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碳氧血红蛋白在呼吸与危重症医学中的研究进展

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摘 要

碳氧血红蛋白(COHb)是反映机体一氧化碳(CO)暴露的特异性生物标志物，其在呼吸与危重症医学领域的诊疗价值日益凸显。本文整理COHb在急性呼吸窘迫综合征、急性肺栓塞、间质性肺病等呼吸系统疾病以及体外膜肺氧合支持、感染、溶血、休克等危重症中的病情评估与预后预测价值；同时归纳COHb检测技术进展、干扰因素、内源性CO的双重病理生理作用及外源性COHb制剂的治疗潜力。临床诊疗过程中动态监测COHb水平，有助于对危重症患者进行早期风险分层与个体化治疗，因此，本文旨在对COHb在危急重症疾病中的预测价值进行综述。

关键词

碳氧血红蛋白，一氧化碳，呼吸与危重症医学，生物标志物

Research Progress of Carboxyhemoglobin in Respiratory and Critical Care Medicine

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Abstract

Carboxyhemoglobin (COHb) is a specific biomarker reflecting the body's carbon monoxide (CO) exposure, and its diagnostic and therapeutic value in the field of respiratory and critical care medicine is increasingly prominent. This article summarizes the evaluation and prognostic value of COHb in acute respiratory distress syndrome, acute pulmonary embolism, interstitial lung disease and other respiratory diseases, as well as in critical diseases such as extracorporeal membrane oxygenation support, infection, hemolysis, shock and so on; At the same time, the progress of COHb detection technology, interference factors, the dual pathophysiological effects of endogenous CO and the therapeutic potential of exogenous COHb preparations were summarized. Dynamic monitoring of COHb levels during clinical diagnosis and treatment is helpful for early risk stratification and individualized treatment of critically ill patients. Therefore, this article aims to review the predictive value of COHb in critically ill patients.

Keywords

Carboxyhemoglobin, Carbon Monoxide, Respiratory and Critical Care Medicine, Biomarker

1. 引言

碳氧血红蛋白(COHb)是一氧化碳(CO)与血红蛋白结合形成的特异性标志物，通常用于诊断 CO 中毒，其在呼吸与危重症医学领域的应用不断拓展。研究表明，非吸烟者 COHb 水平通常低于 2%，吸烟者低于 5%，若其水平超过 9%则提示外源性 CO 暴露。既往 COHb 主要用于诊断 CO 中毒，但其水平与中毒症状及预后无直接关联[1]。随着深入研究发现，环境因素对人群 COHb 水平存在显著影响，如老年人运动时，呼出一氧化碳、COHb 及心率均受环境因素调控[2]；农村地区急性 CO 中毒患者的现场 COHb 检测值与暴露时间直接相关[3]；摩托车、出租车司机等户外职业人群、吸烟者及工作场所事故受害者的 COHb 水平亦因环境污染物暴露存在升高现象，提示 COHb 可作为户外工作人员环境污染物暴露的评估指标[4]。另外，COHb 还能反映机体炎症应激、溶血、组织缺氧等病理状态，在急性呼吸窘迫综合征、体外膜肺氧合支持、感染性疾病、急性肺栓塞等呼吸危重症场景中展现出重要的病情评估与预后预测价值。本文系统梳理 COHb 在呼吸与危重症医学中的研究进展，为临床诊疗与风险分层提供理论支撑。

2. COHb 作为疾病严重程度与预后的生物标志物

2.1. 呼吸系统相关疾病

2.1.1. 急性呼吸窘迫综合征

在急性呼吸窘迫综合征(ARDS)患者的回顾性研究中发现，死亡患者动脉 COHb 高于存活患者，校正急性生理与慢性健康状况评估 II (APACHE II)、序贯器官衰竭评估(SOFA)、简化急性生理学评分 II (SAPS2)评分和氧合指数指标后，COHb 可作为 ARDS 患者死亡率的预后标志物。病情晚期持续升高的 COHb 可提示机体存在持续的氧化与炎症应激、未解决的肺损伤或隐匿性全身性疾病，但其临床应用仍需大规模的多中心队列研究验证[5]。对于接受体外膜肺氧合(ECMO)治疗的 ARDS 患者，平均 COHb 水平与重症监护室(ICU)死亡率相关，其相关截断值可作为临床风险分层指标[6]。接受静脉－静脉体外膜肺氧合(VV

