·综述·

脓毒症所致器官损伤中血管内皮屏障功能障碍的机制及检测方法研究进展

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【摘要】 脓毒症所致多器官功能障碍综合征（MODS）是危重症患者死亡的主要原因，其核心病理环节是血管内皮屏障功能的广泛破坏。内皮屏障的完整性对维持微循环稳态至关重要，脓毒症中失控的炎症反应通过激活内皮细胞、引发氧化应激、破坏细胞间连接、降解糖萼及促进免疫血栓形成等多重机制，导致微血管通透性急剧增加，最终驱动器官功能衰竭。本综述系统阐述了脓毒症中不同器官（如肺脏、心脏、肠道、肾脏、大脑）血管内皮屏障损伤的机制，并重点聚焦于评估屏障功能的方法学进展，以期为不同器官的检测提供最佳的方法。通过详细介绍跨内皮电阻（TEER）测量、荧光示踪剂渗透性测定、伊文思蓝（Evans Blue）渗漏、活体显微镜成像等通用技术，进而深入总结肺脏、肠道、肾脏及大脑等关键靶器官的特异性检测，强调多技术联用、多层次验证在全面评估屏障功能中的重要性。最后，本文总结不同方面检测血管内皮屏障的方法，并展望未来技术创新、临床转化探索的方向，旨在为深入研究脓毒症所致器官损伤中血管内皮功能障碍的病理机制与防治策略提供系统的方法学参考和思路。

【关键词】 脓毒症；多器官功能障碍综合征；血管内皮屏障；通透性；检测方法

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Research advances in mechanisms and detection methods of vascular endothelial barrier dysfunction in sepsis-induced organ injury

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【Abstract】 Sepsis-induced multiple organ dysfunction syndrome (MODS) is the leading cause of mortality in critically ill patients, and widespread disruption of the vascular endothelial barrier represents the central pathological event. The integrity of the endothelial barrier is crucial for maintaining microcirculatory homeostasis. In sepsis, the dysregulated inflammatory response leads to a dramatic increase in microvascular permeability through multiple mechanisms, including endothelial cell activation, oxidative stress, disruption of intercellular junctions, degradation of the glycocalyx, and the promotion of immunothrombosis, ultimately driving organ failure. This review systematically elaborates on the mechanisms underlying vascular endothelial barrier injury across different organs (e.g., the lung, heart, intestine, kidney, and brain) in sepsis, with a particular focus on methodological advances in assessing barrier function, aiming to provide optimal detection strategies for various organs. By detailing universal techniques such as transendothelial electrical resistance (TEER) measurement, fluorescent tracer permeability assays, Evans Blue leakage, and intravital microscopy imaging, it further summarizes specific assessments for key target organs, including the lung, intestine, kidney, and brain. The importance of employing a multi-technique approach and multi-level validation for the comprehensive evaluation of barrier function is emphasized. Finally, this review synthesizes the methods for detecting the vascular endothelial barrier from different perspectives and discusses future directions for technological innovation and clinical translation. The overall goal of this review is to provide a systematic methodological reference and conceptual framework for in-depth research into the pathological mechanisms and therapeutic strategies targeting vascular endothelial dysfunction in sepsis-induced organ injury.

【Key words】 Sepsis; Multiple organ dysfunction syndrome; Vascular endothelial barrier; Permeability; Detection method

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脓毒症是一种由宿主对感染产生功能失调反应引起的危及生命的器官功能障碍[1]。据全球疾病负担研究数据，2017 年全球约有 4 890 万例脓毒症病例，其中 1 100 万例死于脓毒症相关器官功能障碍，是全球公共卫生的主要经济负担[2]。我国重症监护病房（intensive care unit，ICU）中严重脓毒症患病率为 8.7%～37.3%，但该数据基于 ICU，会低估真实发病率[3]。脓毒症始于血管内皮屏障破坏，并导致广泛的器官衰竭[4]。血管内皮通过精细的细胞间连接（如紧密

连接、黏附连接）、内皮糖萼以及复杂的细胞骨架网络，构成分隔血液与组织间的动态半透性屏障[5]。在调节血管平滑肌张力、血管屏障形成、渗透平衡、全身和局部炎症、凝血方面以及免疫调节中扮演重要角色[6]。

