· 综述 ·

急性肺损伤/急性呼吸窘迫综合征的生物标志物

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从 1967 年成人呼吸窘迫综合征被报道[1]，人们逐渐发现各种肺内或肺外疾病导致炎性介质泛滥，肺血管内皮和肺泡上皮受损，无论成人或者儿童均可表现为高通透性肺水肿、肺顺应性减退和顽固性低氧血症，即急性呼吸窘迫综合征（ARDS）[2]。随着人口老龄化，ARDS 已经成为严重的疾病负担[3]。生物标志物的探索有助于 ARDS 早期诊断、病情监测及预后判断，深化人们对 ARDS 发病机制的认识[4]。生物标志物应该是能够反映正常生物学过程或疾病过程或机体对药物治疗反应的客观指标[5]。理想的疾病标志物总是与重要发病环节相关联的，具有生物学合理性。目前，对 ARDS 标志物的探索主要是基于对以下发病机制的认识。

1　炎性损伤与凝血、纤溶异常

肺内炎症反应可以是针对局部感染的防御性反应，也能继发于全身性炎症反应综合征（SIRS）。炎症因子作用网络以及炎症、凝血、纤溶通路的交叉对话共同参与 ARDS 发生发展[6]。细胞因子检测在 ARDS 诊断方面总的表现是令人失望的，在生存预后方面却表现出一定价值[7]，如血浆高水平 IL-6、IL-8 提示不良结局[8-9]。血浆可溶性肿瘤坏死因子受体（sTNFR）-Ⅰ和 sTNFR-Ⅱ高水平同样与高病死率相关，也与器官衰竭日和机械通气日增加相关[10]。众多细胞因子是在相互对话相互影响的复杂整体环境中发挥生物学效应的，孤立地评价单个因子变化可能会产生错误判断[11]。高迁移组蛋白（HMGB）-1 是细胞核 DNA 结合蛋白，在细胞损伤时释放到胞外并诱发炎症反应，严重创伤患者血浆 HMGB-1 水平增加并与 ARDS 的发生以及死亡结局相关联[12]。ARDS 患者发病 48 h 内 C 反应蛋白（CRP）水平与生存率、无器官衰竭日和无机械通气支持日正相关[13]。这可能与高水平 CRP 减少中性粒细胞趋化激活相关[14]。降钙素原（PCT）水平则可能预测社区获得性肺炎相关 ARDS 死亡结局[15]。

中性粒细胞聚集激活是 ARDS 重要发病机制[16]，肺泡中高水平 IL-8 与中性粒细胞聚集激活以及病死率增高相关联[17]。与高静水压肺水肿比较，ARDS 患者血浆和肺水肿液基质金属蛋白酶（MMP）-9 和 IL-8 水平显著增高[18]。IL-8 可能作为中性粒细胞激活标志物用于 ARDS 诊断及预后判断。肺泡巨噬细胞可能参与炎症反应放大和肺损伤进展[19]，脓毒症肺损伤过程中肺泡灌洗液（BALF）巨噬细胞计数持续增加与肺损伤修复和生存预后改善相关[20]。

炎症与促凝、抗纤溶交叉激活是 ARDS 患者肺血管内皮和肺泡上皮细胞损伤的重要机制[6]。组织因子活化、内皮细胞表面血栓调节素（TM）和蛋白 PC 受体脱落并丧失激活蛋白 PC 受体等能力，纤溶酶原激活物抑制因子（PAI）释放增加，共同促发 ARDS 初期高凝状态[21]。ARDS 时肺水肿液和血浆中 PAI-1 水平较心源性肺水肿显著增高并与机械通气时间延长和病死率增加相关[22]，多中心研究证实上述发现[23]。肺水肿液中 TM 增多及 PC 减少可能也有类似预测价值[24]。

2　细胞凋亡、增殖异常及修复障碍

高通透性肺水肿液中可溶性 Fas 和 Fas 配体较高静水压肺水肿液显著增多，前者诱导肺泡上皮细胞凋亡效应可为 Fas 信号通路抑制剂阻断，检测 BALF 中 Fas 和 Fas 配体水平有助于 ARDS 诊断和预后评估[25]。