ECMO)治疗的 ARDS 患者，COHb 水平呈 U 型变化模式：宿主信号通路受损导致产生 CO 过少或出现溶血导致 CO 产生过多，均与较高的死亡率相关。临床中，若 COHb 处于较低水平时实施早期抗氧化、抗炎治疗(如低剂量吸入一氧化碳气体)，可使患者获益，提示 COHb 有望成为 ARDS 患者新型死亡风险预测标志物[7]。因此，对于 ICU 内的 ARDS 患者，建议在入院时检测基线 COHb 水平，此后每 24~48 小时复查一次。特别是在病情出现反复或恶化时，应及时复查，因为晚期持续升高的 COHb 可能提示持续的炎症应激或隐匿性问题。

2.1.2. 急性肺栓塞

急性肺栓塞(APE)作为致死性的呼吸系统疾病，COHb 对其病情及预后的评估价值存在争议。Kakavas 等人研究发现动脉 COHb 可反应 APE 的严重程度，且患者住院死亡的独立预测因素[8]。但 Uzer 等人却发现 APE 患者的 COHb 虽高于对照组，却未超出正常范围，且对预后无统计学意义，该差异可能与前者未排除 CO 中毒、慢性阻塞性肺病、败血症、肺炎、哮喘、药物、吸烟等干扰因素有关[9]。此外，COHb 作为 APE 预后标志物的价值还受被动吸烟、潜在血液疾病及检测时机的影响，被动吸烟暴露程度难以量化，且 COHb 半衰期短导致检测时机直接影响结果准确性。有研究者提出，血液 CO 水平与 APE 患者死亡率正相关，可作为预后预测指标[10]，但该指标同样受吸烟及部分疾病影响，需结合多维度综合评估。

2.1.3. 新生儿肺部发育

新生儿 COHb 水平与肺部发育情况密切相关，是早产儿肺部相关并发症的重要早期预测指标。极早产儿出生后第一周的 COHb 水平，可有效预测支气管肺发育不良(BPD)的发生风险[11]，因 COHb 检测操作简便，可在临床中用于早期识别高危早产儿，及时干预以预防氧化应激相关并发症。极低出生体重儿抗氧化机制尚不完善，中重度 BPD 婴儿在出生早期表现出较高的 COHb 水平，其出生后 5~8 天的 COHb 水平预测中重度 BPD 的曲线下面积(AUC)为 0.882，提示 COHb 比尿路氧化应激标志物更适合作为中重度 BPD 的预测指标[12]。出生后 11~14 天的 COHb 水平结合吸入氧浓度指标，可以成功预测 67%的中度至重度 BPD 发生[13]，但其具体作用机制仍需深入研究。