脓毒症状态下，病原体相关分子模式（pathogen-associated molecular pattern，PAMP）与损伤相关分子模式（damage-associated molecular pattern，DAMP）触发的“炎症风暴”席卷全身，通过氧化应激、糖萼脱落、细胞骨架重构及凝血-炎症交叉对话等多重机制，导致微血管通透性急剧增加，进而驱动组织水肿与器官功能衰竭[7-8]。因此，维持血管内皮屏障的完整性对于大多数器官免受异物和病原体侵害至关重要。然而，尽管内皮屏障损伤的分子机制研究已取得显著进展，但在不同器官环境及疾病阶段如何准确、特异性地评估其功能状态，仍面临巨大挑战。

1　文献检索策略

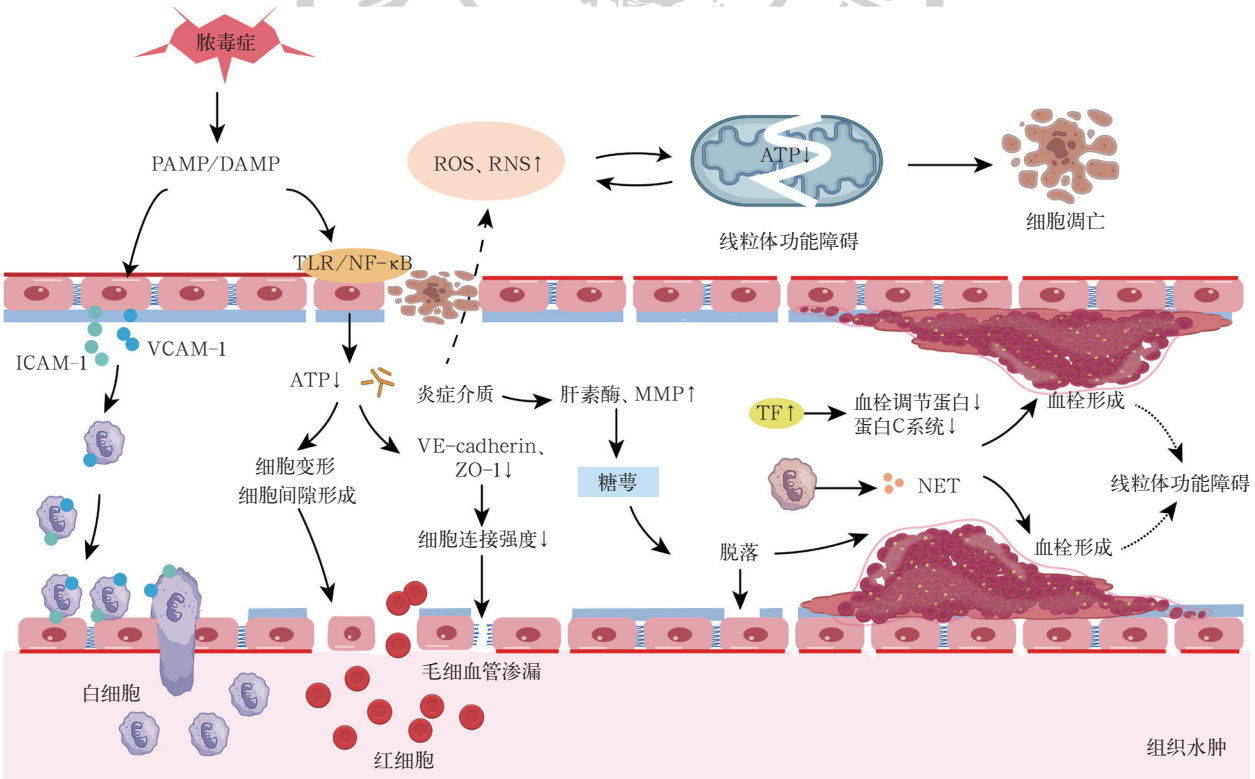
以“脓毒症”“多器官功能障碍综合征”“血管内皮屏障”“内皮通透性”“检测方法”等为中文检索词，在中国知网进行检索；以“sepsis”“multiple organ dysfunction syndrome”“vascular endothelial barrier”“endothelial permeability”“glycocalyx”“detection method”等为英文检索词，在美国国立医学图书馆 PubMed 数据库、科学网（Web of Science）、荷兰医学文摘 Embase 数据库进行检索。检索时间为 2015 年 1 月至 2025 年 4 月。

