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·综　述·

脓毒症休克快速心律失常研究进展

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［摘要］ 快速心律失常是脓毒症休克的重要临床特点，控制不良的持续性心动过速与不良预后密切相关。脓毒症休克相关快速心律失常的发生机制复杂，药物治疗仍然是当今控制脓毒症休克相关心律失常的主要手段。药物选择存在多样性，对抗心律失常药物的选择及使用方法还有待进一步研究。本文主要对脓毒症休克相关快速心律失常的发病机制及治疗等方面的研究进展进行综述。

［关键词］ 脓毒症；脓毒症休克；快速心律失常；发病机制；药物疗法
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Tachyarrhythmia in septic shock: research progress

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［Abstract］ Tachyarrhythmia is an important clinical feature of septic shock. Poorly controlled persistent tachycardia is closely related to poor prognosis. The pathogenesis of septic shock-related tachyarrhythmia is complex, and drug therapy is still the main choice to control septic shock-related arrhythmia. Diversity of drug choices exists, so the selection and use of antiarrhythmic drugs need to be further studied. This article mainly reviews the research progress in the pathogenesis and treatment of septic shock-related tachyarrhythmia.

［Key words］ sepsis; septic shock; tachyarrhythmia; pathogenesis; drug therapy
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脓毒症、脓毒症休克是免疫系统对感染过度反应的结果，可导致致命的器官功能障碍，约占 ICU 患者死亡原因的 30%[1-2]。快速心律失常是脓毒症休克重要的临床特征，并且在已纠正低血容量、贫血、疼痛和躁动等导致心动过速的病因后往往仍持续存在[3]。对脓毒症休克相关快速心律失常的类型及发生率有众多较为一致的报道，Shahreyar 等[4]通过对 170 多万例脓毒症、脓毒症休克患者分析发现各类心律失常的发生率为 28%，其中心房颤动（以下简称房颤）的发生率为 19%，其他依次为心房扑动（以下简称房扑）2%、室性心动过速 2%、阵发性室上性心动过速 0.6%，并且心律失常可导致较高的院内死亡率及较长的住院时间。周淑清和沈涛[5]回顾性分析了 542 例脓毒症及脓毒症休克患者的临床资料，发现快速心律失常的发生率为 27.3%，其中房颤 15.13%、房扑 1.29%、阵发性室上性心动过速 3.14%、室性心动过速 4.43%、心室颤动 3.51%，快速心律失常可增加患者 28 d 死亡率。Herasevich 等[6]分析 180 例脓毒血症、脓毒症休克患者心律失常类型发现，房颤、房扑占 85.5%，窦性心动过速占 12.8%，包括室上性心动过速在内的其他心律失常占 1.7%。众多研究发现，脓毒症休克相关的快速心律失常主要集中在室上性心律失常[7-10]，而以新发房颤发生率最高，约占各类室上性心律失常的 70%[6,11]，而且脓毒症患者随着病情从较轻阶段发展到休克阶段，

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快速心律失常的发生率不断上升。Kuipers等[12]通过meta分析发现，脓毒症、脓毒症休克新发房颤的平均发生率分别是8%、23%。Meierhenrich等[13]报道脓毒症新发房颤（心室率＞110 min^{-1}）的发生率为4.5%，而在脓毒症休克患者中高达46%。脓毒症休克持续性心动过速限制心室充盈，氧耗增加，可诱发心动过速相关的心肌病、心肌抑钝，以及因钙超载导致的多种心肌不良反应[14-17]，与患者短期和长期的不良预后密切相关[12,18-19]，也是死亡率增加的独立危险因素[20]。相反，将心率保持在正常范围内，可提高脓毒症休克患者的生存率[21]，因此及时控制快速心律失常对救治脓毒症休克患者具有十分重要的临床意义。脓毒症休克相关的快速心律失常发生机制复杂，抗心律失常药物一般对血流动力学都有不利影响，致使人们对脓毒症休克抗心律失常的治疗存有困惑。本文主要就脓毒症休克相关的快速心律失常的发病机制及治疗等方面的研究进展进行综述。