2.1.4. 肺功能异常相关疾病

在肺功能异常患者中，哮喘患者的动脉 COHb 水平显著高于对照组，而静脉 COHb 水平与对照组无差异，导致哮喘患者的动静脉 COHb 浓度差异显著增大，提示哮喘患者存在 CO 向组织的异常卸载，临床需采取措施避免高 CO 对气体转移的不利影响[14]。间质性肺病(ILD)患者，尤其是病情加重期，COHb 浓度与炎症指标，如乳酸脱氢酶(LDH)、C 反应蛋白(CRP)、血清表面活性蛋白(SP)等呈显著正相关，与动脉氧分压、预测的肺活量和预测一氧化碳扩散能力呈显著负相关，提示 COHb 可反映 ILD 患者的炎症程度及肺功能受损情况[15]。在慢性阻塞性肺疾病加重期(AECOPD)患者中，入院时的 COHb 水平与侵入性机械通气需求、再住院率及死亡率无相关性，提示其对 AECOPD 患者的预后价值有限[16]。反复肺扩散能力测试会导致 COHb 升高，且屏气时间越长，COHb 升高越显著、一氧化碳扩散能力降低越明显，仅当 COHb ≥ 6%时，一氧化碳扩散能力才会显著降低[17]，临床需关注该检测操作对 COHb 及肺功能指标的干扰。肺功能障碍的患者在高压氧治疗期间 COHb 半衰期显著延长，这与患者合并呼吸衰竭、机械通气相关，传统的 23 分钟 COHb 半衰期会低估 CO 中毒合并心肺功能障碍患者的时机情况，临床需根据患者器官状况动态评估高压氧治疗时机与时长[18]。若医疗条件受限，高流量鼻插管吸氧是降低 COHb 的简单、安全、有效的手段[19]。

2.2. 其他危急重症

2.2.1. ECMO 支持治疗

ECMO 作为危重症患者的终极救治手段，其支持期间的 COHb 水平变化及临床意义备受关注。ECMO

支持后患者的 COHb 水平较支持前升高，年幼患者及 ECMO 持续时间较长与 COHb 水平 ≥2%显著相关[20]，ECMO 管路与插管产生的机械剪切力可引发红细胞机械性破坏(溶血)，其释放的游离血红蛋白经血红素氧合酶分解产生大量内源性 CO，进而导致 COHb 水平显著升高[21]，临床需对 ECMO 患者的 COHb 水平进行持续监测并及时干预。ECMO 相关性溶血是常见的并发症，VV ECMO 患者中多达 29%的受访患者发生显著溶血，动脉－静脉体外膜肺氧合(VA ECMO)溶血发生率甚至更高[22] [23]。而患者的 COHb 水平与溶血率、住院生存率相关，高 COHb 水平可作为触发溶血干预治疗的信号[24]，该结论仍需前瞻性试验验证。对于所有 ECMO 支持的患者，应将 COHb 纳入每日的常规监测指标。当临床怀疑溶血(如血浆游离血红蛋白升高、血红蛋白进行性下降)或出现氧合器功能障碍迹象时，应增加监测频率至每 12 小时一次，以便早期发现 ECMO 相关性溶血。此外，COHb 在 ECMO 氧合困难或功能障碍中具有警示信号的作用，氧合器膜内微血栓引发的溶血会导致 COHb 水平升高，氧合器更换期间 COHb 逐渐升高，更换后逐步下降，提示 COHb 可作为氧合器诱导溶血的早期标志物及氧合器更换时机的预测指标[25] [26]。但需注意，氧合器寿命与 COHb 水平无相关性，功能性氧合器不会导致 COHb 升高。

2.2.2. 感染性疾病

COHb 在感染性疾病中具有潜在的病情评估及预后预测价值，其水平变化可反映机体的炎症状态。人类内毒素血症模型证实，炎症可显著升高体内 CO 水平，为 COHb 作为感染相关生物标志物提供了病理生理依据[27]。在监测传统指标(乳酸、SOFA)的同时，观察 COHb 的动态变化趋势。若在积极抗感染治疗后，COHb 水平随之下降，可能提示治疗有效；反之，则需警惕治疗失败或存在未控制的感染灶/溶血。在儿科急诊中，COHb 可作为宫内感染(IBI)的生物标志物，用于发热新生儿的风险分层[28]。早产新生儿晚发败血症(LOS)初期，COHb 水平显著升高，使用抗生素后逐渐降低，与降钙素原(PCT)、CRP、中性粒细胞与淋巴细胞比值(NLR)等败血症标志物联合使用时，COHb 变化水平可显著提高早产儿晚发型败血症评估准确性[29]，且 COHb ≥ 1.55%是其预测早产儿 LOS 的最佳阈值[30]。细菌性败血症患者中 COHb 水平与乳酸、PCT、CRP 呈正相关，其水平变化可快速反映细菌性败血症或感染性休克的病情结果，且具有成本效益比高、可床旁检测的优势。但 COHb 在感染性疾病中的应用也存在局限性，社区获得性肺炎患者的 COHb 浓度虽有升高，却不能作为诊断及临床严重程度预测的指标[31]。新生儿 COHb 受年龄、孕周、血红蛋白浓度等多种因素影响，校正这些协变量后，败血症的发生与 COHb 水平无显著相关性[32]。因此，COHb 在感染性疾病中的临床应用仍需大规模临床试验验证。