文献纳入标准：① 与脓毒症所致血管内皮屏障损伤机制及检测方法相关的实验研究和临床研究；② 文献类型为研究性论著和综述。文献排除标准：① 与研究内容不相关的文献；② 内容重复的文献；③ 无法获取全文的文献；④ 非中英文文献。根据纳入与排除标准，最终纳入文献 128 篇，其中，中文文献 3 篇、英文文献 125 篇。

2　脓毒症所致器官损伤中血管内皮屏障损伤的共同机制

血管内皮作为覆盖于血管内表面的单层结构，由内皮细胞、基底膜、细胞外基质及内皮糖萼共同构成，在维持微循环稳态中发挥核心作用[9]。脓毒症中，内皮功能障碍是关键病理环节之一，主要表现为促炎、促凝状态及屏障功能受损，最终导致毛细血管渗漏、微循环衰竭与多器官功能障碍综合征（multiple organ dysfunction syndrome，MODS）[10]（图 1）。

2.1　炎症介质风暴与内皮细胞激活：内皮细胞在脓毒症中兼具炎症“靶点”与“源头”的双重角色[11]。PAMP 和 DAMP 通过 Toll 样受体（Toll-like receptor，TLR）/ 核转录因子-κB（nuclear factor-κB，NF-κB）通路激活免疫细胞和内皮细胞，释放大量炎性因子〔如白细胞介素（interleukin，IL）、趋化因子、干扰素、肿瘤坏死因子（tumor necrosis factor，TNF）等〕，并上调细胞间黏附分子-1（intercelluar adhesion molecule-1，ICAM-1）、血管细胞黏附分子-1（VCAM-1）、E-选择素等黏附分子，促进白细胞滚动、黏附及渗出。同时，炎症介质诱



注：PAMP 为病原体相关分子模式，DAMP 为损伤相关分子模式，TLR 为 Toll 样受体，NF-κB 为核转录因子-κB，ROS 为活性氧，RNS 为活性氮，ATP 为三磷酸腺苷，ICAM-1 为细胞间黏附分子-1，VCAM-1 为血管细胞黏附分子-1，VE-cadherin 为 VE-钙黏蛋白，ZO-1 为紧密连接蛋白-1，MMP 为基质金属蛋白酶，TF 为组织因子，NET 为中性粒细胞外诱捕网

图 1　脓毒症所致血管内皮屏障功能障碍的核心机制示意图

导活性氧（reactive oxygen species，ROS）和活性氮（reactive nitrogen species，RNS）大量生成，进一步加剧内皮损伤与屏障破坏[12-13]。

2.2 氧化应激与线粒体功能障碍：脓毒症中炎症激活还原型烟酰胺腺嘌呤二核苷酸磷酸（reduced nicotinamide adenine dinucleotide phosphate，NADPH）氧化酶及诱生型一氧化氮合酶，导致 ROS 和 RNS 爆发性生成[14]。进而损害线粒体电子传递链，引起三磷酸腺苷（adenosine triphosphate，ATP）合成抑制，钙离子（Ca^{2+}）稳态紊乱及线粒体 DNA 损伤[15]。同时，线粒体功能障碍又进一步促进 ROS 生成，最终导致细胞凋亡和屏障通透性增加[16]。

2.3 细胞骨架重构与连接蛋白破坏：内皮屏障结构的维持高度依赖于细胞骨架稳定性和细胞间连接完整性[17]。脓毒症中，炎症介质和氧化应激可激活 Rho/Rac[18]、p38 丝裂原活化蛋白激酶（p38 mitogen-activated protein kinase，p38 MAPK）/ 热休克蛋白 27（heat shock protein，HSP27）[19]等信号通路，引起肌球蛋白轻链磷酸化，触发肌动 - 球蛋白收缩、细胞形变及间隙形成。同时，VE- 钙黏蛋白（VE-cadherin）在炎症刺激下发生磷酸化、不稳定和内化[20]；紧密连接蛋白〔如闭锁蛋白（occludin），密封蛋白（claudin），ZO-1〕表达下调且分布紊乱，直接削弱细胞间连接强度，共同导致血管通透性显著升高[21]。

