S113-S115.

[17] O Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure [J]. JAMA, 2009, 301(14): 1439.

[18] Edelmann F, Bobenko A, Gelbrich G, et al. Exercise training in diastolic heart failure (Ex-DHF): rationale and design of a multicentre, prospective, randomized, controlled, parallel group trial [J]. Eur J Heart Fail, 2017, 19(8): 1067-1074.

[19] 中国康复医学会心血管病专业委员会. 中国心脏康复与二级预防指南 2018 精要[J]. 中华内科杂志, 2018, 57(11): 802-810.

[20] Fletcher GF, Ades PA, Kligfield P, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association [J]. Circulation, 2013, 128(8): 873-934.

[21] Balady GJ, Williams MA, Ades PA, et al. Core components of cardiac rehabilitation/secondary prevention programs: 2007 update: a scientific statement from the American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee, the Council on Clinical Cardiology; the Councils on Cardiovascular Nursing, Epidemiology and Prevention, and Nutrition, Physical Activity, and Metabolism; and the American Association of Cardiovascular and Pulmonary Rehabilitation [J]. Circulation, 2007, 115(20): 2675-2682.

[22] Piepoli MF, Corra U, Benzer W, et al. Secondary prevention through cardiac rehabilitation: from knowledge to implementation. A position paper from the cardiac rehabilitation section of the European Association of Cardiovascular Prevention and Rehabilitation [J]. Eur J Cardiovasc Prev Rehabil, 2010, 17(1): 1-17.

[23] 中华医学会心血管病学分会, 中国康复医学会心血管病专业委员会, 中国老年学学会心脑血管病专业委员会. 冠心病康复与二级预防中国专家共识[J]. 中华心血管病杂志, 2013, 41(4): 267-275.

[24] Uddin J, Zwisler AD, Lewinter C, et al. Predictors of exercise capacity following exercise-based rehabilitation in patients with coronary heart disease and heart failure: a meta-regression analysis [J]. Eur J Prev Cardiol, 2016, 23(7): 683-693.

[25] Angadi SS, Mookadam F, Lee CD, et al. High-intensity interval training vs. moderate-intensity continuous exercise training in heart failure with preserved ejection fraction: a pilot study [J]. J Appl Physiol (1985), 2015, 119(6): 753-758.

[26] Hambrecht R, Niebauer J, Marburger C, et al. Various intensities of leisure time physical activity in patients with coronary artery disease: effects on cardiorespiratory fitness and progression of coronary atherosclerotic lesions [J]. J Am Coll Cardiol, 1993, 22(2): 468-477.

[27] Aragam KG, Dai D, Neely ML, et al. Gaps in referral to cardiac rehabilitation of patients undergoing percutaneous coronary intervention in the United States [J]. J Am Coll Cardiol, 2015, 65(19): 2079-2088.

[28] Pirruccello JP, Traynor KC, Natarajan P, et al. An electronic cardiac rehabilitation referral system increases cardiac rehabilitation referrals [J]. Coron Artery Dis, 2017, 28(4): 342-345.

[29] 胡大一. 我国心脏康复的困局、机遇及十年规划[J]. 中华全科医师杂志, 2014, 5(13): 329-330.

收稿日期: 2019-03-18

脓毒症型心肌病的研究进展

王颖骅[1] 何奔[2]

(1. 上海交通大学附属胸科医院重症监护科, 上海 200030; 2. 上海交通大学附属胸科医院心内科, 上海 200030)

【摘要】 脓毒血症致心肌抑制又称为脓毒症型心肌病。18% ~65% 的脓毒症患者会出现心肌抑制, 死亡率为 40% ~70%, 发病 7 ~19 d 后心功能可能恢复, 其病因、发病机制不明, 治疗也无特异性。脓毒症引起的复杂的心肌炎症反应和线粒体非稳态, 最终导致心肌功能不全。脓毒症致心肌抑制成为影响脓毒症预后的重要因素。现就脓毒症型心肌病的发病机制、临床诊断和治疗进展做一总结。

