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高氧对心脏手术患者预后影响的研究进展

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摘　要

心脏手术中会常规使用超生理水平的高氧，特别是在体外循环(Cardiopulmonary Bypass, CPB)期间，以防止手术和/或CPB引起的非生理性细胞缺氧。然而高氧对心脏手术患者的术后不利影响表明这种做法可能是有害的。本文系统综述了高氧在心脏手术中使用的风险，从高氧的氧化应激和心血管效应的损伤生理机制展开讨论，并根据国内外最新的临床证据分析高氧对心脏手术患者术后心肌损伤、肺部并发症、急性肾损伤、神经系统并发症及溶血与出血的发生风险的影响，以便为临床早期干预和改善患者预后提供理论依据。

关键词

心脏手术，体外循环，高氧，活性氧，预后

Research Progress on the Effect of Hyperoxia on the Prognosis of Patients Undergoing Cardiac Surgery

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Abstract

Supraphysiological levels of hyperoxia are routinely used during cardiac surgery, especially during cardiopulmonary bypass (CPB), to prevent non-physiologic cellular hypoxia induced by surgery and/or CPB. However, the adverse postoperative effects of hyperoxia in patients undergoing cardiac surgery suggest that this practice may be harmful. This article systematically reviews the risks of hyperoxia use in cardiac surgery, discusses the oxidative stress of hyperoxia and the dam-

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age physiological mechanism of cardiovascular effects, and analyzes the effects of hyperoxia on postoperative myocardial injury, pulmonary complications, acute kidney injury, nervous system complications, and the risk of hemolysis and hemorrhage in patients undergoing cardiac surgery according to the latest clinical evidence at home and abroad, in order to provide a theoretical basis for early clinical intervention and improve the prognosis of patients.

Keywords

Cardiac Surgery, Cardiopulmonary Bypass, Hyperoxia, Reactive Oxygen Species, Prognosis

1. 引言

心脏手术在全麻机械通气和 CPB 期间通常会使用较高的吸入氧浓度(Fractional Concentration of Inspired Oxygen, FiO_2)以提高动脉血氧分压(Arterial Partial Pressure of Oxygen, PaO_2)作为预防缺氧的措施[1]。在此期间 PaO_2 经常会高于正常生理水平，超过 200 mmHg 甚至达到 300 mmHg 及以上的情况并不少见，这被认为是有益的氧气储备[2] [3]。然而，由于心脏手术患者本身存在的心肌功能障碍及手术过程中的微循环灌注异质性、低体温及低血容量等病理生理特点，这些都有可能导致组织氧输送和氧消耗之间的不平衡。由于 CPB 期间低流量和高流量毛细血管的微循环异质性增加，组织的氧气输送受到威胁。氧气扩散距离的增加可能会损害氧气输送和器官功能。在一项观察性研究中，通过评估心脏手术围术期微循环灌注并分析其与血流动力学、氧合参数的关系。结果发现微循环不均匀性在 CPB 后显著升高[4]。理论上，吸入高浓度氧可以使 PaO_2 升高从而消除这一问题[5]，但实际情况却极为复杂。高氧可引起直接的血管收缩和氧化应激反应，增加微循环异质性，加重缺血再灌注损伤，并对相关靶器官如心脏、肺、肾脏、脑及血液系统等造成损害。为此，本文系统回顾了心脏手术期间高氧对患者预后影响的相关文献，为此类患者优化术中氧策略提供参考。

2. 高氧的生理机制

2.1. 氧化应激

活性氧(Reactive Oxygen Species, ROS)是生物正常有氧代谢过程中的副产物，包括氧离子、过氧化物和含氧自由基等。ROS 在动物细胞中的重要来源是线粒体，在线粒体中还存在多种抗氧化分子来解毒有氧代谢过程中产生的 ROS，从而维持细胞代谢平衡。这种平衡可能在高氧或缺血再灌注的条件下被打破，造成 ROS 产生速率增加，引发信号传导途径失调和大分子损伤。ROS 相关的氧毒性体现为氧化应激，对核酸、蛋白质和脂质造成损伤，加重炎症反应，并可能导致细胞死亡，最终破坏正常生理[6]。高氧状态下广泛的氧化应激损伤和氧依赖性信号传导过程失调会导致严重的病理变化，有时甚至是永久性的，这种失衡已涉及到多种疾病的发病机制[7]。Sanders 等[8]在暴露于 100%氧的绵羊微血管内皮细胞悬浮液中观察到 ROS 的形成增加。在分离的猪肺线粒体中，当 PaO_2 增加超过 20%时观察到更高的 ROS 产生速率[9]。