1　脓毒症休克相关快速心律失常的发病机制

1.1　儿茶酚胺对心脏的毒性作用　儿茶酚胺是体内调节心血管功能十分重要的神经递质，包括多巴胺、去甲肾上腺素和肾上腺素。脓毒症休克时交感-肾上腺髓质系统兴奋，去甲肾上腺素和肾上腺素大量释放入血，血液内儿茶酚胺水平较正常生理状态下升高几十倍甚至上千倍。随着血循环中内生性儿茶酚胺的增加，β受体数量下调、对儿茶酚胺敏感性下降[22-26]，需要补充外源性儿茶酚胺类物质维持血液循环，从而使心脏暴露于大量儿茶酚胺中。心脏上具有丰富的β受体，最容易受到交感神经的过度刺激，Tang和Liu[27]对脓毒症动物模型的研究发现，在脓毒症早期（发病9 h之前）β受体表达增加，在大量的儿茶酚胺的作用下，心脏的兴奋性、传导性、自律性显著升高，并出现一系列诸如快速心律失常、舒张期功能受损、心肌缺血等不良后果[28]。心脏在大量的儿茶酚胺长时间作用下，可发生冠状动脉痉挛、微循环功能障碍等[29]，造成心肌缺血，从而大大增加各种快速心律失常的发生风险[30-31]。心脏β受体受到强烈刺激后导致的心肌需氧与供氧的失衡、代谢的变化、细胞凋亡及心肌坏死可造成心肌适应性不良重构，从而导致心脏结构性改变[17,29,32-33]，还可诱发各种快速心律失常。

1.2　自主神经功能受损　自主神经功能不论在生理还是病理条件下，对机体心血管系统的平衡发挥了关键性作用，在脓毒症、脓毒症休克时自主神经功能受损，导致迷走-交感神经张力处于失衡状态，交感神经兴奋，迷走神经受抑制，心率变异度降低[34-37]，且表现为心率增快[38]。脓毒症自主神经功能受损的机制虽然还不十分明确，但此现象已被大量的实验证实。Ramchandra等[39]给意识清醒的羊注入大肠埃希菌后对区域交感神经活性变化进行的研究发现，心脏的交感神经活性增加，并伴有心率明显增快。Vayssettes-Courchay等[40]也发现注射内毒素的麻醉大鼠肾脏的交感神经活性明显增加，并与心动过速有很强的关联性。Gholami等[41]报道，全身炎症与心脏对胆碱能刺激的反应性降低有关，这可能导致心脏起搏细胞部分脱离自主副交感神经控制。另一项研究也表明，IL-6受体在小鼠心房中表达及重组IL-6在隔离心房中孵育都会损害对胆碱能刺激的负变时性反应[42]。这些报道[41-42]反映了脓毒症诱导下窦房结与胆碱能神经控制的解耦联，可以解释全身炎症期间心率变异度降低及心率增快的原因。另有研究发现，脓毒症可导致中枢自主神经功能系统受损，心脏自主中枢神经元和神经胶质细胞的凋亡增加，导致心率变异功能丧失，心率增快[43]。

1.3　炎症　脓毒症、脓毒症休克时的炎症反应除可造成植物神经功能损害外，大量炎症介质及炎症细胞可直接作用于心肌细胞，促进心律失常的发生，如IL-6增加了成人心肌细胞L型钙离子通道电流及降低了心肌肌浆网钙-ATP酶的表达，从而改变心肌细胞的电生理性能，诱发心律失常[44]。Lee等[45]发现，TNF-α直接作用于兔子的心肌细胞，降低了心肌细胞钙-ATP酶的表达，使心肌细胞易于发生延迟后去极化而导致房颤。Zuo等[46]报道，TNF-α通过活性氧迅速增加钙离子自发性释放，促进心律失常的发生。另有研究发现，急性炎症时TNF-α和IL-1β可能会促进钙离子从肌浆网泄漏，促进心肌细胞的触发活动，导致心律失常[47]。除以上炎症因子外，其他炎症分子如IL-1、IL-2、IL-8、IL-10等都与房颤等心律失常的发生有关[48]。不仅是炎症因子，炎症细胞本身也直接与心肌细胞发生相互作用，改变心肌细胞的电生理活性，诱发心律