2.4 糖萼损伤与微循环障碍：内皮糖萼是维持血管屏障及微循环功能的重要结构，其损伤被认为是内皮损伤的早期敏感标志物[22]。主要成分硫酸乙酰肝素蛋白聚糖和糖胺聚糖通过产生负电荷屏障调节血管通透性，以阻止大分子逸出到组织中[23]。脓毒症时 TNF-α 和 IL-6 等炎症因子上调肝素酶及基质金属蛋白酶（matrix metalloproteinase，MMP），引起糖萼降解脱落，导致负电荷屏障丧失、黏附分子暴露，促进白细胞与血小板黏附、微血栓形成、血管反应性下降及组织水肿，显著加剧微循环障碍[24-25]。

2.5 凝血 - 炎症交叉对话与微血栓形成：在脓毒症中，炎症与凝血密切联系。促炎因子上调组织因子（tissue factor，TF）的表达[26]、下调血栓调节蛋白和蛋白 C 系统[27]，导致促凝优势。同时，活化的中性粒细胞释放中性粒细胞胞外诱捕网（neutrophil extracellular trap，NET）、DAMP 及糖萼降解直接损伤内皮细胞、暴露内皮下胶原，激活血小板和凝血系统，导致微血管内纤维蛋白沉积、微血栓广泛形成及凝血功能障碍，进一步加重器官损伤[28-29]。

脓毒症中，PAMP 与 DAMP 触发的失控性炎症反应，协同驱动炎症风暴、氧化应激、糖萼脱落及凝血紊乱等核心病理过程。这些过程共同导致内皮细胞连接破坏与微血栓形成，最终引起微血管通透性急剧增加、组织水肿及缺氧，进而推动 MODS 的发生。

3　血管内皮屏障功能的检测方法学总览与技术比较

血管内皮屏障由内皮细胞通过紧密连接、黏附连接、间隙连接和桥粒共同维持[30]，脓毒症可致其广泛受损。为全面评估其结构与功能变化，目前已形成涵盖体外功能、分子结构、在体通透性及动态成像的多维度检测体系（表 1），以下分类概述。

3.1 跨内皮细胞电阻测量：跨内皮电阻（transendothelial electrical resistance，TEER）测量是体外评估内皮细胞单层屏障完整性和渗透性的一种敏感、可靠和无创的方法，可对屏障功能的动态变化进行时间依赖性和无损监测[52]。

3.2 连接蛋白的表达：蛋白质免疫印迹试验（Western blotting）可检测 VE-cadherin、occludin、claudin、ZO-1 等连接蛋白及骨架相关蛋白的表达与磷酸化修饰[53]。免疫荧光（immunofluorescence，IF）和免疫组化（immunohistochemistry，IHC）可直观定位上述蛋白的分布[54]。电镜（如透射电镜和扫描电镜）可观察到细胞间连接及糖萼的超微结构[55]。

3.3 组织学染色：苏木素 - 伊红（hematoxylineosin，HE）染色和过碘酸希夫（periodic acid-Schiff reaction，PAS）染色可评

表 1　血管内皮屏障功能检测方法的优点、局限和应用场景

方法	优点	局限	应用场景
TEER 测量[31-33]	灵敏；可靠；实时定量评估体外屏障功能的金标准	数值易受因素影响间接测量；仅反映离子通透性，无法区分旁细胞和跨细胞途径	药物 / 化合物对屏障功能的体外筛选；屏障相关分子机制的探索
连接蛋白的表达[34-36]	可检测连接蛋白及骨架蛋白的表达与磷酸化修饰；直观定位蛋白分布；观察细胞间连接及糖萼超微结构	依赖特异性抗体；电镜样本制备复杂；多为静态观察	屏障损伤的分子机制验证；连接蛋白表达与分布变化评估；糖萼超微结构观察
组织学染色[37-39]	直观定位；特异性；突出细胞和组织的精细结构	静态观察；样本处理复杂；染色伪影和潜在的组织损失	病理诊断；区分细胞成分；观察内皮连接蛋白的表达与分布
伊文思蓝测定[40-42]	操作简便；可视化标记的脉管系统	具有生物毒性；低灵敏度；可能导致假阳性结果	监测蛋白质从血流渗漏到间质组织的程度；粗略估计血容量、淋巴结检测、肿瘤定位等
荧光或放射性标记分子渗出法[43-45]	定量；动态；可视化；高稳定性和灵敏度	荧光漂白；存在安全问题	血管分割；定量评估体内或体外血管对大分子的通透性；脉管系统成像；
活体显微镜技术[46-48]	高时空分辨率；可在活体生理条件下开展动态、实时、量化分析	成像深度有限；需外科手术制备观察窗；数据量大	用于研究活体动物的各种生物过程
血管内皮特异性生物标志物检测[49-51]	简单；无创 / 微创；早期预警；动态监测；取样方便	特异性不足；易受因素影响	早期诊断；临床预后预测；风险评估和疗效监测