ARDS 初期 2 型肺泡上皮细胞即开始沿肺泡间隔再生，伴有新生血管形成，标志增殖修复开始，随后纤维增生过程逐渐占据优势[26]。角质细胞生长因子（KGF）和肝细胞生长因子（HGF）是诱导 2 型肺泡上皮细胞增殖的强有力刺激原，二者可否作为 ARDS 标志物存在矛盾报道[27-28]。其他促进细胞增殖及细胞外基质修复标志物的价值，如转化生长因子（TGF）-α、血管内皮细胞生长因子（VEGF）、前胶原肽Ⅲ（PCPⅢ）等，同样存在诸多争议[29-34]。

3　肺内气体-血液交换屏障损伤

气血屏障受损是 ARDS 的重要特征[35]，标志毛细血管内皮、肺泡上皮以及细胞外基质等屏障结构损伤的分子，可能用于 ARDS 诊断、危险分层和预后评估。

van Willebrand 因子（vWF）是血管内皮细胞损伤标志物。ARDS 患者血浆和肺水肿液中高水平 vWF 可预示死亡结局，并与机械通气时间延长相关[36-38]。检测肺水肿液和血浆中细胞间黏附分子（ICAM）-1 水平有助于肺水肿鉴别诊断[39]，大样本临床研究中也发现高水平 ICAM-1 与病死率高、机械通气支持时间延长独立相关[40]。ARDS 患者血浆选择素 P 水平高于无 ARDS 的脓毒症患者，并且高水平选择素 P 与死亡结局相关[41]。但另一项包括胰腺炎、多发伤、肠穿孔等病种的小样本研究显示，研究初始血浆选

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择素 E 和选择素 P 水平在有无发生 ARDS 的患者之间差异无统计学意义[42]。血管生成素（Ang）-1 和 Ang-2 是内皮细胞表面 Tie-2 酪氨酸激酶受体的天然配体，前者稳定血管屏障功能，后者作为 Tie-2 受体拮抗物增加内皮细胞通透性[43]。严重脓毒症较轻症患者血清 Ang-2 水平显著增高，并与动脉血低氧合水平（氧分压与吸氧浓度比值小于 200）相关。ARDS 患者血浆和肺水肿液中 Ang-2 水平高于高静水压性肺水肿患者[44]。此后发现 ARDS 患者血清 Ang-2 和 vWF 水平较非 ARDS 患者显著增高且与肺渗漏严重程度呈正相关，Ang-1 和 VEGF 则没有表现出这种特点[45]。

上皮细胞损伤影响肺泡内水肿液清除，表面活性物质分泌减少也会显著增加肺泡内剪切张力加重肺损伤[46-47]。仅有内皮损伤不足以引起肺泡内大量液体集聚，除非同时造成上皮结构损伤[48]。表面活性蛋白（SP）由 2 型肺泡上皮细胞合成分泌，ARDS 患者插管通气初期血浆 SP-A 水平增高与机械通气时间延长相关，肺水肿液中 SP-D 水平降低则与病死率增加和动脉血氧合下降相关[49]。另一项研究发现 ARDS 患者血浆中 SP-A 和 SP-D 均增加，肺水肿液中 SP-D 显著下降出现在死亡患者和氧合水平严重下降者[50]。大样本研究显示血浆 SP-A 水平与 ARDS 不良预后无相关性，血浆 SP-D 增加则与病死率增高、机械通气时间以及器官衰竭时间延长独立相关，保护性通气显著减少血浆 SP-D 水平[51]。高级糖基化终末产物受体（RAGE）是跨膜免疫球蛋白受体，在 1 型肺泡上皮细胞基底侧表面大量表达[52]，可能是肺上皮损伤的较好标志物。肺损伤模型大鼠血浆和肺水肿液中 RAGE 显著增加，而 ARDS 患者血浆和肺水肿液中 RAGE 较高静水压肺水肿患者增高[53]。肺移植患者血浆 RAGE 水平与机械通气支持日和 ICU 住院日延长正相关[54]。一宗针对肺移植患者保护性通气的大样本研究显示，移植后血浆 RAGE 水平增高与不良临床结局相关性仅表现在接受高潮气量通气的患者，减少潮气量使血浆 RAGE 水平显著下降[55]。