失常[49]。炎症细胞还可以通过对心房组织的浸润，致使心房电重构、结构重构，导致房颤的发生[50]。

1.4　电解质紊乱　脓毒症、脓毒症休克时大量儿茶酚胺物质作用于β受体，激活细胞膜上 Na^+-K^+-ATP 酶，使细胞外的钾向细胞内转移[51-52]，导致低钾血症。脓毒症时肾素－血管紧张素－醛固酮系统激活，继发性醛固酮增多，以及利尿剂、外源性胰岛素的使用等因素都会导致低血钾，低血钾时心肌兴奋性升高、自律性增加，易产生异位节律而形成各种快速心律失常。低钙血症也是脓毒症的主要临床特征，脓毒症相关的低钙血症高达 70%，在炎症介质的刺激下，细胞膜的完整性受损、钙通道功能障碍等因素导致大量钙离子内流是脓毒症相关低钙血症的主要因素[53]，低血钙时心肌兴奋性升高，动作电位平台期延长，心肌不应期亦延长，容易诱发各种快速心律失常。脓毒症也是低镁血症独立的影响因素[54]，低镁血症增加了严重脓毒症患者的死亡率[55]，低水平的镁会引起严重的心脏改变[56]，特别是心肌电生理特性改变，如 Na^+-K^+-ATP 酶失灵，导致心肌细胞静息电位负值显著变小和相对去极化，心肌兴奋性升高。低镁血症时，镁对钠的阻断作用减弱而内流相对加速，心肌快反应自律细胞自动去极化加速，自律性升高，从而诱发房颤、室上性心动过速、心室颤动等心律失常[57]。低镁血症还会通过影响钾、钙的代谢，导致或加重低钾血症和低钙血症[58-59]，进一步促进心律失常的发生。

2　脓毒症休克相关快速心律失常的治疗

快速心律失常是脓毒症、脓毒症休克重要的临床表现之一，快速心率的控制对脓毒症，特别是脓毒症休克患者稳定血流动力学、改善心脏舒张功能等方面具有十分重要的作用[60]。越来越多的证据表明在危重患者中单独控制心率就可改善血流动力学，而不依赖于心律转复至窦性心律[61-62]，心率的下降可伴随着心脏每博输出指数的升高，中心静脉压的下降，反映了心肌工作效益的提升[17]。近年来对脓毒症患者的心率控制越来越受到人们的重视，抗心律失常的治疗应针对其发生机制进行针对性处理，在纠正容量、贫血、控制体温及抗感染、减轻炎症反应、尽量减少儿茶酚胺类药物的基础上使用抗心律失常药非常必要。