在进行 CPB 的心脏手术期间，主动脉开放之后发生缺血心肌的再灌注。再灌注阶段的特征是 ROS

的产生增加、细胞内和线粒体钙的失调、微血管功能障碍和过度活跃的免疫反应。这种有害的事件组合被称为缺血－再灌注损伤。高氧会放大这种损伤，引发 ROS 爆发并诱发全身炎症反应，导致严重的术后器官功能障碍。

2.2. 心血管效应

高氧环境对心脏和外周血管系统有多种影响。高氧可直接引起血管收缩，导致全身血管阻力增加以及冠状血管阻力增加。有研究发现，在健康志愿者中，高氧导致全身血管阻力 12%，心排量减少 10% [10]。这种血管收缩效应同样地在脑[11]、视网膜[12]和骨骼肌[13]中得到证实。对于健康志愿者，高氧所致血管收缩会使下肢血流量减少高达 30% [14]。另有研究表明，冠脉疾病的患者对高氧的反应是相似的，当吸入 100%纯氧时，冠状动脉阻力增加了 23%，而这种效果也会因输注维生素 C 而消除[15]。已有动物研究发现，高氧性血管收缩幅度与氧暴露程度成正比[16]。血管舒张剂一氧化氮(NO)的生物利用度降低可能是导致血管收缩的主要因素[17]。冠状动脉收缩引起冠脉血流减少，影响心肌氧输送，可增加缺血易感性并降低心肌收缩力[1] [18]。一项研究显示，健康受试者的冠状动脉血流下降的平均幅度为 17.1%，而冠心病患者下降的平均幅度在 7.9%~28.9%之间[19]。

高氧可对心肌细胞产生特定的作用，特别是在缺血事件发生后。已有研究证实高氧会损伤心肌线粒体的代谢，这可能加剧心肌功能障碍[20]。高氧还可产生直接的负性肌力作用。高氧通过改变心肌细胞的钙平衡导致舒张功能障碍，诱导心律失常、心肌细胞肥大、凋亡或坏死[21]。这些不利影响可能会在 CPB 缺血再灌注期间被增强，导致冠状动脉和全身微循环灌注的恶化。在兔的 CPB 模型中，高氧条件下再灌注表现出更明显的氧化应激和炎症反应，加重心肌细胞损伤，损害左心室收缩功能[22]。

3. 临床证据

3.1. 肺部并发症

心脏手术的 CPB 期间肺仅依靠支气管动脉供血，因此易受缺血再灌注的影响，同时 CPB 激活严重的全身炎症反导致肺毛应细血管通透性增加，引起术后肺损伤[23]。而高氧会引起 ROS 稳态的改变，造成肺泡－毛细血管屏障的破坏，导致肺泡上皮细胞死亡，肺顺应性降低，影响气体交换，产生高氧性肺损伤[24]。有研究表明，ROS 对呼吸肌，特别是膈肌的收缩功能产生不利影响，可能会延长机械通气时间[25]。因此，CPB 期间肺暴露于高氧血症可能进一步损害肺功能从而导致不良的临床结局发生。

Ihnken 等[26]进行的一项小规模随机对照试验按照 CPB 期间 PaO_2 将心脏手术患者随机分为高氧组(PaO_2 > 400 mmHg)和常氧组(PaO_2 ≥ 140 mmHg)，研究结果表明高氧组患者术后 5 天肺活量和一秒用力呼气量显著降低。一项 246 例心脏手术患者的高氧急性肺损伤的研究显示，在 CPB 期间接受不同程度的高氧后，暴露于重度高氧组(PaO_2 > 300 mmHg)的患者术后感染并发症更多，术后机械通气时间延长，住院时间延长[27]。最新的一项大型的回顾性研究得出相似结果，Douin 等[28]分析了 CPB 前、后和 CPB 期间的高氧血症(PaO_2 > 200 mmHg)与术后 30 天内肺部并发症发生率之间关系，结果表明 CPB 期间高氧血症与术后肺部并发症显著相关，且 PaO_2 与肺部并发症发生率呈剂量相关性，并且在 CPB 前短时间的高氧血症也与术后肺部并发症的发生有相关性。而另一项大型回顾性研究则发现，CPB 期间 PaO_2 的增加与术后肺功能(以术后 6 h 的 PaO_2/FiO_2 测量)无显著相关性，而亚组分析显示，PaO_2 的增加与高危患者术后 PaO_2/FiO_2 比值呈弱相关性[29]。除了 CPB 期间灌注的高氧合血液的影响外，心脏手术中通过呼吸道输送到肺泡的高浓度氧气也可能是有害的[30]。Pizov 等[31]的研究将心脏手术患者分为高氧组(FiO_2 = 100%)和常氧组(CPB 前 FiO_2 = 50%，CPB 期间 FiO_2 = 21%)，结果显示常氧组的患者能更快恢复到术前肺功能(PaO_2/FiO_2 值)且手术结束时，作为急性肺损伤的潜在标志物 TNF-α 和 IL-8 在高氧组患者中显著增加。