【关键词】 脓毒症; 心肌抑制; 心肌病; 线粒体

【DOI】 10. 16806/j. cnki. issn. 1004-3934. 2019. 08. 020

Septic Cardiomyopathy

WANG Yinghua[1], HE Ben[2]

(1. *ICU*, *Shanghai Chest Hospital*, *Shanghai Jiao Tong University*, *Shanghai* 200030, *China*; 2. *Department of Cardiology*, *Shanghai Chest Hospital*, *Shanghai Jiao Tong University*, *Shanghai* 200030, *China*)

基金项目: 国家自然科学基金重点项目(81830010)

通讯作者: 何奔, E-mail: drheben@126. com

【**Abstract**】Septic cardiomyopathy is known as sepsis-induced myocardial depression. 18% ~ 65% septic patients suffered from myocardial depression and its mortality rate is 40% ~ 70%. Heart function may recover in 7 ~ 19 days after the onset of sepsis. The etiology, pathogenesis and treatment of septic cardiomyopathy are uncertain except that sepsis leads to a complex intramyocardial inflammatory response and mitochondrial non-homeostasis, which may result in myocardial dysfunction. Since sepsis-induced myocardial depression is recognized as a major predictor of prognosis, the recent findings about pathogenesis, diagnosis and manipulation are reviewed in this article.

【**Key words**】Sepsis; Myocardial depression; Cardiomyopathy; Mitochondria

脓毒血症致心肌抑制又称为脓毒症型心肌病，是脓毒血症引起的心功能不全。18% ~ 65% 的脓毒症患者会出现心肌抑制，临床表现为心室扩张、舒张和收缩功能障碍，抗感染治疗不能改善心功能，发病 7 ~ 19 d 后心功能可能恢复[1]。1984 年，Parker 首次应用放射性核素血管造影技术证实脓毒症心肌抑制的存在。同年，Ozier 应用床旁超声技术也证实脓毒症心肌抑制。50 年来，这种现象的病因未明确，机制多元化，治疗无特异性。因其死亡率为 40% ~ 70%[2-3]，脓毒症致心肌抑制成为影响脓毒症预后的重要因素。现就脓毒症型心肌病的发病机制、临床诊断和治疗做一总结。

1 脓毒症型心肌病的机制研究

脓毒症型心肌病的机制研究进展可归纳为两个部份：线粒体相关机制，以炎症反应及氧化应激为主的非线粒体机制。

1.1 非线粒体机制

1.1.1 Toll 样受体介导的炎症反应

病原相关分子模式通过 Toll 样受体（Toll-like receptors, TLRs）引起炎症反应和心肌细胞凋亡，TLRs 激活单核巨噬细胞系统，促进巨噬细胞在炎症局部的聚集、增生和活化，增强其黏附吞噬作用，增加循环系统中炎症细胞因子，放大心肌细胞内炎症反应，促进心肌细胞凋亡。研究指出，敲除 TLRs 对脓毒症后心肌损害有保护作用[4-5]；病原也可通过其他内源性受体激活炎性小体、核苷酸结合寡聚化结构域样受体蛋白 3，从而引起炎症反应[6]；炎症反应还可通过影响机体激素的合成，下调线粒体基因[7]。TLRs 通过多种细胞内信号转导如核因子 κB、丝裂原活化蛋白激酶（mitogen-activated protein kinase, MAPKs）、Notch1 基因（Notch1）、磷脂酰肌醇-3-激酶 γ（phosphatidylinositol 3 kinase γ, PI3Kγ）等途径产生炎症因子和干扰素，诱发基因产物。舒伐他汀为一种降血脂药物，既可稳定血管内斑块，还可抑制炎症因子，抑制 TLR4/核因子 κB 途径，而减少脓毒血症引起的心肌损害[8]。有研究者用 MicroRNA-146b 抑制 Notch1 途径，保护小鼠心肌免于脓毒症的炎症反应，减少心肌细胞凋亡[9]。也有研究发现 PI3Kγ 基因敲除小鼠对脓毒症诱导的心肌抑制有保护作用[10]。