2.1　β-受体拮抗剂　β-受体拮抗剂过去很少用于治疗脓毒症休克，特别是对伴有脓毒性心肌病的患者。因为β-受体拮抗剂具有降低血压、负性肌力等作用，并对已经有心肌抑钝的心脏进一步造成泵衰竭。但近年来随着儿茶酚胺类物质在脓毒症、脓毒性心肌病中的作用机制逐渐揭示，β-受体拮抗剂在脓毒症治疗中受到人们的重视，越来越多的证据表明，β-受体拮抗剂不但能控制脓毒症、脓毒症休克患者的心率，改善舒张期心室充盈，而且还具有提高心脏、血管对儿茶酚胺的敏感性，降低血清中 TNF-α、IL-6 等促炎因子水平，对增强心脏收缩力、保护心脏功能都起到重要作用[3,63-65]。艾司洛尔是高选择性β1-受体拮抗剂，起效快、作用时间短，是常用的脓毒症休克相关快速心律失常治疗药物，但其有效性和安全性尚有争议[66]。Morelli 等[67]证实艾司洛尔在降低脓毒症休克患者心率的同时不会增加不良事件的发生，给脓毒症休克患者静脉注射艾司洛尔控制心率治疗是可行的。一些实验证据表明，艾司洛尔即使小剂量服用也能发挥全身抗炎功效，并对血管张力有一定的改善作用，避免了低血压等副作用[63]。在脓毒症休克动物模型中也发现，艾司洛尔能增加心脏每搏输出量[68]，明显提高存活率[69]。但 Levy 等[70]报道称，艾司洛尔治疗脓毒症休克 6 h、以降低 20% 的心率为目标时，心率下降的同时低血压的发生风险增加，心脏指数下降。Cocchi 等[71]在艾司洛尔治疗脓毒症休克心动过速的临床研究中也没有发现令人期待的结果，治疗组 12 h 的升压药需求比对照组明显增加，两组休克逆转的时间、无休克天数、需要肾脏替代治疗及机械通气均无显著差异。在炎症标志物方面，除了艾司洛尔组 CRP 低于对照组外，两组间 TNF-α、IL-4、IL-6、IL-10 等均无差异。以上众多的研究结果表明，推荐以艾司洛尔为代表的β1-受体拮抗剂常规应用于脓毒症患者之前，还需要更多的研究来解开临床的重要问题，诸如对血流动力学的影响、在具有不同风险亚群患者中的使用及给药时间等问题均需大型临床试验进一步确认。

2.2　胺碘酮　胺碘酮属Ⅲ类抗心律失常药物，对 I_{Na}、I_{ca}（L）、I_k、I_{k1}、I_{t0} 等多种离子通道均有抑制作用，具有控制节律和速率的作用。由于胺碘酮对血流动力学和心肌收缩力影响较小[72-74]，在脓毒症休克相关快速心律失常治疗中也不失为一种选择，有报道称胺碘酮是治疗脓毒症休克伴新发房颤

的最常用药物[13,75]，但其没有明显的改善心功能、抗炎等作用，且有室性心动过速等多种不良反应，药物半衰期长达数周，停药后作用可持续4～6周，治疗效果难以确定[75-76]。有研究认为，胺碘酮可能会比较适合心脏指数≤2.5 L/（min·m^2）的脓毒症心源性休克患者的治疗，但对这组亚群的疗效还有待进一步研究[74]。

2.3　普罗帕酮　普罗帕酮属ⅠC类抗心律失常药物，除明显的阻滞钠通道作用外，具有竞争性地作用β受体，还尚有微弱的钙拮抗作用，也是临床上十分常用的抗心律失常药。研究显示，与胺碘酮相比，普罗帕酮对新发房颤的复律成功率高，转复时间短[77-78]。Balik等[78]比较了普罗帕酮与胺碘酮、美托洛尔治疗脓毒症休克室上性心律失常的疗效，认为普罗帕酮安全、有效、可以耐受。但有学者认为基于该研究的设计很难得出普罗帕酮治疗效果与胺碘酮相当的结论[10]。总体而言，普罗帕酮对脓毒症、脓毒症休克相关快速心律失常的疗效研究不多，特别是对血流动力学的影响还缺乏全面的评价。