注：TEER 为跨内皮电阻

估组织水肿、炎症细胞浸润等病理变化[56]，联合 IF 和 IHC 技术可精确定位 CD31、VE-cadherin 等内皮标志物，半定量评估连接结构的完整性、分布及表达变化[57-58]。

3.4 伊文思蓝（Evans Blue）测定：通过伊文思蓝测定荧光强度来量化染料-白蛋白外渗程度，可间接反映血管内皮屏障的通透性变化[59-60]，是一种重复且准确的血管通透性改变评估方法[61]。

3.5 荧光或放射性标记分子渗出法：荧光或放射性标记分子〔如异硫氰酸荧光素（fluorescein isothiocyanate，FITC）-葡聚糖〕渗出法可定量评估体内外通透性[62]，常与 TEER 互补使用[63]。

3.6 活体显微镜技术：活体显微镜可实时、动态地记录示踪剂从血管内渗出的过程[64]，并同步观察白细胞-内皮相互作用及微循环指标[65]。

3.7 血管内皮特异性生物标志物检测：酶联免疫吸附试验（enzyme-linked immunosorbent assay，ELISA）检测血液中血栓调节蛋白、E-选择素、ICAM-1 等内皮源性标志物，为临床无创评估内皮损伤提供了窗口[66-67]。

4 脓毒症中各器官血管内皮屏障功能障碍与特异性检测策略

脓毒症诱导的内皮屏障功能障碍是 MODS 发生发展的关键推动因素。针对不同器官的血管生物学特性，需采取针对性的评估策略（表 2），以下分述各靶器官的核心病理特点与推荐检测组合。

4.1 肺脏—急性呼吸窘迫综合征（acute respiratory distress syndrome，ARDS）与肺泡-毛细血管屏障：在脓毒症中，肺作为易受累的器官之一，可发展为 ARDS，表现为难治性低氧血症、呼吸窘迫和非心源性肺水肿[68]。肺泡-毛细血管屏障是肺气体交换的结构基础，其破坏导致富含蛋白的液体渗漏至间质和肺泡腔，是 ARDS 的病理核心[69]。

功能层面，肺湿重/干重（wet/dry weight，W/D）比值可量化肺水肿的严重程度[70]；伊文思蓝含量/肺干重是血管渗漏的直接指标[71]；支气管肺泡灌洗液（bronchoalveolar lavage fluid，BALF）蛋白浓度测定可直接反映屏障对大分子的通透性[72]；肺血管通透性指数（pulmonary vascular permeability index，PVPI）通过血管外肺水/肺血容量比值间接评估屏障完整性[73]，与 BALF 蛋白含量均呈现良好的相关性[74]。结构层面，透射电镜可观察糖萼变薄与结构松散[75]。实时活体成像和荧光显微血管造影可实时记录示踪剂从血管腔向组织间隙的渗漏过程[76-77]。此外，通过量化应力纤维覆盖面积、细胞间裂隙数量/细胞核总数比值及 VE-cadherin 染色完整性 3 个参数，可评估内皮单层结构完整性[78]。TEER 和 XPerT 测定则可对内皮单层屏障功能进行体外动态定量评估[79]。联合 Western blotting 和 IF 可检测脂多糖（lipopolysaccharide，LPS）诱导的 VE-cadherin、occludin、ZO-1 等连接蛋白的表达下调与分布紊乱；磷脂酶 C（phospholipase C，PLC）-蛋白激酶 C（protein kinase C，PKC）-黏着斑激酶（focal adhesion kinase，FAK）[80]和 R-脊椎蛋白 3（R-spondin-3，RSPO3）/富含亮氨酸重复序列的 G 蛋白偶联受体 4（leucine-rich repeat-containing G-protein coupled receptor 4，LGR4）[81]通路可保护内皮屏障。

