· 综述 ·

脓毒症内皮细胞损伤和凝血功能障碍相关的生物标记物

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【关键词】 脓毒症； 内皮细胞； 凝血功能； 生物标记物

脓毒症是宿主防御系统对入侵病原微生物产生的过度炎症反应。脓毒症的临床表现各不相同，疾病严重程度也受入侵的病原微生物、患者的遗传背景、共存疾病状态、临床干预时机和其他支持治疗手段的影响；同时发生急性器官功能障碍时被认为是重症感染；虽然经过充分的水化治疗，但仍不能维持血压而影响到组织灌注时被认为是感染性休克[1]。重症感染是影响发病率和病死率的主要原因，也是重症监护病房(ICU)患者最主要的死亡原因。

近年研究表明脓毒症的主要特点之一是微循环功能障碍。微循环功能障碍的病理生理过程分为高凝状态导致的血栓形成和血管内皮细胞功能障碍两部分[2]。脓毒症时炎症因子的刺激使组织因子(TF)表达增加，启动外源性凝血途径，从而导致高凝状态和纤溶抑制，这种特异性高凝状态致使循环系统中微血栓形成；炎症因子作用于内皮细胞，使内皮细胞活化，并与活化的白细胞相互作用，最后出现高凝和炎症反应，并形成恶性循环，最终导致微血管的阻塞、微循环出血和组织循环状态恶化[3]。由于入侵的病原微生物、发病部位、相关的共存疾病、疾病进展速度和程度、有无并发症等不同，使得脓毒症的治疗很复杂。早期目标导向治疗取得的效果强调了早期诊断的重要性[4]，但是脓毒症的异质性使我们很难确定诊断并区分疾病的严重性。基于此，在临床上检测内皮细胞损伤和凝血功能障碍相关的标记物，对于确诊、指导治疗和判断预后有积极意义。

1 脓毒症时内皮细胞功能障碍

1.1 脓毒症时内皮细胞损伤：内皮细胞位于血管内表面呈单层排列，作为血管内腔的一层屏障，使器官与血流及身体其他部分相隔离，并防止血管内凝血的发生。内皮细胞具有三大功能：①参与新生血管的形成，这在胚胎形成和器官形成中很重要[5]；②在成年机体中，内皮细胞有助于维持稳态，包括液体、电解质和蛋白在血管内外的转运和细胞的迁移，并调节血流；③对稳态的失衡作出反应，如炎症、凝血和乏氧、低灌注[6]。但内皮细胞具有时间和地点依赖的特性，因此对刺激的反应也具有器官特异性[7]。脓毒症过程中，在炎症介质作用下及其与白细胞相互作用，早期即发生内皮细胞活化和损伤，并在全身炎症反应的病理生理过程中起关键作用。与髓样细胞相似，内皮细胞是对入侵的病原微生物作出反应的一线细胞[8]。由于内皮细胞覆盖在血管表面，它们和实质器官紧密接触，因此，内皮细胞活化和损伤与器官功能障碍关系密切。内皮细胞可以传递多种生物学信息，是联系局部和全身免疫反应的纽带。内皮细胞被认为是炎症的来源，也是炎症的作用目标。局部内皮细胞的活化是使炎症局限的关键；然而，全身内皮细胞活化可以导致微血管病变，微血管通透性增加，白细胞黏附和迁移，活性氧家族的活化，血管扩张和细胞因子的产生并致使组织乏氧，最终导致器官功能障碍甚至死亡[9]。