1.1.2 外泌体

外泌体包括复杂 RNA 和蛋白质的小膜泡，参与细胞间信号通路。有文献指出，脓毒症患者血浆中的外泌体参与脓毒症型心肌病的炎症反应和氧化应激作用[11]。

1.1.3 氧化应激

脓毒症激活多种炎症因子，刺激血管内皮产生大量一氧化氮产物活性氮（reactive nitrogen species, RNS），血管内大量炎症细胞产生氧化应激产物活性氧（reactive oxygen species, ROS）。ROS 和 RNS 通过环腺苷酸/蛋白激酶 A（cAMP/PKA）和环鸟苷酸/蛋白激酶 G（cGMP/PKG）信号途径损害线粒体代谢，破坏线粒体凋亡，损伤血管内皮[12]。ROS 和 RNS 还可作用于血管紧张素受体，诱导心肌细胞凋亡。有实验发现，α1、α2 和 β3 血管紧张素受体抑制剂通过阻断天冬氨酸特异性半胱氨酸蛋白酶（caspase 3/8/9）通路，减少黏附分子表达，调节 T 型钙通道，在脓毒症心肌抑制中起保护作用[13-16]；应用低浓度一氧化碳能减轻氧化应激途径引起的炎症反应[6]；microRNA155 可减轻小鼠的氧化应激反应，减少脓毒症对血管内皮受体的损伤，改善脓毒症引起的心功能不全[17]；依达拉奉和麦角固醇分别作用于缺氧诱导因子 1/血红素加氧酶 1 和核因子 E2 相关因子信号通路，降低氧化应激反应[18-19]，保护心肌。

1.2 线粒体相关机制

线粒体除产生 ATP，还参与许多细胞功能，包括钙离子归巢、激素代谢、温度调节、氧化应激反应、细胞信号转导，在细胞死亡和凋亡中也起关键作用。许多心血管疾病的主要病理生理机制是线粒体功能异常和生成障碍，如心力衰竭和缺血再灌注损伤。线粒体已成为最具治疗潜能的探索方向。由于脓毒症型心肌病表现为可逆的细胞器官功能障碍，极少有细胞死亡，所以脓毒症型心肌病的发病机制可能是细胞能量代谢障碍和线粒体功能障碍。

1.2.1 线粒体能量代谢和钙超载

心肌细胞能量代谢的主要场所是线粒体，心肌线粒体主要的供能来自 ATP。虽然目前无人类心肌线

粒体的在体研究,但研究人类其他脏器线粒体的文献很多。线粒体功能障碍程度与脓毒症严重程度和预后相关。大量啮齿动物和细胞实验证实,脓毒症型心肌病线粒体功能障碍包括:电子转运及氧化磷酸化异常、线粒体膜电位和酸碱度(pH 值)梯度异常,进而导致 ATP 下降,供氧下降,呼吸链复合物下降。氧化应激反应阻断线粒体氧化磷酸化,最终导致 ATP 合成减少[12]。在猪脓毒血症模型中发现,脓毒症致心肌抑制源于线粒体的能量代谢障碍,及其引起的钙通道失调,最终导致"钙超载"[20]。

1.2.2　线粒体动力学、生成和自噬

线粒体融合、裂解、生成和自噬,是失功线粒体替换和清除、环境适应、保持效率的核心过程,也是线粒体能始终精确调控细胞代谢的关键。研究表明,脓毒症 24 h 内的大鼠心脏,可观察到线粒体的融合、裂解的形态学改变;融合相关蛋白(线粒体融合蛋白 1、线粒体融合蛋白 2、视神经萎缩蛋白 1)和裂解相关蛋白(动力相关蛋白 1),表现为失衡状态[21-23]。线粒体功能异常导致的氧化应激产物释放,超过线粒体抗氧化能力时,产物积聚,影响信号转导系统。同时,氧化应激也抑制线粒体呼吸链,导致线粒体 DNA 异常、偶联异常、生成和自噬障碍,进而影响心肌细胞结构和功能的修复[24]。在因脓毒症死亡的人心脏组织线粒体研究中发现,编码 ATP 生成的线粒体基因大量减少[25]。因此,线粒体结构基因的重新编码和恢复线粒体动力学平衡成为机制研究热点。