2.2.3. 手术相关场景

在妇科、泌尿外科、肝胆外科手术过程中，电切术产生的 CO 会被机体吸收，导致患者 COHb 水平变化，其中双极电切术的 CO 全身吸收是可重复现象，吸收量与体液流失量正相关，严重时可引发患者血流动力学异常，心电图紊乱以及 COHb 水平显著升高，甚至导致组织缺血。临床中，实施广泛双极电切术前，需与麻醉团队评估心肌缺血风险，术中心电图提示缺血时应立即停止手术；术后麻醉恢复时间超预期的患者，建议在手术结束时及术后麻醉复苏期监测 COHb，并将 COHb 中毒纳入鉴别诊断，并通过反复检测 COHb、吸氧、心脏监测进行管理[33]-[36]。

心脏相关手术中，COHb 与体外循环心脏手术患者的溶血生物标志物、风险因素呈中度相关性[37]。入住 ICU 的心脏手术患者，COHb ≥ 1.4%是术后急性肾损伤的独立危险因素，可作为风险分层和人群筛选的生物标志物[38]。但在儿童体外循环心脏手术中[39]，溶血组与非溶血组最大 COHb 水平无显著差异，提示 COHb 对儿童心脏手术溶血的预测能力有限。

2.2.4. CO 中毒

CO 中毒的核心病理生理机制为组织缺氧状态下，CO 从血液中转移至血管外组织[40]。CO 中毒患者

的初始血乳酸水平可用于风险分层，尤其是预测住院时间，以 COHb 升高确诊 CO 中毒，再以血乳酸 ≥ 1.85 mmol/L 评估组织缺氧严重程度，二者联合可精准判断是否需要高压氧治疗，优化急诊分诊决策[41] [42]。有动物实验证实，封闭的压力支持通气系统可显著缩短 COHb 半衰期，在消除 CO 方面优于非再呼吸面罩[43]。支持性机械通气下 COHb 浓度随治疗时间呈线性下降趋势，为 CO 中毒急性期的呼吸支持策略与病情监测提供了重要临床依据[44]。临床上确诊或高度怀疑 CO 中毒的患者，在初始治疗(如高流量吸氧或高压氧治疗)期间，应每 2~4 小时监测一次 COHb，以评估 CO 清除效率并指导后续治疗决策。

2.2.5. 休克

在失血性休克大鼠复苏模型中，COHb 具有双重作用：可减轻氧化损伤、抑制细胞凋亡与自噬，但同时会加重再灌注期间的炎症反应，其作用时间可能影响再灌注结局[45]。院外心脏骤停患者，低水平 COHb 与预后不良相关，可能与血红素氧合酶激活不足导致内源性 CO 生成匮乏以及严重酸中毒抑制 CO 结合，导致机体缺乏 CO 的保护作用有关[46]。心肺复苏期间，将 COHb 降至 10%所需的心肺复苏时间延长，但该水平更有利于自主循环的成功恢复[47]，临床中计算心肺复苏期间的 COHb 半衰期，有助于判断复苏努力的最佳持续时间，并指导高压氧或体外生命支持治疗。