越来越多的证据表明白细胞-内皮细胞相互作用在炎症导致内皮细胞损伤中发挥重要作用[10]。黏附分子如免疫球蛋白超家族、选择素、整合素等介导了白细胞和内皮细胞间的相互作用。肿瘤坏死因子(TNF)、白细胞介素-1(IL-1)及凝血酶启动 E-选择素的合成和表达，或导致 P-选择素在内皮细胞上快速表达，促进白细胞与活化内皮细胞间的黏附[11]。黏附后的中性粒细胞分泌髓过氧化物酶、组织蛋白酶 G、弹力蛋白酶等，并产生活性氧家族，以引起内皮细胞活化或损伤[10]。内皮细胞活化后，血栓调节蛋白(TM)和内皮细胞蛋白 C 受体(EPCR)下调，纤溶酶原激活物抑制剂-1(PAI-1)或血管性血友病因子(vWF)表达增多，且内皮损伤导致血液接触到内皮下的胶原、vWF 和纤维连接蛋白等促凝成分，从而促进凝血。因此，炎症时白细胞-内皮细胞相互作用及内皮细胞损伤是脓毒症时微血管血栓形成、内皮细胞通透性增加及发生多器官功能障碍综合征(MODS)的关键[12]。

1.2 内皮细胞损伤的生物标记物：在炎症刺激下，内皮细胞失去正常的抗凝活性而转变为促凝，产生黏附分子、血管活性物质、炎症介质和趋化因子，其中可能具有临床指导意义的生物标记物如下。

1.2.1 循环内皮细胞(cECs)：生理状态下，内皮细胞紧密贴附于细胞外基质，且邻近的内皮细胞通过特殊的结构相互作用(如黏着连接和紧密连接)，形成一个紧密的屏障以防止血管渗漏和白细胞迁移到间质。正常情况下，凋亡的内皮细胞<0.1%，据报道，脂多糖可导致体外内皮细胞凋亡，在部分实验中也证实其可导致体内内皮细胞凋亡[13]。体外实验中，内皮细胞凋亡引发促凝状态[14]。脓毒症和感染性休克死亡患者的 cECs 增加更明显，表明 cECs 与器官功能障碍和血管损伤严重程度呈正相关[15-16]。近年来 cECs 被认为是内皮细胞损伤和凋亡的细胞指示剂，是内皮损伤的直接标志物。由于凋亡内皮细胞从基底膜脱落后可迅速从循环中被清除，因此很难在体内检测。目前尚无简便的定量监测方法，需进一步研究加以评价。

1.2.2 循环内皮祖细胞(cEPCs)：研究表明，内皮祖细胞(EPCs)在维持血管内皮细胞完整性中发挥了重要作用[17]。EPCs 来源于骨髓，足以分化为成熟的内皮细胞。在健康个体，外周血中仅有少量的 cEPCs。EPCs 表型上的标志是表达特异性造血标志物 CD34、干细胞标志物 CD133 和内皮细胞标志物血管内皮生长因子受体-2(VEGFR-2)。

在病理情况下，内皮细胞从血管腔脱落进入到循环系统，与此同时，周围成熟的内皮细胞发生迁移和再生以促进内

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皮层重建。然而，成熟的内皮细胞再生能力很弱，其修复受损血管内皮细胞的能力有限，因此，EPCs 从骨髓中动员并在外周血循环中明显增加[18]。这个过程主要依赖于金属蛋白酶的活化和黏附分子的上调，金属蛋白酶促进 EPCs 从骨髓基质中释放，黏附分子促进这些细胞进入血循环[19]，并主要由某些可溶性分子如血管内皮生长因子(VEGF)、粒-巨噬细胞集落刺激因子和促红细胞生成素介导。在病理情况下，血清中这些可溶性分子浓度戏剧性增加，使 cEPCs 增多。近年有证据表明，cEPCs 不仅在血管损伤，而且在重症感染的内皮细胞重建中起关键作用[18]。脓毒症患者 cEPCs 水平较健康个体增高 4 倍，在脓毒症发生后 6 h 即明显升高，72 h 达峰值。因此，监测脓毒症患者外周血 cEPCs 有助于早期诊断并判断预后[20]。研究表明，脓毒症患者 cEPCs 比例与存活率呈正相关[21]。