4.2 肠道—细菌/毒素易位与肠血管屏障（gut vascular barrier，GVB）：肠道在脓毒症中既是损伤靶点，也是驱动全身炎症的“发动机”[82]。GVB 是多重肠道屏障（例如上皮、黏液屏障、肠道微生物群）系统的核心组成部分，能有效阻止病原菌和管腔成分侵入门静脉和肝脏[83]。LPS 导致肠壁水肿、组织缺氧和肠道通透性增加，进而促进菌血症和内毒素血症，是脓毒症恶化的重要推动因素[84]。

血清 FITC-葡聚糖水平可动态反映肠血管通透性[85]；口服造影剂的磁共振成像（magnetic resonance imaging，MRI）可无创评估肠壁水肿和通透性变化[86]；血清二胺氧化酶（diamine oxidase，DAO）活性是反映 GVB 完整性和肠道上皮细胞健康状态的敏感血液标志物[87]。形态学层面，HE 染色联合 IF/IHC 可观察隐窝结构扭曲及 occludin、ZO-1 的表达下调与分布改变[88]；透射电镜和扫描电镜可观察血管与肠道超微结构[89]；TEER 结合肠道类器官可用于药物和益生菌等屏障保护效果筛选[90-91]。无菌采集肠系膜淋巴结、肝脏组织进行细菌培养，培养阳性是判定 GVB 功能失效、发生细菌易位的直接证据[92]。

4.3 肾脏—脓毒症相关急性肾损伤（sepsis-associated acute kidney injury，SA-AKI）与肾小球内皮和肾小管周毛细血管（peritubular capillaries，PTC）网络：肾脏拥有体内最丰富且

表 2　各器官的血管内皮检测方法

器官	核心病理特点	特有方法
肺脏	肺泡-毛细血管屏障损伤→ ARDS	伊文思蓝含量/肺干重、PVPI 与 BALF 蛋白浓度、糖萼透射电子显微镜、量化屏障结构破坏、荧光显微血管造影
肠道	肠血管屏障损伤→细菌易位	口服造影剂的磁共振成像、血清标志物（DAO）、组织细菌培养与易位分析
肾脏	肾小球/PTC 屏障损伤→ SA-AKI	肾微血管室激光显微解剖技术、对比增强超声成像与侧流暗场成像、肾功能生化指标
大脑	BBB 损伤→ SAE	脑组织含水量测定、影像学（NIR、DCE）、GFP-大肠杆菌易位测定、神经血管糖萼的完整性、脑组织的通透性的技术、血清标志物（S100B）
心脏	心肌微血管内皮屏障→脓毒症诱导的心肌损伤	明胶墨水灌注实验、甲襞毛细血管镜、外周动脉张力检测法、血池 MRI、心肌造影负荷超声心动图

注：ARDS 为急性呼吸窘迫综合征，PVPI 为肺血管通透性指数，BALF 为支气管肺泡灌洗液，DAO 为二胺氧化酶，PTC 为肾小管周毛细血管，SA-AKI 为脓毒症相关急性肾损伤，BBB 为血脑屏障，SAE 为脓毒症相关性脑病，NIR 为近红外成像，DCE 为动态对比增强，GFP 为绿色荧光蛋白，S100B 为 S100 蛋白质，MRI 为磁共振成像

高度异质性的内皮细胞群，包括肾小球内皮和 PTC 网络[93]。脓毒症中，肾小球滤过屏障分子筛功能丧失和 PTC 微循环衰竭是肾脏内皮损伤的核心表现，两者共同驱动 SA-AKI 的发生[94]。