2.2.6. 溶血

溶血是机体内 COHb 水平升高的主要原因，COHb 可作为溶血的可靠诊断生物标志物。在 ICU 贫血成年患者中，以 2.0%为阈值，COHb 诊断溶血性贫血的准确性优于 LDH 和非结合胆红素，LDH/COHb 比值升高，与肺动脉高压、血管内溶血并发症及全因死亡率升高密切相关[48] [49]。ABO 血型不合的新生儿中，COHb 水平升高且与光疗需求出现时间正相关，提示 COHb 可作为高血红蛋白的标志物，用于早期识别胆红素快速升高的新生儿，及早诊断引发重度高胆红素血症的溶血性疾病[50] [51]。此外，250 ppm 的 CO 暴露不会使新生儿 COHb 达到诱导急性神经系统异常的浓度，且可有效保护缺氧缺血性损伤后的皮质体积[52]，为新生儿缺氧缺血性脑病的辅助治疗提供了新思路。

3. COHb 检测技术的进展与挑战

3.1. 检测方法对比

COHb 检测技术已从传统的有创检测向无创、快速、床旁检测发展，不同检测方法各有优势与适用场景，且部分无创技术的准确性已得到临床验证。血气分析是 COHb 检测的经典方法，多波脉搏碳氧血氧仪检测结果与之高度相关；脉冲光谱法可同时准确检测低氧血症与 COHb [53]。多波脉搏碳氧血氧仪对于非选择性急诊患者的 COHb 检测具有可接受的偏差和精度，可用于隐匿性 CO 中毒的筛查[54]，在高压氧治疗期间其一致性界限为±6% [55]。其检测准确性受动脉血氧饱和度(SaO_2)影响，仅当 SaO_2 > 85%时可准确读取碳氧血红蛋白饱和度，检测值与真实 COHb 值的偏差波动在−6%~+4%之间[56] [57]。在镰状细胞病儿童中，该技术虽略微高估 COHb 水平，但与有创设备检测结果高度一致，亦可用于确认 ABO 同种异体免疫婴儿的溶血[58] [59]。紧急情况下，无创脉搏碳氧血氧仪可降低疑似 CO 中毒患者的隐性中毒相关的发病率与死亡率[60]。

此外，无创脉搏碳氧血氧仪可作为吸烟状态的验证工具，吸烟者吸烟后其检测的 COHb 水平显著升高，可用于术前、术后戒烟管理及提高吸烟自我报告的准确性[61]。新型检测技术也为 COHb 检测提供了更多选择：基于 128 波长原理的 CO-血氧定量法与顶空气相色谱－火焰离子化检测－原子吸收分光光度法(HS-GC-FID-AAS)在全血 COHb 测定中具有良好的可比性与准确性，可实现血液 COHb 浓度的精准检测，具有潜在临床应用前景[62] [63]。廉价的袖珍红外扫描仪、智能手机可检测到单滴血中 >15%的 COHb，精度满足初步临床筛查需求，为发展中国家开发低成本诊断工具提供了方向[64]。

3.2. 干扰因素分析

COHb 检测结果的解读需充分考虑各类干扰因素，避免因检测偏差导致误诊、漏诊，常见的干扰因素主要包括外源性物质代谢及检测试剂的影响。二氯甲烷(DCM)经肝脏代谢可生成 CO，直接升高机体 COHb 水平，并延长 COHb 半衰期，仅凭检测值难以区分 DCM 中毒与单纯 CO 中毒。亚硝酸盐/硝酸盐可诱发高铁血红蛋白血症，干扰分光光度法的检测原理，导致 COHb 假性升高；硫化氢生成的硫血红蛋白会破坏血红蛋白检测体系，影响 COHb 定量准确性[65]。羟钴胺是临床治疗 CO 中毒的常用药物，其可通过光谱吸收干扰导致 COHb 检测值严重失真，应尽量在羟钴胺给药前采集血液样本检测 COHb；若患者生命体征异常，无需等待检测结果，应立即行高压氧治疗，待羟钴胺代谢(约 24~48 小时)后再复测 COHb [66]。