1.2.3　内皮细胞特异性分子-1(ESM-1)：ESM-1 是一种硫酸皮肤素蛋白多糖，由肺和肾的血管内皮细胞表达，可以在人血中检测到。ESM-1 在脓毒症发生数小时后产生，是一种晚期介质，通过直接和 CD11a/CD18 整合素连接以阻断其与细胞间黏附分子-1 的连接[22]。2001 年 Béchard 等[23]通过酶联免疫吸附法(ELISA)观察脓毒症患者 ESM-1 水平变化并评价其作为诊断和预后指标的价值。结果表明，ESM-1 与公认的内皮细胞活化和损伤标记物 vWF 明显相关，且对于预测脓毒症患者发生感染性休克和死亡的价值高于 vWF，其可能成为评估脓毒症患者疾病严重程度和预后的一项新的标记物。

1.2.4　可溶性血栓调节蛋白(sTM)：TM 是存在于内皮细胞表面的一种具有抗凝作用的跨膜糖蛋白，与凝血酶相互作用，促进蛋白 C(PC)的活化。sTM 是蛋白水解酶降解 TM 形成的。sTM 仅在内皮细胞严重受损时从内皮细胞表面释放入血，其他刺激并不能导致其释放[24]，因此被认为是内皮细胞损伤的标记物，其水平升高反映了血管内皮细胞的抗凝功能下降。脓毒症和器官功能障碍患者血浆中 sTM 水平是非脓毒症患者的 1.5～5.0 倍[25]。因为循环中 sTM 主要由肾脏清除，肾功能障碍患者 sTM 水平更高[26]。但是，即使血浆中 sTM 水平受肾功能障碍影响，其仍然与器官损伤或内皮细胞损伤保持很好的相关性[27]。有研究表明，脓毒症导致的弥散性血管内凝血(DIC)及 MODS 患者血清 sTM 浓度增高[28]，因此，sTM 是预测脓毒症患者发生 DIC 和 MODS，甚至是死亡的一项独立指标。

1.2.5　可溶性 E-选择素(sE-选择素)：E-选择素也被称为内皮细胞-白细胞黏附分子-1(ELAM-1)或 CD62E，是一种内皮细胞跨膜糖蛋白，急性炎症反应时由活化的内皮细胞产生，在中性粒细胞迁移至损伤部位过程中起关键作用。它参与黏附反应的第一步，即白细胞的滚动，是后续白细胞牢固黏附和迁移的先决条件，促进感染和损伤的发生。这种分子仅特异性地在内皮细胞表达，几乎均由诱导产生[29]。炎症介质如 TNF-α、IL-1β或内毒素在内皮细胞内转录水平调节 E-选择素的合成。E-选择素在内皮细胞表面的表达发生在细胞活化后 4～24 h，并在内皮细胞表面释放出 sE-选择素，其最大释放发生在内皮细胞活化后 6～12 h，在 24 h 完全消失。因此，sE-选择素被认为是免疫活化和免疫反应的早期可靠性标志物。2006 年 Harrington 等[30]通过实验证实循环中 sE-选择素浓度可作为内皮细胞凋亡的标志。在确定发生脓毒症患者中 sE-选择素水平增高了 3～8 倍，成人脓毒症患者 sE-选择素水平与血流动力学功能障碍及多器官功能衰竭呈正相关[31]。

1.2.6　血管生成素-2(Ang-2)：Ang 是由 Ang-1、Ang-2、Ang-3、Ang-4 组成的配体家族。其中 Ang-1 和 Ang-2 为内皮源性血管生长因子，在正常或病理状态下的血管生成中发挥重要作用。Ang-1、Ang-2 均与酪氨酸激酶受体(Tie-2)相结合，但其作用却截然相反。Tie-2主要存在于内皮细胞表面，Ang-1是 Tie-2 的激动剂，促进内皮细胞稳定，维持血管完整性，抑制血管渗漏，减少炎症基因表达，防止白细胞聚集和迁移；而 Ang-2 是 Tie-2 的拮抗剂，促进内皮细胞活化，并以剂量依赖方式促进内皮细胞发生炎症反应[32]。Ang-2 由内皮细胞产生，存在于 Weibel-Palade 小体(WPBs)中，因此，在内皮细胞活化或损伤早期 Ang-2 水平即增高，并作为内皮细胞活化和功能障碍的潜在标记物[33]。