肺泡上皮和肺血管内皮之间由细胞外基质填充，多种基质糖蛋白和蛋白聚糖降解产物均被研究作为 ARDS 标志物。例如，锁链素是弹性蛋白的稳定降解产物，可经尿排出体外，ARDS 患者尿锁链素水平显著高于心源性肺水肿者，但另一组无肺水肿者的尿锁链素水平却高于 ARDS 患者[56]。ARDS 患者尿锁链素与尿肌酐比值增高提示死亡风险增加，小潮气量通气支持下该比值增加较少[57]。又如，ARDS 患者血浆和肺水肿液层黏连蛋白 γ2 片段显著增加与病死率增加存在一定相关[58]。

4 联合标志物检测

ARDS 发病过程涉及多个关键环节，似乎很难找到单个标志物可以反映全部发病过程。联合 RAGE、Ang-2、PCP Ⅲ、BNP（脑钠肽）、IL-10、TNF-α、IL-8 等鉴别 ARDS 与胸部影像学正常的重症创伤及高静水压肺水肿，其受试者工作特征曲线下面积（AUCROC）为 0.86（95% *CI*：0.82～0.92）[59]。联合检测 ARDS 早期血浆中炎症（IL-6、IL-8）、凝血（TM、PC）、纤溶（PAI-1）、内皮损伤（ICAM-1）等标志物，发现除了 IL-6 以外其余标志物水平在存活者和非存活者之间差异具有统计学意义，多元分析去除人口学因素和某些临床因素影响后显示 IL-8、ICAM-1、PC 与高死亡风险独立相关[60]。将临床特征和生物标志物结合可进一步提高预测的准确性，Ware 等[61]结合 APACHE Ⅲ、器官衰竭情况、年龄、基础病因、肺泡动脉氧分压差、气道平台压等预测 ARDS 患者 60 d 死亡结局，其 AUC = 0.82，联合检测 vWF、SP-D、TNFR-I、IL-6、IL-8、ICAM-1、PC、PAI-1 等 8 个标志物，其 AUC = 0.85，8 个标志物中死亡预测准确性最高的是 IL-8 和 SP-D，这或许提示炎症与肺泡上皮损伤是 ARDS 发病的关键环节。

5 几个值得关注的新标志物

转录后修饰的血浆蛋白能够反映炎症性疾病严重度及病情进展[62]，其中血浆硝基化蛋白定量有助于脓毒症与 ARDS 诊断[63]。1-磷酸鞘氨醇受体 3（S1PR3）是调节细胞增殖和血管通透性的关键信号分子，血管内皮细胞在内毒素、凝血酶等刺激下释放硝基化 S1PR3 增多，这种硝基化蛋白可增加体外培养的血管内皮细胞通透性，而使用小干扰 RNA 技术减少其释放可显著改善内皮屏障功能，肺损伤小鼠血浆硝基化 S1PR3 水平增加，ARDS 患者血浆 S1PR3 水平增加与死亡风险增高相关，血浆总 S1PR3 大于 251 pg/mL 诊断脓毒症相关 ARDS 的敏感性和特异性分别为 74% 和 65%[64]。正五聚蛋白 3（PTX3）参与固有免疫调节，在多种肺损伤动物模型中表达并与肺损伤程度正相关[65]。内毒素造模后 PTX3 缺陷小鼠无论是炎症反应强度和细胞凋亡水平、肺损伤程度均较野生型小鼠明显加重[66]。ARDS 患者血浆 PTX3 水平与临床肺损伤评分、肺外器官衰竭数目、生存结局显著相关[67]。PTX3 作为 ARDS 标志物的价值值得深入研究。脂钙蛋白 2（LCN2）或中性粒细胞明胶酶关联运脂蛋白（NGAL）组成性表达于中性粒细胞并储存在其特异性颗粒中，炎症状态下上皮组织表达增加[68]。LCN2 基因缺陷鼠心脏移植后缺血再灌注损伤部位中性粒细胞募集量较野生型鼠显著减少，提示 LCN2 调节炎症部位中性粒细胞趋化激活[69]。LCN2 也可能参与氧化应激损伤[70]和细胞凋亡调节[71-73]。多中心临床研究显示联合检测 NGAL、PC、IL-1 受体拮抗物有助于判断脓毒症相关器官损伤及预测死亡结局，其 AUC 分别为 0.80 和 0.79[74]。LCN2/NGAL 具有小相对分子质量、胞外分泌性以及蛋白酶抗性等便于体外检测的特点[75]，NGAL 有希望成为具有临床实用价值的脓毒症相关急性肺损伤标志物。