2.4　伊伐布雷定　伊伐布雷定通过选择性和特异性抑制窦房结I_f电流而降低心率，因其没有负性肌力和降低血压作用而受到人们关注，并被推荐治疗左室射血分数（left ventricular ejection fraction，LVEF）降低（LVEF≤35%）且心率≥70 min^{-1}的慢性心力衰竭患者[79]。近年来多个临床试验和临床研究探讨了伊伐布雷定治疗脓毒症休克和多器官衰竭的作用，均未得出结论性和一致性的结果，特别是该药在脓毒症休克患者血流动力学、血管升压药物抵抗和炎症标志等方面没有观察到显著的效果[80-83]。由于伊伐布雷定特异性地作用于窦房结细胞，因而对房性心动过速、交界性心动过速等快速心律失常均没有明确的疗效，这在很大程度上限制了该药的应用。此外，伊伐布雷特有增加房颤发生率及延长Q-T间期、窦房结恢复时间等不良反应[84-86]，因为存在心律失常的潜在风险，因此伊伐布雷定的安全性仍需谨慎监测。

2.5　α2受体激动剂　该药作用于中枢及外周血管α2受体，具有抑制交感神经活性、降低循环中儿茶酚胺含量、减慢心率等作用。以右美托咪定为代表的α2受体激动剂是ICU中用于有创通气的镇静药物，现有证据表明，右美托咪定在脓毒症休克治疗中具有上调α1受体表达、增加血管α1受体对儿茶酚胺的敏感性及抗炎等作用[76,87-88]。在脓毒症休克动物模型中证实，静脉输注中枢α2受体激动剂右美托咪定，血管对儿茶酚胺和血管紧张素的反应几乎完全恢复至脓毒症休克前的状态[89]。近年，人们针对右美托咪定对脓毒症休克血流动力学的影响也做了一些探索性研究。Miranda等[90]研究发现，右美托咪定在降低心率的同时并没有降低平均动脉压。Cioccari等[91]的研究显示与对照组相比，脓毒症休克患者使用右美托咪定治疗后第1个48 h内对升压药的需求并未增加。但近期的研究发现，右美托咪定与较低的血管加压素需求有关，以维持脓毒症休克中相同的平均动脉压目标[91-92]。虽然以上为一些探索性研究，对评估血流动力学的影响也不够全面，但对治疗脓毒症休克相关快速心律失常，特别是同时需要镇静的患者提供了很好的借鉴。

2.6　非二氢吡啶类钙离子拮抗剂　维拉帕米是临床上十分常用的抗心律失常药，众多研究发现以维拉帕米为代表的非二氢吡啶类钙离子拮抗剂在脓毒症休克中通过减少TNF等促炎因子的释放及增加抗炎因子IL-10的产生，降低脓毒症、脓毒症休克的死亡率[92-94]。近年来有研究发现，维拉帕米可以减少脓毒症休克细胞内钙超载，改善患者预后，为维拉帕米在治疗脓毒症中的使用提供了新靶点[53]。但维拉帕米具有降低窦房结自律性、减慢传导、负性肌力等药理作用，会增加心力衰竭、心源性休克的风险，因而维拉帕米对脓毒症休克快速相关心律失常的治疗效果及安全性还有待进一步评估。

2.7　洋地黄类药　洋地黄类药物在脓毒症、脓毒症休克相关快速心律失常中的应用并不常见，但早年就有研究证实，洋地黄类药在脓毒症、脓毒症休克中具有逆转内毒素诱导的心肌收缩力下降、提高每搏输出量及心输出量等积极效果[95-97]。近年也有研究发现，洋地黄类药在减慢脓毒症患者心率的同时能明显改善血流动力学[6]。这些结果值得人们对该药在治疗脓毒症休克相关快速心律失常的有效性和安全性方面做进一步评估。

3　小　结

快速心律失常是脓毒症、脓毒症休克重要的危险因素，控制好快速心律失常大大降低了心脏能量需求，从而在能量受损的情况下使心肌能量产生和消耗之间建立较好的平衡[98]，对改善病情具有

积极意义。脓毒症、脓毒症休克相关快速心律失常的发病机制复杂，在治疗上还有许多争议，抗心律失常药物的选择及使用方法还有待进一步研究。

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