2　脓毒症型心肌病的诊断

脓毒症型心肌病是脓毒症引起的心肌抑制,表现为患者感染后外周血管功能障碍和心功能不全,其临床特征经历两个过程,代偿期和失代偿期。在代偿期,脓毒症引起外周血管阻力降低,液体复苏使心脏舒张末容量增加,从而代偿心肌收缩功能障碍引起的心排血量降低;在失代偿期,心肌舒张功能障碍,导致低心排血量和休克,临床上,使用 SOFA 评分(Sequential Organ Failure Assessment)不仅有助区分脓毒症合并脏器功能损害的高危患者,也有助及时发现脓毒症型心肌病[26]。

血清中肌酸激酶、肌钙蛋白 T 和 I、脑钠肽是临床常用的心肌损伤的诊断指标,肿瘤坏死因子-α、白介素-6、白介素-8、白介素-10 和中性粒细胞明胶酶相关脂质运载蛋白也可作为脓毒症型心肌病的参考指标[27],这些指标升高反映脓毒症时心肌耗氧供需失衡,导致心功能损害。

心脏超声作为无创简便的临床评估工具,是诊断脓毒症型心肌病最重要的手段之一,是目前评估脓毒症心肌抑制的"金标准"。床旁心脏超声不仅可测量反映脓毒症型心肌病患者急性心室扩张的左室舒张末容积,也可计算心室射血分数下降,同时估算出患者的每搏量,还可通过二尖瓣口血流分析和组织多普勒评估心脏舒张功能障碍。二尖瓣舒张早期峰值流速(E)、舒张晚期峰值流速(A)、E/A 和二尖瓣环舒张早期峰值速度(e′)、舒张晚期峰值速度(a′)、e′/a′ 和 E/e′为常用评估心脏舒张功能的指标。E/e′ > 15 cm/s 和/或 e < 8 cm/s 常提示舒张功能障碍。研究指出,与脓毒症死亡率密切相关的不是心肌收缩功能障碍,而是心肌舒张功能障碍[1]。此外,应变和应变率、斑点追踪技术和速度向量成像等技术都能有效提供诊断心肌功能障碍的依据,在治疗后心功能恢复状态评估中也有重要作用[28-29]。

现在,脓毒症患者应用有创血流动力学监测,如 Swan-Gans 导管和脉搏指示连续心排血量,可连续监测右房压、肺动脉压、肺动脉嵌顿压、心排血量、中心静脉压、肺循环阻力、外周血管阻力,甚至血管外肺水的含量,实现实时、动态监测脓毒症患者心排血量的改变和外周血管阻力的变化[5]。

3　脓毒症型心肌病的治疗策略

脓毒症致心肌抑制是增加脓毒血症死亡率的最主要因素,目前仍无特效的治疗手段,抗感染治疗并不能逆转其病程。针对脓毒症 6 h 内启用有效的抗感染治疗,早期液体复苏,血管活性药物应用,维持组织灌注,平均动脉压≥65 mm Hg(1 mm Hg = 0.133 3 kPa),静脉血氧饱和度≥65%,中心静脉压维持 8 ~ 12 mm Hg,尿量维持 0.5 mL/(kg · h),应用床旁心脏超声和有创血流动力学监测,动态评估脓毒症休克状况、心功能和外周阻力,调节补液和血管活性药物用量[30-31]。去甲肾上腺素在改善外周血管功能和预防心房颤动的优势已证实[30];常用的血管活性药物多巴酚丁胺增加心肌耗氧和心率,可引起心肌缺血,增加死亡率[32];Zangrillo 等[33]对 7 个研究共 246 例脓毒症患者进行荟萃分析,发现左西孟旦较多巴酚丁胺明显降低死亡率;Morelli 等[34-35]应用 β 受体阻滞剂进行一项 RCT 研究,结果表明,β 受体阻滞剂通过降低脓毒症患者心率,减少心肌氧耗,降低了 28 d 死亡率达 50%。针对心肌抑制炎症反应和氧化反应的激素和氧化还原剂治疗,目前处于动物实验阶段。