近年来发现，Ang-2 是调节内皮细胞活化的关键物质，其作为内皮细胞的一种自分泌介质，通过活化内皮细胞局部自分泌过程加重组织低灌注和炎症反应，还可以增加内皮细胞对 TNF-α 的敏感性[34]。无 Ang-2 存在时，TNF-α 浓度达到 40 ng/L 方能激活内皮细胞，但当 Ang-2 浓度达到 2 000 ng/L 时，TNF-α 浓度为 5 ng/L 即能引起内皮细胞活化，表达黏附分子并促进白细胞黏附到内皮细胞[35]。脓毒症时循环中 Ang-2 水平增高，且其增高程度与疾病严重程度和肺血管渗漏相关，是预测病死率强烈而独立的指标[36]。甚至有研究表明，血循环中 Ang-2 水平比急性生理学与慢性健康状况评分系统 Ⅱ (APACHE Ⅱ)评分预测危重患者病死率还要更好[37]。尽管人们对脓毒症患者 Ang-2 的增高越来越关注，但确切机制并不清楚。有研究表明，脓毒症患者 Ang-2 水平增高与疾病严重程度和内皮细胞活化程度呈正相关，与内皮细胞一氧化氮生物利用率呈负相关[38]。通过反应性充血性外周动脉张力测量(RH-PAT)检测到 Ang-2 与内皮细胞功能相关[39]。因此，Ang-2 是反映脓毒症患者内皮细胞功能及判断预后很有意义的生物标记物。

2　脓毒症时凝血功能障碍

2.1　脓毒症时凝血系统活化：从 20 世纪 60 年代就有小样本研究探讨了宿主对感染的全身反应，并证明其是与凝血活化、抗凝物质消耗、纤溶抑制、内皮细胞损伤和炎症相关的过程[40]。脓毒症时炎症和凝血的关系很复杂，感染通过多种分子和细胞机制促进凝血活化，其中主要的机制可能是单核/巨噬细胞释放促炎细胞因子如 IL-6、IL-1β 和 TNF，这些细胞因子促进 TF 在单核细胞和内皮细胞表达，从而启动外源性凝血途径。同时，凝血酶、F Ⅹa、TF-F Ⅻa 复合物抑制内源性抗凝物质如抗凝血酶、活化蛋白 C(APC)发挥作用并促进全身炎症反应发生[41]。炎症和凝血之间这种紧密的联系，也是导致器官功能障碍和死亡的原因。过去 20 年的研究发现，APC 是惟一有效的替代治疗脓毒症的药物，这强烈提示了凝血系统在脓毒症发展过程中的重要性[42]。