4. 内源性 CO 的病理生理机制：双刃剑效应

内源性 CO 的细胞保护作用主要通过抗炎、抗凋亡及抗增殖机制实现，在缺血再灌注损伤中具有重要的保护潜力[67]。当内源性 CO 生成过多，或机体对 CO 的清除能力下降时，会产生明显的毒性作用。CO 与血红蛋白的结合能力远高于氧气，可竞争性结合血红蛋白导致血氧运输能力下降[68]，抑制组织的有氧代谢，引发组织缺氧，并激活炎症级联反应，加重组织损伤[69]。CO 可透过血脑屏障损伤神经系统，还可影响心肌收缩力及血管张力，导致心律失常、血压异常等心血管功能紊乱[70] [71]。

5. 外源性 COHb 制剂的治疗潜力

随着对 COHb 及内源性 CO 病理生理作用的深入研究，外源性 COHb 相关制剂的开发与临床应用成为新兴研究领域，为危重症的治疗提供了新的思路，目前已有多种制剂在动物实验中证实有效，部分进入临床试验阶段。聚乙二醇化牛碳氧血红蛋白(SANGUINATE)是一种兼具 CO 与氧气输送功能的双模式治疗药物，不仅可用于治疗缺氧，还可干预炎症、再灌注损伤等病理过程[72]。SANGUINATE 在脑卒中、急性肾损伤、失血性休克、心肌梗死等疾病模型中疗效显著，可通过增加缺血组织侧支灌注、改善肾皮质微循环、增加血管反应性、减少心肌梗死面积等机制发挥治疗作用[73]-[75]，同时，可稳定危重贫血患者的病情，为挽救生命的干预措施争取时间，且不会影响体外循环回路的性能[76] [77]。该药物已完成 I 期临床试验，结果显示其安全性良好、耐受性佳，未出现严重不良反应，具有良好的临床转化前景[78]。

合成肽 IRL 2500 是一种高选择性内皮素 B 型受体拮抗剂，可增强 COHb 在空气中的 CO 释放，但其具有溶血活性，限制了临床应用；而 IRL 2500 类似物可在增强 COHb 释放 CO 的同时避免溶血，且具有水溶性改善、溶血活性降低的优势，为开发治疗 CO 中毒的小分子疗法开辟了新道路[79]。膜控制体外一氧化碳释放系统(ECCORS)是一种新型的精准 CO 输送系统，在猪 VA ECMO 模型中，该系统可根据机体 COHb 水平精确控制 CO 的产生与输送，实现自主、自动的反馈控制；结合基于机器学习的数学建模，可进一步提高该系统的预测能力，为未来高精度、个体化的系统 CO 输送提供了技术基础[80]。

6. 总结与展望

综上，COHb 的临床意义已不再局限于急性 CO 中毒的辅助诊断，在多种呼吸危重症场景下，它能够为病情评估、预后预测以及风险分层提供相对客观的临床依据。临床医生应将 COHb 视为一个动态、多维的危重症标志物。例如，在 ECMO、心脏手术等有创支持或操作后，COHb 突然或进行性升高是提示溶血的信号；在严重感染、ARDS、休克等状态下，COHb 水平可辅助评估全身炎症和氧化应激的严重程度；在 ARDS、心脏术后、严重感染等情况下，高 COHb 水平是提示死亡率和并发症风险增加的潜在生物标志物。然而，现阶段对其临床潜在价值尚不确切，仍需要大规模队列研究验证后形成业界共识。后

续需依托更多高质量多中心研究，明确不同疾病状态下 COHb 的诊断阈值，规范检测方法，进一步挖掘其作为生物标志物与治疗靶点的潜力，推动其在呼吸与危重症领域的规范化应用。

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