鉴于以上研究结果表明 CPB 期间严重高氧血症与术后肺部并发症存在一定相关性，CPB 期间应更严格控制 PaO_2，同时需要更多的前瞻性研究来确定高氧血症和肺结局的关系。

3.2. 心肌损伤

缺血心肌再灌注和 CPB 的全身不良反应是心脏手术预后的决定因素，也是引起心肌损伤的主要原因。在主动脉阻断被移除并且冠状动脉灌注重新开始之后，心肌特别容易受到 ROS 介导的损伤，而高氧增加了再灌注期产生 ROS 的底物和随后的损伤[32]。高氧相关的心血管效应及对再灌注损伤的增强都可能导致心脏手术期间冠状动脉和全身灌注受损，引起术后心肌损伤[33]。

Topcu [34]等在 CPB 期间直接采取冠状窦血样来测量心肌氧化标志物，得出与高氧相比，常氧可降低成人冠状动脉旁路移植术患者心肌氧化应激水平，但在临床结局方面并无差异。在一项前瞻性的试验中，Smit 等[35]将 50 例接受冠脉搭桥术的患者随机分配到 CPB 期间中度高氧组(PaO_2: 200 mmHg~220 mmHg)和常氧组(PaO_2: 130 mmHg~150 mmHg)，两组在心肌损伤结局并无显著差异。在另一项 440 例随机对照研究显示，采用高氧和常氧策略的两组的患者的术后心血管并发症发生率无差异[36]。Inoue 等[37]进行了一项关于冠状动脉旁路移植术的研究，以验证再灌注时氧化损伤因 PaO_2 升高而加剧的假设。一组患者在 CPB 主动脉开放再灌注时接受高氧(PaO_2: 450 mmHg~550 mmHg)处理，而第二组的患者被分配为降低 PaO_2 组(PaO_2: 200 mmHg~250 mmHg)。他们发现，降低 PaO_2 组可减轻氧化性心肌损伤。另有研究表明，在高氧条件下再灌注时，患者在 CPB 脱机时使用血管活性药物频率更高[38]。这提示心脏手术中高氧的时机可能是一个重要因素，高氧的损害主要发生在主动脉开放进入再灌注时期。因此应严格控制再灌注期氧合策略，避免高氧的损害。

3.3. 急性肾脏损伤

心脏手术患者术后极易发生急性肾损伤(Acute Kidney Injury, AKI)，据报道其发生率约 15%~50%，且 AKI 的发生率和死亡率的增加独立相关[39]。CPB 下行心脏手术过程中，外周组织输送的氧会影响肾脏氧供，特别是肾髓质，因此 CPB 中一般保证高氧来增加外周输送氧。最新研究表明，高氧会损害心脏病变患者的肾循环[40]。此外，高氧的氧化应激会加重再灌注损伤并进一步损害肾脏。Toraman 等[41]探讨了关于心脏手术 CPB 期间不同 FiO_2 与术后 AKI 可能性，但结果并无显著差异。在一项 298 例随机对照试验中，CPB 期间避免高氧(PaO_2: 75 mmHg~90 mmHg)的策略同样没有降低术后 AKI 的发生率[42]。而 Bae 等[43]在一项大型回顾性研究中采用不同的 PaO_2 阈值面积(PaO_2 × 暴露时间)进行敏感性分析，结果发现术中高氧与术后 AKI 的发生风险显著相关，并计算出 $PaO_2 > 300$ mmHg 时，PaO_2 每增加 100 mmHg，持续 1 小时，发生 AKI 增加的风险为 9.4%。研究[41] [42]的结果主要基于静态 PaO_2 值，而 Bae 等[43]的研究将高氧暴露时间纳入考虑，这可能在一定程度上解释了与其他研究结果矛盾的原因。而 Nam 等[44]在最新的一项针对非停跳冠脉搭桥手术的研究中发现，相对于 30%的 FiO_2 而言，80%的 FiO_2 显著降低了术后 AKI 发生率，并改善了血流动力学，但该研究未提到术中 PaO_2 水平。

