以及室性心动过速/心室颤动的发生。在MI大鼠模型中发现[2]，功能性缺乏ETB可增强交感神经促VA作用，导致心肌缺血大鼠病死率增加。

2.4 心脏交感神经反射调节

交感神经过度激活在心衰和致死性心律失常的发病机制中起着重要作用，主要通过心脏交感神经反射调节[20]。研究[21]表明：抑制心脏交感传入可减弱心脏重构，并改善心血管功能障碍。心脏交感传入末端包含瞬时受体电位香草酸1受体[22]，鞘内注射其选择性受体激动剂树脂毒素可以抑制交感神经活动传入。在冠状动脉闭塞的大鼠模型中，将树脂毒素注入胸2/3间隙[23]，2周后发现鞘内注射树脂毒素可以保护心脏免受压力超负荷引起的心脏重构和功能障碍的影响。同时，鞘内注射树脂毒素抑制基线心脏交感神经张力，导致交感神经活动频率和幅度下降；此外，鞘内注射树脂毒素可引起血液中去甲肾上腺素水平下降，这表明其对交感神经递质释放具有抑制作用。电生理结果显示：鞘内注射树脂毒素可显著逆转APD的缩短，降低室性心动过速的易感性和相关风险，这可能成为有效预防致死性心律失常的新方法。

2.5 Marshall 韧带

Marshall韧带(ligament of Marshall，LOM)作为“心包残留皱襞”于1850年首次被提出，此韧带是由胚胎发育期左侧腔静脉退行产物形成。LOM韧带远端中存在很多交感神经元[24-25]，刺激LOM韧带远端可显著升高血压并缩短ERP，提示刺激LOM韧带远端可激活心脏交感神经系统。LOM韧带远端消融可降低急性MI期间心率变异性和血清去甲肾上腺素浓度而延长ERP[24]。此外，LOM韧带远端消融也可抑制LSG刺激引起的血压升高，并降低MI或联合LSG刺激导致VA的发生率。研究[26]发现：急性MI期间选择性消融LOM远端抑制VA的发生，可能与减少心肌细胞间缝隙连接蛋白43(connexin 43，Cx43)丢失，抑制氧化应激、细胞凋亡和炎症有关；这是由于LSG和心室之间的交感神经管受损，导致心脏交感神经活动减少。

3 交感神经对其他促心律失常发生机制的影响

3.1 氧化应激

氧化应激、细胞凋亡和炎症参与缺血性心律失常的发生[27]，超氧化物抑制剂可有效减少缺血性心律失常，交感神经激活可增加氧化应激和细胞凋亡水平[28]。有研究[29]证实：心脏自主神经系统与炎症之间存在相关性。TNF-α、IL-6和基质金属蛋白酶(matrix metalloproteinase，MMP)是梗死心肌中发生电重构时升高的关键细胞因子[30]，可增加VA发生的风险。丙二醛及过氧化物酶体增殖物激活受体γ共激活因子1α(peroxisome proliferator-activated receptor-γ coactlvator-1α，PGC-1α)是氧化应激系统中起关键作用的转录调节因子[31]。B淋巴细胞瘤-2相关X蛋白(Bcl-2 associated X protein，Bax)及半胱氨酸天冬氨酸特异性蛋白酶-3(cysteine aspartic acid specific protease-3，caspase-3)参与细胞凋亡过程[28]。研究[26]发现：AMI患者血清中TNF-α、IL-6和丙二醛浓度升高及Bax、caspase-3蛋白表达增加，而LOM韧带远端消融可以减弱这些变化。这表明急性MI期间高水平的氧化应激、细胞凋亡和炎症反应，可通过减弱心脏交感神经活动而被抑制。

在MI小鼠模型中[32]发现：较高水平氧化应激和细胞凋亡伴随着L型Ca^{2+}通道活性增强及Ca^{2+}超载。此外，氧化应激可能通过改变Na^{+}、Ca^{2+}和K^{+}离子稳态，调控电压门控离子通道活性及诱导Cx43重构而促进VA的发生。

3.2 电重构

自主神经系统可改变急性MI期间Cx43的表达[33]，Cx43是心脏电刺激传播中的主要缝隙连接蛋白质[34]。正常情况下，Cx43有结构、数量及空间分布的特异性，MI后Cx43重构导致心肌局部电耦联紊乱，传导速度减慢、单向传导阻滞及电传导不协调，进而形成复杂的异质波阵面扩展径路，为心律失常发生创造条件[35]。缝隙连接增强剂Rotigaptide通过增加插入式功能间隙连接耦联来提高传导速度[36]。Rotigaptide可有效预防MI期间程序性刺激诱发的折返性VA，并在持续性室颤期间降低除颤阈值及MI后心律失常的风险[37]。研究[26]发现：急性MI期间Cx43表达下调，LOM韧带远端消融可通过减弱心脏交感神经活动来减少

Cx43丢失；MI时短期缝隙连接调节可能代表了一种新颖的治疗策略。

4 结语

MI后VA的发生是导致患者病情加重和高病死率的重要原因之一。VA的发生是交感神经过度激活、电重构及细胞因子等多种机制共同参与的结果。不断探索其发生机制可为临床中预防恶性心律失常的发生以及开发抗心律失常药物提供新的切入点。

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