2.2　凝血功能障碍的生物标记物

2.2.1　PC：PC 是维生素 K 依赖的糖蛋白，其在凝血酶-TM 复合体作用下转化成 APC 而发挥生物学活性[43]。与 EPCR 连接后，PC 活化速度增加 20 倍。APC

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具有抗凝、促进纤溶、抗炎、细胞保护和抗凋亡作用[44]。据统计，85%以上的重症感染患者 PC 水平降低[42]，且大多数脓毒症患者在临床症状出现前 PC 水平已下降，并持续存在于疾病的整个过程，死亡患者尤为明显，在恢复并存活的患者会逐渐升高至正常[45]。有研究表明，PC 水平下降诊断重症感染患者和感染性休克患者分别早于临床诊断 16 h 和 12 h[46]。脓毒症患者基础 PC 水平下降与预后不良相关，包括机械通气时间、住 ICU 时间、发生休克的时间和病死率[45]。在诊断重症感染后的第 1 日，PC 水平的变化与预后高度相关，甚至可以区分出存活和死亡[47]。且有研究证实，与常规应用的凝血指标相比，PC 水平可能是一种更早期、更敏感、更准确反映预后的标志物，并很可能成为监测 APC 治疗效果的一项指标[48]。因此，PC 水平是诊断脓毒症和判断脓毒症相关病死率的标志物，其绝对水平与发病率和病死率相关，而与年龄、感染的病原微生物、是否存在休克、DIC、高凝状态及疾病严重程度无关[49]。动态监测 PC 水平可能有益于脓毒症的预后判断并评估患者对治疗的反应，但需进一步研究并监测其在多个时间点的序列变化以提供更可靠的临床数据来评价 PC 作为危重患者生物标记物的意义。一项评价 PC 作为生物标记物监测脓毒症和 MODS 患者治疗意义的 Ⅱb 期临床研究(RESPOND 研究)结果表明，重症感染患者应用重组人 APC 治疗后体内 PC 水平可恢复正常，28 d 病死率降低(10.3%比 32.0%，$P<0.000\ 1$)，从而得出重症感染患者 PC 水平与病死率相关的结论，但仍需要开展 Ⅲ 期临床研究进一步证实[50]。

2.2.2 可溶性组织因子(sTF)：TF 是炎症引起凝血活化的启动子，正常状况下，TF 并不存在于血管系统，而是存在于血-组织屏障中，因此，一旦内皮屏障破坏就会使循环中产生 TF，从而快速启动凝血[51]。重症感染时，促炎细胞因子刺激单核细胞等表达 TF，导致全身凝血活化。在内毒素血症或菌血症模型中，阻断 TF 活性可以完全抑制炎症导致的凝血酶产生；抑制 IL-6 可以完全阻断 TF 依赖的凝血酶产生，而抑制其他炎症因子却无此效应，说明在体内 TF 的表达主要依赖于 IL-6[52]。最近，在血循环中发现了游离形式的 TF 片断(缺乏外显子 5)，即 sTF，其具有促凝活性[53]。sTF 是在细胞因子刺激下由内皮细胞释放，可能会作为炎症导致凝血活化的临床标记物[54]。

2.2.3 血管性血友病因子裂解蛋白酶(ADAMTS13)：ADAMTS13 是近年来新发现的一种高度特异的金属蛋白酶，在肝脏以一个完整长度进行表达和分泌，半衰期接近 48～72 h[55]。多中心研究提示，ADAMTS13 的正常范围为 0.4～2.0 kU/L，其活性在女性人群高于男性，且在 40 岁以上人群中与年龄呈负相关[55]。ADAMTS13 的主要和特异性底物是 vWF，其在降解超大分子血管性血友病因子(ULVWF)中发挥重要作用。这种 ULVWF 多聚体可由内皮细胞分泌或储存于血小板内。ADAMTS13 可以在内皮细胞表面水解 ULVWF 多聚体，从而阻止这种大的多聚体进入循环中[56]。没有这种加工过程，从内皮细胞分泌的 ULVWF 多聚体就会进入循环并导致血管内血小板聚集及广泛的微血管血栓形成[57]。

近年来研究表明，重症感染患者的 ADAMTS13 活性改变以及后续的 vWF 多聚体变化可导致血小板减少性紫癜、血管内凝血和微循环衰竭的发生[58]。重症感染患者的 ADAMTS13 水平可以低于 0.1 kU/L，是正常状态时血浆中活性的 10%，同时伴有 vWF 明显增加，而且这种变化的程度与器官衰竭和 28 d 病死率增加有关[59]。在脓毒症所导致的 DIC 患者中，ADAMTS13 活性随着炎症加重，有不同程度下降，伴有血浆中 ULVWF增多，DIC 评分增高，血小板计数减少，内皮细胞功能失调，器官功能障碍甚至死亡[59]。一项用血浆交换治疗脓毒症所导致 MODS 患儿的研究显示，血浆 ADAMTS13 活性下降，但血浆交换可恢复 ADAMTS13 的活性并改善器官功能，存活率提高[60]。这些研究表明，ADAMTS13 在微血管血栓形成和 DIC 有关的器官功能障碍中起关键作用，血浆中 ADAMTS13 蛋白减少和大量的 ULVWF 可以作为脓毒症促凝状态的生物标记物。