6 总结与展望

目前没有多中心临床研究证据支持单个标志物或者某个标志物组合可以独立预测 ARDS 发病风险或可用于早期诊断[76-77]。以下标志物可用于 ARDS 预后并得到较为一致的多中心临床研究结果支持：vWF、SP-D、sTNFR、IL-6、IL-8、ICAM-1、PC、PAI-1。RAGE 与 Ang-2 具有潜在临床价值用于 ARDS 的早期诊断和危险分层，但其准确性仍有待多中心研究结果证实。S1PR3、PTX3、NGAL 等具备作为 ARDS 标志物的生物学合理性，但是否必要开展大规模临床研究尚需更多的基础研究证据。

高级生命活动的复杂性使得我们对疾病的认识在大多

数时候是局限的，有时甚至是错误的。基于对发病机制的认识寻找疾病标志物难以避免研究者本身存在的认知偏倚，错误研究方向会浪费大量精力。基因组学、蛋白质组学和代谢组学的进步扩大了对疾病分子病理的认知宽度和深度，也扩大了疾病标志物的候选范围。例如，运用基因表达芯片技术在 ARDS 患者和动物模型中发现前 B 细胞集落强化因子（PBEF）表达增加，DNA 测序显示 PBEF 基因存在单核苷酸多态性，其中某些变异与 ARDS 发生风险增加相关，PBEF 可能作为 ARDS 标志物[78]。随着高通量组学研究平台改进和生物信息学工具的日益完善，未来有可能发现新的疾病易感基因和分子标志物用于 ARDS 早期诊断、危险分层以及预后评估。

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《中华急诊医学杂志》是由中华医学会主办、中国科学技术协会主管的, 代表我国急诊医学水平的高级学术期刊, 覆盖国内所有省、自治区、直辖市, 并与国际急诊医学界积极交流。《中华急诊医学杂志》设有述评、专家论坛、基础研究、临床研究、经验交流、院前急救、学科建设、病例报告、综述、继续医学教育等栏目, 及时报道我国急诊医学最新进展及中华医学会相关信息, 内容丰富, 信息量大, 充分反映了我国急诊医学的特色。

目前,《中华急诊医学杂志》已被国内外多家检索系统收录, 2005 年获得中国科协的“自然科学基础性、高科技学术期刊”经费资助, 2006 年获得了“中国科协 2006 年精品科技期刊工程”的资助, 2007 年获得“中国科协 2007 年精品科技期刊工程延续项目”资助, 2008 年获得了“中国科协 2008 年精品科技期刊工程延续项目”资助, 2009 年获得了中国科协精品科技期刊示范项目称号; 在 2010 年中华医学会第 24 次全国会员代表大会上, 荣获优秀期刊称号。在 2014 年 9 月中国科学技术信息研究所主办的“中国科技论文统计结果发布会”上,《中华急诊医学杂志》入选 2014 年中国精品科技期刊。

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