目前，只有少数研究讨论高氧对心脏手术后 AKI 的影响，而现有的临床对照试验及观察性研究的结果矛盾不一，尚不能推断高氧血症与 AKI 发病之间的因果关系。

3.4. 神经系统并发症

谵妄是心脏手术后最常见的神经系统并发症之一，术后谵妄的发生与患者长期预后发展有关，如认知能力下降和功能障碍，导致患者生活质量恶化[45]。此外，术后谵妄与高死亡率、住院时间延长相关。CPB 期间，高氧通过脱氮而减少气体微栓作用常被认为具有脑保护作用[32]，然而，最新证据表明高氧也可能对神经功能出现损害。这种不利影响的潜在机制包括高氧诱导的血管收缩对脑血流量影响以及氧

化应激导致的神经元损伤。

一项对老年心脏手术患者进行的回顾性研究显示，CPB 期间重度高氧与老年患者术后谵妄的发生显著相关[46]。另一项前瞻性研究也得出类似结果。Lopez 等[47]利用脑血氧仪来分析术中高氧脑灌注的预后，结果表明缺血前后脑氧合过度均与术后谵妄发生率增加密切相关，且有证据表明高氧对氧化损伤的增强可能介导了这种相关性。而 Shaefi 等[48]进行的另一项试验将 100 例冠脉搭桥手术患者随机分配至常氧组(CPB 前后：PaO_2 > 70 mmHg，CBP 期间 PaO_2：100~150 mmHg)与手术全程保持 FiO_2 为 100%的高氧组，结果未观察到两组之间的术后认知功能差异。另一项大型回顾性研究纳入了 1018 名接受 CPB 心脏手术的患者，研究结果也未能证明 CPB 期间高氧与术后 6 周认知功能之间的关系[49]。在 Abou-Arab 等[50]类似的研究中也未显示出不同氧策略在神经结局方面的差异。这些临床研究表明高氧可能与心脏手术患者的短期神经结局如谵妄的关联更为密切，而对于长期的认知功能下降的影响并未得到证实。未来需要更多高氧的短期和长期后果的前瞻性研究来阐明心脏手术中高氧对神经功能的影响。

3.5. 溶血与出血

氧化应激已被证明会破坏红细胞膜的脆性，在高氧环境下，红细胞持续暴露在过量 ROS 下而产生不稳定性引发溶血。与高氧血症一样，心脏手术 CPB 期间可通过产生 ROS 增加氧化应激。在两者双重损伤下溶血加剧。一项关于儿童和婴幼儿行心脏手术的研究发现在 CPB 开始时、CPB 结束时以及再灌注后 2 小时和 24 小时获得 100 名患者的血浆样本，以评估无细胞血浆血红蛋白水平，通过多变量分析发现，年龄较小和平均 PaO_2 × CPB 持续时间较高被确定为严重溶血的危险因素，结论认为年龄较小、暴露于氧气和 CPB 时间是溶血的危险因素[51]。此外，高氧血症与血流量变化、毛细血管损伤、血管内溶血和血小板功能障碍有关。但关于高氧血症对出血和输血需求影响的研究是有限的。一项纳入 78 名接受二尖瓣置换术的研究发现高氧血症组术后出血量显著增加，且 CPB 期间及术后的出血量和输血需求均较高。出血量和输血需求的增加是显著影响心脏手术患者发病率和死亡率的因素[52]。尽管如此，通过 CPB 输送氧气是一个容易改变的风险因素，仍需要更多的前瞻性研究来评估高氧血症与溶血以及出血之间的关系。

4. 总结与展望

本文系统性的回顾了高氧对于心脏手术患者预后的影响。高氧对心脏手术患者不利的生理机制主要是氧化应激和心血管效应的损伤。高氧对缺血再灌注损伤的放大也是导致术后器官功能障碍的重要原因。目前的证据表明，高氧血症可能与术后肺部并发症、心肌损伤、肾损伤、神经系统并发症以及溶血与出血的发生风险增加有关。就现有的研究而言，CPB 时期高氧的时机可能成为关键因素，特别是再灌注时期应谨慎使用高氧，但现有证据不足以明确最佳的氧策略。此外，大部分研究多集中在 CPB 时期的高氧，缺乏对 CPB 前后麻醉管理的高氧研究。因此，今后有必要针对心脏手术患者的 CPB 不同阶段和麻醉管理分别进行氧策略研究以期为术中管理决策提供信息。

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