结构评估方面，透射电镜可观察肾小球内皮细胞形态异常及紧密连接消失[95]。肾组织 IF/IHC 标记 CD31、E-选择素和 VE-cadherin 可评估内皮连接完整性[96]。微循环评估方面，活体显微镜可直接观察肾小球及 PTC 血流动态与白细胞黏附[97]；对比增强超声成像与侧流暗场成像可评估肾脏血流动力学状态[98]。此外，肾微血管室激光显微解剖技术可分离肾微血管用于后续分子机制研究[99]。功能层面，伊文思蓝和 FITC-葡聚糖渗出实验可定量肾血管通透性[100]，后者常与 TEER 互补联用[101]。临床上，尿白蛋白/肌酐比值（urine albumin/creatine ratio，UACR）和血清胱抑素 C 可反映肾小球屏障功能[96, 102]；中性粒细胞弹性蛋白酶和髓过氧化物酶等与微循环缺陷直接相关[103]。

4.4 大脑—脓毒症相关性脑病（sepsis-associated encephalopathy，SAE）与血脑屏障（blood-brain barrier，BBB）：SAE 是一种在无直接中枢神经系统感染的情况下出现的弥漫性脑功能障碍，其发生发展与 BBB 的破坏密切相关。BBB 由脑内皮细胞及其紧密连接、周细胞和星形胶质细胞足突等共同构成高度选择性动态界面[104]。脓毒症中 LPS 通过直接损伤内皮、破坏紧密连接及激活胶质细胞等多条途径增加 BBB 通透性，导致神经炎症和脑水肿[105-106]。

在体层面，如双光子显微镜和近红外成像（near infrared，NIR）、动态对比增强（dynamic contrast enhanced，DCE）和 T1 加权 MRI 均可评估 BBB 完整性[107-108]；深度学习来源的毛细血管输入函数可提升 BBB 通透性测量的效率[109]；脑组织含水量测定可定量血管源性脑水肿[110]。示踪剂渗漏法（如荧光素钠测定、14C-蔗糖空间测定法、免疫球蛋白 G（immunoglobulin G，IgG）、白蛋白-Alexa 荧光偶联物及辣根过氧化物酶等）可从不同分子大小层面反映屏障损伤程度[111-112]。体外层面，TEER 和 FITC-葡聚糖扩散实验是 BBB 模型通透性评估的常用手段[113]。分子层面，IF 和 Western blotting 可检测 occludin、claudin-5、ZO-1 等紧密连接蛋白的表达与分布[114]；共聚焦显微镜与透射电镜可观察 BBB 超微结构[115]；双光子显微镜及质谱等方法有助于了解神经血管糖萼的完整性[112]。绿色荧光蛋白（green fluorescent protein，GFP）-大肠杆菌易位测定可作为 BBB 功能缺损的支持性证据[116]。血清 S100 蛋白质（S100 protein，S100B）水平升高是 BBB 破坏的间接临床标志物[117]。

4.5 心脏—脓毒症诱导的心肌损伤与心肌微血管内皮屏障：脓毒症中，心脏功能障碍表现为血流动力学不稳定、终末器官低灌注和心肌抑制[118]。脓毒症诱导的心肌损伤中，心肌微血管内皮屏障破坏导致间质水肿、毛细血管栓塞和微循环灌注障碍，是心功能抑制的关键环节[119]。

结构层面，ELISA、Western blotting 及流式细胞术等方法可检测连接蛋白、细胞骨架蛋白及渗出心肌中的白蛋白的表达，评估内皮屏障结构完整性[120]。透射电镜可观察微血管超微结构变化[121]；凝集素染色和镧染色电镜可定量与可视化糖萼损伤[122]；原位末端转移酶标记法（terminal-deoxynucleotidyl transferase-mediated dUTP-biotin nick end labeling assay，TUNEL）染色可评估内皮细胞凋亡[123]。液相色谱-串联质谱可系统分析屏障相关蛋白的变化，差异表达蛋白热图对其进行可视化[119]。功能层面，FITC-白蛋白/葡聚糖渗漏、伊文思蓝渗出、明胶墨水灌注和 TEER 测定可从不同维度评估内皮屏障通透性[124-125]。冠状血管内皮依赖性血管舒张检测可评估内皮细胞信号传导能力[126]。在体评估方面，心肌造影负荷超声心动图可早期诊断冠状动脉微血管功能障碍[127]；外周动脉张力检测法可识别内皮功能障碍[128]；激光多普勒灌注测量和血池 MRI 可评估心肌微血管反应性[129]；甲襞毛细血管镜检查则可能成为预测心脏微血管受累的辅助工具[130]。