4　总结和展望

脓毒症型心肌病是脓毒症致死的主要原因之一。脓毒症患者出现心功能降低和外周血管阻力异常即可诊断为脓毒症型心肌病。心脏超声在早期诊断和预后评估中作用显著,尽早启动有效的抗感染治疗、早期液体复苏和应用去甲肾上腺素是目前肯定的治

疗方式。由于抗感染治疗并不能改变脓毒症型心肌病的进程，将来从发病机制方面研究其致病途径、进展规律，从而控制炎症反应、过度氧化应激反应、线粒体动力学失衡等，有机会早期诊断并且逆转脓毒症型心肌病向心功能衰竭方向发展。

参 考 文 献

[1] Han SJ, Tae HL, Cho HB, et al. Risk factors and outcomes of sepsis-induced myocardial dysfunction and stress-induced cardiomyopathy in sepsis or septic shock. a comparative retrospective study [J]. Medicine, 2018, 97: 13(e0263).

[2] Prescott HC, Angus DC. Enhancing recovery from sepsis: a review [J]. JAMA, 2018, 319(1): 62-75.

[3] Karnad DR, Saseedharan S. Myocardial dysfunction in sepsis and septic shock [J]. Assoc Physicians India, 2017, 65(12): 11-12.

[4] Robert RE, Ashley NS, Mark JF, et al. Pathophysiology, echocardiographic evaluation, biomarker findings, and prognostic implications of septic cardiomyopathy: a review of the literature [J]. Crit Care, 2018, 22: 112-126.

[5] Zhou D, Zhu Y, Ouyang MZ, et al. Knockout of Toll-like receptor 4 improves survival and cardiac function in a murine model of severe sepsis [J]. Mol Med Rep, 2018, 17(4): 5368-5375.

[6] Unuma K, Aki T, Nagano S, et al. The down-regulation of cardiac contractile proteins underlies myocardial depression during sepsis and is mitigated by carbon monoxide [J]. Biochem Biophys Res Commun, 2018, 495(2): 1668-1674.

[7] Elio A, Enrico F, Katia D, et al. Myocardial depression in sepsis: from pathogenesis to clinical manifestations and treatment [J]. J Crit Care, 2014, 29: 500-511.

[8] Wang Y, Zhang L, Zhao X, et al. An experimental study of the protective effect of simvastatin on sepsis-induced myocardial depression in rats [J]. Biomed Pharmacother, 2017, 94: 705-711.

[9] Wang X, Yu Y. MiR-146b protect against sepsis induced mice myocardial injury through inhibition of Notch1 [J]. J Mol Histol, 2018, 49(4): 411-417.

[10] Ndongson-Dongmo B, Heller R, Hoyer D, et al. Phosphoinositide 3-kinase gamma controls inflammation-induced myocardial depression via sequential cAMP and iNOS signalling [J]. Cardiovasc Res, 2015, 108(2): 243-253.

[11] Juliana MR, Ludmila RPF, Gustavo HE, et al. Exosomes from patients with septic shock convey miRNAs related to inflammation and cell cycle regulation: new signaling pathways in sepsis? [J]. Crit Care, 2018, 22: 68-79.

[12] Stanzani G, Duchen MR, Singer M. The role of mitochondria in sepsis-induced cardiomyopathy [J]. Biochim Biophys Acta Mol Basis Dis, 2019, 1865(4): 759-773.

[13] Jacek H. Heartfelt sepsis: microvascular injury due to genomic storm [J]. Kardiol Pol, 2018, 76(8): 1203-1216.

[14] Yang N, Shi X, Zhang B, et al. The trend of β3-adrenergic receptor in the development of septic myocardial depression: a lipopolysaccharide-induced rat septic shock model [J]. Cardiology, 2018, 139: 234-244.

[15] Yu X, Wang Y, Yang D, et al. α2A-adrenergic blockade attenuates septic cardiomyopathy by increasing cardiac norepinephrine concentration and inhibiting cardiac endothelial activation [J]. Sci Rep, 2018, 8: 5478-5493.

