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Kounis综合征的诊治研究进展

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摘　要

Kounis综合征(Kounis Syndrome, KS)是一种基于过敏反应的急性冠状动脉综合征(Acute Coronary Syndrome, ACS)，目前可分为三种类型：血管痉挛性过敏性心绞痛(I型)、过敏性心肌梗死(II型)和支架血栓形成(III型)。KS发病率并不低，尤其是在急诊抢救室，但由于其缺乏特征的临床表现及体征，以及医生对其鲜少了解，在临床上较难与其他急症鉴别，目前尚无标准诊疗方案，主要依靠心血管和过敏性临床症状和体征，以及实验室、心电图、超声心动图和血管造影证据。本文就KS的诊断与治疗研究进展综述如下。

关键词

Kounis综合征，过敏反应，急性冠脉综合征

Research Progress in Diagnosis and Treatment of Kounis Syndrome

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Abstract

Kounis syndrome (KS) is an acute coronary syndrome (ACS) based on allergic reaction. At present, it can be divided into three types: vasospasm allergic angina (type I), allergic myocardial infarction (type II) and stent thrombosis (type III). The incidence rate of KS is not low, especially in the

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emergency room. However, due to its lack of characteristic clinical manifestations and signs, and doctors' little understanding of it, it is difficult to differentiate KS from other emergencies clinically. At present, there is no standard diagnosis and treatment plan, which mainly depends on cardiovascular and allergic clinical symptoms and signs, as well as laboratory, electrocardiogram, echocardiography and angiographic evidence. This article reviews the progress in diagnosis and treatment of KS.

Keywords

Kounis Syndrome, Allergic Reaction, Acute Coronary Syndrome

1. 引言

Kounis 综合征是指在过敏或过敏反应中发生与肥大细胞和血小板活化相关的急性冠脉综合征[1]。1950 年，Pfister 和 Plice [2]发表了首篇关于 Kounis 综合征的病例报告：一名 49 岁男子在服用青霉素后出现急性心肌梗死并出现荨麻疹，但当时并未引起重视，直到 1991 年，Kounis 和 Zavras [3]在一篇文章中引入了“过敏性心绞痛”和“过敏性心肌梗死”这两个术语，也就是现在的“Kounis 综合征”。KS 目前可分为三种类型：血管痉挛性过敏性心绞痛(I 型)、过敏性心肌梗死(II 型)和支架血栓形成(III 型) [4] [5]。Helbling [6]等人的一项回顾性研究估算了该病的发病率：约为每年每 10 万居民 7.9~9.6 例，该作者认为由于漏诊、未识别和未确诊病例，疾病的发病率被严重低估。但在过去二十年中，随着医生对该疾病的认知不断提高，KS 的病例报道在世界范围内屡见不鲜[7]。

2. KS 的发病机制

因为与 KS 相关的大多数文献为病例报告所以至今确切发病机制仍然难以捉摸。目前主要生理机制被归类为与肥大细胞相关疾病和炎症细胞相互作用相关的 ACS。肥大细胞广泛存在于心脏组织中，并优先位于冠状动脉斑块部位[8] [9] [10]。肥大细胞可浸润斑块侵蚀或破裂的区域，同时也可作用于未受损的平滑肌细胞。有研究显示，冠状动脉斑块患者的心脏肥大细胞负荷比健康人的冠状动脉高 200 倍[11]。具体作用机制可概述为以下步骤：第一步：肥大细胞的激活。在过敏反应期间，肥大细胞通过与高亲和力受体 FcεRIs 抗原结合的免疫球蛋白 E(IgE)交联而被激活，其次也可发生在过敏毒素如 C3a 和 C5a、腺苷或其他刺激物的存在下[12]。第二步：激活导致多种预先形成的炎症介质如组胺、类胰蛋白酶和糜蛋白酶以及新产生的花生四烯酸衍生介质、细胞因子和趋化因子的释放[13]。第三步：肥大细胞诱导的介质释放对冠状动脉有许多影响，包括血管痉挛、斑块破裂和血栓形成。如组胺释放可导致冠状动脉收缩、舒张压降低和内膜增厚，这可能导致冠状动脉斑块破裂和随后的冠状动脉血栓形成[3] [11]。组胺还可以启动血小板活化和聚集；白三烯是有效的血管收缩剂，而凝乳酶和组织蛋白酶 D 可能会将血管紧张素 I 转化为血管紧张素 II，是一种有效的血管收缩剂[1]。

目前已知的致病因素包括在日常临床实践中广泛使用的药物，如非甾体抗炎药(NSAIDs)和镇痛药[14]、抗生素[15] [16] [17]、抗肿瘤药[18]、质子泵抑制剂[19]、造影剂[20] [21]、皮质类固醇[22] [23] [24]、抗高血压药物[25]以及其他[26] [27]，以及环境暴露[28]、昆虫叮咬[29] [30] [31]、食物[32] [33]和支架[34]

[35]。据文献报道，药物是 KS 最常见的病因[36]。在 Abdelghany [37]等人对 175 例 KS 病例报告的一篇综述中，最常见的诱因是抗生素(27.4%)和昆虫叮咬(23.4%)。