5　总结与展望

本文系统阐述了脓毒症中血管内皮屏障功能障碍的核心机制，并以此为框架梳理了用于揭示这些机制、评估其功能后果的多维度检测技术。血管内皮屏障功能障碍是脓毒症诱发 MODS 的核心病理环节，其评估依赖于涵盖功能、结构、在体成像及分子检测的多维度技术体系。针对该领域研究方法繁多但缺乏共识的现状，本文提出以下建议：① 坚持“功能-结构-分子”多维验证原则，构建证据链。单一检测指标易产生偏倚，可靠的研究应联合应用功能测定、形态观察和分子检测。例如，在评估肺损伤时，应将体内（如伊文思蓝渗漏）或体外（如 TEER 测量）通透性测定与实时活体成像和荧光显微血管造影动态观察肺泡毛细血管屏障以及连接蛋白的分布与表达检测（如 VE-cadherin 免疫荧光）相结合。这种多层次互证策略能确保所观察到的通透性变化具有坚实的结构与分子基础，避免将非特异性损伤误判为屏障功能障碍。② 依据靶器官的血管生物学特性，选择与优化特异性检测策略。不同器官的内皮屏障具有高度异质性，研究方法需“量体裁衣”。例如，对于 BBB，应优先采用影像学评估 BBB（如 DCE-MRI 等）了解整体通透性变化，辅以 TEER 测量和特异性示踪剂渗漏法（如荧光素钠），因其对离子和小分子通透性极为敏感；对于 GVB，需关注其“细菌易位”的病理终点，因此 FITC-葡聚糖通透性测定是揭示 GVB“如何漏”及“漏多少”的最佳动态功能工具，而肠系膜淋巴结细菌培养是判断 GVB“是否失效”的终极标准；对于肾脏，应区分肾小球滤过屏障与 PTC 网络，分别采用 UACR 和活体显微镜观察 PTC 血流等针对性方法。③ 重视动态与早期评估，将糖萼完整性作为屏障损伤的敏感指标。血管内皮糖萼的降解是脓毒症内皮激活和屏障破坏的始动环节与敏感标志。研究方法不应仅局限于终末期的严重渗漏。在实验设计中，应纳入血浆糖萼成分（如 syndecan-1）的检测，并利用活体显微镜或电子显微镜对微血管糖萼进行早期、动态的形态学观察。这有助于在可逆阶段识别内皮损伤，并为干预时间窗提供依据。④ 在体外模型中模拟体内病理

生理压力，提升研究的相关性。传统静态 Transwell 模型无法充分模拟脓毒症时的剪切力变化、免疫细胞相互作用及间质压力。建议在条件允许时，采用微流控器官芯片技术，构建具有生理流动、多细胞共培养的屏障模型，以更真实地复现临床病理过程；在细胞实验中，除 LPS 刺激外，可联合使用细胞因子混合物〔如 TNF-α+γ- 干扰素（interferon-γ，IFN-γ）〕或患者血浆进行刺激，以更好地模拟体内复杂的炎症环境。同时，体外模型的 TEER 和通透性数据需谨慎解读，并尽可能用体内实验进行验证。

尽管检测方法众多，该领域仍缺乏统一、标准化的方法。不同检测方法在其适用范围、分辨率、通量和临床可行性方面各具优势和局限性，研究者需根据科学问题、模型系统及目标器官的特点进行合理选择和多重验证。同时多数技术仍局限于基础研究，与临床需求存在显著脱节。以下方向值得未来重点关注：① 推动检测体系的标准化与临床转化，发展无创、床旁化的评估工具，实现脓毒症患者内皮功能的早期诊断与风险分层；② 加强跨学科合作，整合工程学、影像学与临床医学，突破技术瓶颈；③ 融合新兴技术趋势，如人工智能与机器学习，对显微影像和组学数据进行深度挖掘，实现屏障功能的自动化、高通量分析；同时进一步拓展类器官 / 芯片等模型在个性化医疗中的应用。通过持续优化方法、建立共识并推动创新技术临床转化，为深入揭示脓毒症血管内皮屏障损伤机制及其精准防治开辟新的路径。

利益冲突　所有作者声明不存在利益冲突

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