[16] Li H, Xing Y, Yang D, et al. Alpha-1 adrenergic receptor agonist phenylephrine inhibits sepsis-induced cardiomyocyte apoptosis and cardiac dysfunction via activating ERK1/2 signal pathaway [J]. Shock, 2019, 52(1): 122-133

[17] Vasques NF, Laundos TL, Cerqueira RJ, et al. MicroRNA-155 amplifies nitric oxide/cGMP signaling and impairs vascular angiotensin Ⅱ reactivity in septic shock [J]. Crit Care Med, 2018, 46(9): e945-e954.

[18] He C, Zhang W, Li S, et al. Edaravone improves septic cardiac function by inducing an HIF-1α/HO-1 pathway [J]. Oxi Med Cell Longev, 2018, 2018: 5216383.

[19] Xu J, Lin C, Wang T, et al. Ergosterol attenuates LPS-induced myocardial injury by modulating oxidative stress and apoptosis in rats [J]. Cell Physiol Biochem, 2018, 48: 583-592.

[20] Dagmar J, Michaela M, Jan H, et al. Cellular mechanisms of myocardial depression in porcine septic shock [J]. Front Physiol, 2018, 9: 726.

[21] Vanasco V, Saez T, Magnani ND, et al. Cardiac mitochondrial biogenesis in endotoxemia is not accompanied by mitochondrial function recovery [J]. Free Radic Biol Med, 2014, 77: 1-9.

[22] Sánchez-Villamil JP, D'Annunzio V, Finocchietto P, et al. Cardiac-specifc overexpression of thioredoxin 1 attenuates mitochondrial and myocardial dysfunction in septic mice [J]. Int J Biochem Cell Biol, 2016, 81: 323-324.

[23] Gonzalez AS, Elguero ME, Finocchietto P, et al. Abnormal mitochondrial fusion-fission balance contributes to the progression of experimental sepsis [J]. Free Radic Res, 2014, 48(7): 769-783.

[24] Pan P, Wang X, Liu D. The potential mechanism of mitochondrial dysfunction in septic cardiomyopathy [J]. J Int Med Res, 2018, 46(6): 2157-2169.

[25] Matkovich SJ, Khiami BA, IEfimov IR, et al. Widespread down-regulation of cardiac mitochondrial and sarcomeric genes in patients with sepsis [J]. Crit Care Med, 2017, 45(3): 407-414.

[26] Walley KR. Sepsis-induced myocardial dysfunction [J]. Curr Opin Crit Care, 2018, 24(4): 292-299.

[27] Masson S1, Caironi P, Fanizza C, et al. Sequential N-terminal pro-B-type natriuretic peptide and high-sensitivity cardiac troponin measurements during albumin replacement in patients with severe sepsis or septic shock [J]. Crit Care Med, 2016, 44(4): 707-716.

[28] Sanfilippo F, Corredor C, Fletcher N, et al. Left ventricular systolic function evaluated by strain echocardiography and relationship with mortality in patients with severe sepsis or septic shock: a systematic review and meta-analysis [J]. Crit Care, 2018, 22: 183-195.

[29] Vallabhajosyula S, Pruthi S, Shah S, et al. Basic and advanced echocardiographic evaluation of myocardial dysfunction in sepsis and septic shock [J]. Anaesth Intensive Care, 2018, 46(1): 13-24.

[30] Liu YC. Yu MM, Shou ST, et al. Sepsis-induced cardiomyopathy: mechanisms and treatments [J]. Front Immunol, 2017, 8: 1021.

[31] Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2012 [J]. Crit Care Med, 2013, 41: 580-637.

[32] Sato R, Nasu M. Time to re-think the use of dobutamine in sepsis [J]. J Intensive Care, 2017, 5: 65.

[33] Zangrillo A, Putzu A, Monaco F, et al. Levosimendan reduces mortality in patients with severe sepsis and septic shock: a meta-analysis of randomized trials [J]. J Crit Care, 2015, 30(5): 908-913.

[34] Duan EH, Oczkowski SJ, Belley-Cote E, et al. beta-Blockers in sepsis: protocol for a systematic review and meta-analysis of randomised control trials [J]. BMJ Open, 2016, 6(6): e012466.

[35] Morelli A, Ertmer C, Westphai M, et al. Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock: a randomized clinical trial [J]. JAMA, 2013, 310(16): 1683-1691.

收稿日期：2019-03-09