最近已有直接检测 ADAMTS13 抗原水平的新的 ELISA 试剂盒，可以计算活性/蛋白比例，但仍需要更快速、敏感和简单的自动检测程序以更可靠、准确地检测 ADAMTS13 活性[61]。

2.2.4 多糖包被(glycocalyx)：多糖包被是广泛存在于血管内皮管腔侧的一层带负电荷的网[62]，所有循环细胞与其密切接触，包含氨基葡聚糖(GAGs)、肝素硫酸多糖(HSPGs)、糖蛋白、透明质酸和其他膜相关蛋白。多糖包被在包括凝血启动在内的脓毒症相关的所有过程中，以及内皮其他功能如维持血管屏障、一氧化氮介导的血管扩张、抗氧化等过程中均发挥作用[63]。近来研究表明，特异性破坏多糖包被可以在数分钟内产生凝血酶并引起血小板黏附[64]，但其与内皮间相互调节作用仍需进一步研究。

3 总 结

过去 30 年危重病医学取得了长足进步，但是脓毒症导致的病死率没有实质性改善，微循环功能障碍是发生多器官功能障碍甚至死亡的主要因素，其中内皮细胞及相关的促凝效应起决定作用，因此内皮细胞损伤和凝血功能障碍相关的生物标记物对于早期诊断、指导治疗和判断预后可能具有指导意义，尚需更多的临床研究进一步验证。

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本刊常用的不需要标注中文的缩略语

急性肺损伤(ALI)
急性呼吸窘迫综合征(ARDS)
严重急性呼吸综合征(SARS)
全身炎症反应综合征(SIRS)
多器官功能障碍综合征(MODS)
多器官功能衰竭(MOF)
重症监护病房(ICU)
急性生理学与慢性健康状况评分系统(APACHE)
心肺复苏(CPR)
磁共振成像(MRI)
随机对照研究(RCT)
肿瘤坏死因子(TNF)
白细胞介素(IL)
核转录因子-κB(NF-κB)
动脉血二氧化碳分压($PaCO_2$)
动脉血氧分压(PaO_2)
脉搏血氧饱和度(SpO_2)
氧合指数(PaO_2/FiO_2)
一氧化氮(NO)
一氧化碳(CO)
丙氨酸转氨酶(ALT)
天冬氨酸转氨酶(AST)
异硫氰酸荧光素(FITC)
四甲基偶氮唑盐(MTT)
脂多糖(LPS)
盲肠结扎穿孔术(CLP)
支气管肺泡灌洗液(BALF)
磷酸盐缓冲液(PBS)
乙二胺四乙酸(EDTA)
3,3′-二氨基联苯胺(DAB)
逆转录-聚合酶链反应(RT-PCR)
蛋白质免疫印迹法(Western blotting)
酶联免疫吸附法(ELISA)
原位末端缺刻标记法(TUNEL)
链霉素-亲和素-生物素-过氧化物酶法(SABC)
十二烷基硫酸钠-聚丙烯酰胺凝胶电泳(SDS-PAGE)
天冬氨酸特异性半胱氨酸蛋白酶(caspase)
β-肌动蛋白(β-actin)
三磷酸甘油醛脱氢酶(GAPDH)
苏木素-伊红染色(HE 染色)
美国食品与药物管理局(FDA)
世界卫生组织(WHO)
美国心脏病学会(ACC)
美国胸科医师协会(ACCP)
危重病医学会(SCCM)
欧洲危重病医学会(ESICM)
美国心脏协会(AHA)

万方数据

脓毒症内皮细胞损伤和凝血功能障碍相关的生物标记物

万方数据 WANFANG DATA 文献链接

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