3. KS 的诊断

1) 临床表现。① 心脏症状：约 86.6%的患者会出现胸痛，这是最常见的症状。与 ACS 疼痛类似，它被描述为压榨性疼痛，并且可能放射至颈部、下颌或手臂。并且可伴随出汗、面色苍白、恶心、呕吐、心悸和气短；② 过敏症状：过敏症状的跨度非常广泛，从轻微症状到威胁生命均可发生。常见症状包括荨麻疹、皮疹、粘膜受累、面部水肿、喘息、低血压和休克。2) 过敏史：25%的患者有已知的过敏史或曾经经历过过敏反应。所以必须详细记录患者的药物及食物过敏史，包括既往对对碘造影剂的过敏情况。3) 辅助检查。① 实验室检查：KS 的实验室检查多无特异性，对疾病的诊断意义不大，常见的检测指标有嗜酸性粒细胞，心脏生物标志物(CK-MB，肌钙蛋白)，C-反应蛋白以及 IgE 水平，值得一提的是建议应在出现初始症状后的半小时和随后的 2 小时内每 30 分钟测量一次类胰蛋白酶[37]。② 心电图：心电图变化通常是短暂的且无特征性，通常发生在疼痛发作期间。ST 段抬高型心肌梗死(ST-Elevation Myocardial Infarction, STEMI)是 KS 最常见的心电图改变。目前没有特定的变化来区分 KS 和非过敏性 ACS。KS 的心电图报告可提示心肌缺血(ST 段压低和 T 波倒置)、窦性心动过速或心动过缓、心脏传导阻滞、心房颤动、心室颤动、异位心率、QRS 波和 QT 延长的 ST-T 变化等[38]。③ 超声心动图：在 KS 中，超声心动图研究可能会显示受累动脉分布的局部壁运动异常[39]。与急性心肌炎不同，在该冠状动脉区域，心肌的心内膜下层会受到影响，此点可帮助区分 KS 与急性心肌炎[40]。

4. KS 的治疗

目前 KS 的治疗尚无规范治疗方案，治疗存在一定困难。保持心肌血运重建的同时处理过敏反应是治疗 KS 的主要原则[41]。当患者出现急性冠状动脉综合征时，应根据 ACS 指南进行治疗，且目前大多数数据来自病例报告。而且更为复杂的是一些用于治疗 KS 心脏症状的药物会使过敏反应恶化，而其他用于治疗过敏症状的药物则会加重心脏功能紊乱。① I 型：对于 I 型 KS 来说，治疗过敏反应一般情况下可以减轻心脏症状：糖皮质类固醇可抑制动脉高反应性并减轻炎症[42]，但尚未证明可预防双相反应[43]；H1 和 H2 受体拮抗剂也可减少过敏症状，但在使用时应缓慢静脉推注，此类药物可能导致低血压并恶化冠状动脉的灌注[30]；若血压正常时可使用钙通道阻滞剂(Calcium Channel Blocker, CCB)和硝酸酯类有助于消除超敏反应引起的血管痉挛，但硝酸甘油必须谨慎使用，因为可能会导致低血压和心动过速，并使过敏反应进一步恶化[44]；由于肾上腺素会加重心肌缺血，诱发冠状动脉血管痉挛和心律失常，因此在 KS 中应谨慎使用。但是当患者过敏反应风险超过了心肌缺血恶化的风险时可酌情考虑使用[45]。② II 型：II 型患者的治疗方法与 ACS 相似，并辅以抗组胺药和类固醇[46]。必要时可使用硝酸酯和 CCB 等血管扩张剂[47]。③ III 型患者的治疗也应遵循 ACS 指南。当需要时，支架内血栓的抽吸对于组织学分析和血栓嗜酸性粒细胞和肥大细胞的染色至关重要[46]，这些可能提示过敏反应，并对患者的后续治疗产生影响，此外，部分学者认为如果患者在冠状动脉支架置入后出现过敏反应，类固醇、抗组胺药和肥大细胞稳定剂(如色甘酸钠)可帮助缓解过敏症状，并采用脱敏疗法[46]。同时部分学者认为若通过相关实验确认患者对镍钛合金过敏，且脱敏失败，则可能需要移除植入支架[48]。

5. 预后

经过治疗 KS 通常预后良好，大多数患者完全康复。KS 的 I 型是最常见的。在这种类型中，由于过敏症状的早期出现，早期识别和治疗是可能的。由此产生的冠状动脉血管痉挛可以用血管扩张剂逆转，

根据以前的报道，其预后也很好。总的来说，KS 的严重并发症是罕见的：心源性休克发生率为 2.3%。心脏骤停的发生率为 6.3%。总死亡率为 2.9% [49]。

6. KS 与新型冠状病毒肺炎

新型冠状肺炎病毒是一种可影响心血管系统、消化系统、血液系统、呼吸系统、神经系统等多系统的病毒，新冠肺炎诱导的过度免疫反应伴随着细胞因子的失控释放，最终导致细胞因子风暴似乎是这些并发症的常见发病机制。新型冠状病毒肺炎患者的心肌损伤可归因于冠状动脉痉挛、斑块破裂和微血栓形成、缺氧损伤或细胞因子风暴[50]，其病理生理与库尼斯综合征的三种分类有许多相似之处。此外，KS 也出现在接种预防新冠肺炎疫苗后的病例中，新冠肺炎相关疫苗辅料如聚山梨酯、聚乙二醇(PEG)和氨丁三醇同时也构成潜在的过敏性物质[51] [52]，所以 KS 的诊疗思路同时也为新冠肺炎导致的心肌损伤提供了新的治疗方向。

7. 总结

Kounis 综合征并不是一种罕见的疾病，而是一种诊断不足和认识不足的疾病，该疾病临床表现广泛，病因不断增加，包括药物、造影剂、食品、虫刺、支架等。在急诊，尤其是在当前新型冠状病毒肺炎大流行的基调下，在治疗出现心脏病和过敏症状的患者时，必须保持高度警惕。该综合征有三种类型，治疗过敏反应可以减轻心脏症状，但在存在心肌血运障碍时，则应遵循 ACS 指南。

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