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高压氧在治疗糖尿病视网膜病变中的应用进展

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摘要：糖尿病视网膜病变是糖尿病最常见、最主要的微血管并发症之一，其高发病率、高致盲率特征严重威胁着人类的健康和生存质量。长期的高糖状态导致视网膜缺血缺氧是糖尿病视网膜病变的主要发病原因。控制高血糖和改善组织缺氧无疑是防治糖尿病微血管病变的有效方法之一。而高压氧治疗是许多急慢性疾病的首选或辅助治疗方法。已有大量证据表明，高压氧治疗对视网膜静脉阻塞及黄斑囊样水肿、缺血性视神经病变、中心性浆液性脉络膜视网膜病变等眼病安全有效。本文就高压氧在糖尿病视网膜病变中的应用进行综述和讨论。

关键词：糖尿病；糖尿病视网膜病变；缺氧诱导因子；高压氧

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Advances of Hyperbaric Oxygen Therapy in Diabetic Retinopathy

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ABSTRACT: Diabetic retinopathy (DR) is one of the most common and severe microvascular complications of diabetes mellitus. The characteristics of high incidence rate and high blinding rate affects the health and quality of life seriously. Long-term high sugar state can cause retinal ischemia and oxygen Which is the main reason of Diabetic retinopathy. So control hyperglycemia and improve the hypoxia is undoubtedly the prevention and control of diabetes microvascular lesions one of the effective ways. Hyperbaric oxygen therapy is aprmiary or adjuvant therapeutic method for various acute or chronic diseases .There are substantial evidences showing its safety and efficacy in many eye diseases such as retinal vein occlusion and hemorrhagic optic neuropathy, central serous retinopathy choroid, etc. This paper hyperbaric oxygen in diabetic retinopathy were reviewed and discussed the application.In the present review, we will focus on the concept of advances of hyperbaric oxygen therapy in diabetic retinopathy.

Keywords: Diabetes; Diabetic retinopathy; Hypoxia inducible factor; Hyperbaric oxygen

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前言

糖尿病视网膜病变（diabetic retinopathy，DR）是糖尿病重要的微血管并发症之一，已经成为视力损伤和致盲的重要原因。糖尿病视网膜病变在糖尿病并发症的发病率中高达 24%-70%，是一种不可逆的，进行性发展的慢性疾病。国际糖尿病联盟的糖尿病地图（Diabetes Atlas）数据显示，2010 年糖尿病患者人数达到 2.85 亿，约占全世界成人的 7%[1]。近年来调查研究资料显示，糖尿病视网膜病变导致患者失明的发生率仍不断增长。糖尿病视网膜病变的发病率高、致盲率高的特点，给人们的生活带来极大的影响，威胁着人类的生活质量。尽早预防和治疗糖尿病视网膜病变是医学领域面临的重大课题，受到了国内外医学界的广泛关注。所以寻找治疗糖尿病视网膜病变的有效手段是极其必要的。

糖尿病视网膜病变的发病机制极其复杂，目前尚未完全阐明，认为与遗传易感性、胰岛素抵抗、高血糖、氧化应激等多方面因素的相互影响有关。长期的高血糖状态以及视网膜的缺血、缺氧是糖尿病视网膜病变发生的主要原因[2,3]。高血糖引起的氧化应激反应是共同的发病机制，进而引起多元醇代谢途径的激活、糖基化终末产物过量产生、蛋白激酶 C 激活、免疫炎症因子等。糖尿病患者高血糖引起视网膜细胞内的山梨醇和果糖蓄积，使细胞遭到损伤，微血管的完整性受到破坏，内皮细胞增殖，微血管管腔狭窄血循环障碍，引起视网膜局部血流量调节障碍[4]，同时细胞及细胞外基质发生非酶糖化和 AGEs 的形成和堆积，导致白细胞黏滞性增加及血视网膜屏障的破坏，血液粘度增高、异常血小板粘附和凝集等引起基底膜增厚，血管壁通透性增高，特别是微血栓形成，进一步加重微血管损伤，进而导致视网膜组织慢性缺血低氧[5]。临床研究显示，缺氧可促进糖尿病微血管病变的发生发展。

糖尿病视网膜病变早期即出现视网膜缺血缺氧，进而导致一系列细胞因子紊乱，局部内环境失衡。HIF(hypoxia-inducible factor，HIF) HIF 是调控细胞氧气平衡以及缺氧应答反应中的重要调节因子。在糖尿病状态下视网膜组织中 HIF -1A 表达增加，可能通过上调 VEGF 表达促进新生血管形成以减少缺血对局部组织造成的损伤[6]。低氧诱导因子作为基因转录的生理调节因子，依赖 HIF 的基因表达广泛影响机体葡萄糖代谢、血流的供应、细胞的增殖和血管生长以及能量代谢[7,8]。研究表明，所有细胞内的缺氧反应似乎均有低氧诱导因子的存在[9]。Chiu 等[10]提出了高血糖 -HIF 通路。正常氧环境下，在高血糖 -HIF 通路中，糖代谢紊乱导致多元醇代谢途径活化、糖基化终末产物形成以及生长因子、活性氧自由基、炎性介质等可通过损害蛋白

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酶体系统减少 HIF 降解和活化核因子 κB 来增加 HIF 基因的表达。细胞质中升高的 HIF 可作为从有氧呼吸到无氧糖酵解之间转换的开关,还可在高血糖损伤溶酶体酶的同时增加自体吞噬,上述两种效应共同导致溶酶体内脂褐素积聚。而缺氧环境下,糖代谢紊乱的产物可与 HIF 启动子结合,从而增强 HIF mRNA 的表达[11],提高血管内皮细胞生长因子的表达[12,13]。实验证明,常氧条件下 HIF mRNA: 表达低于检测水平,7%低氧处理 30 Min 后 HIF mRNA:明显被诱导出来,60Min 时达到高峰[14]。Ozaki 等[15]对早产儿视网膜病变动物模型研究发现,在视网膜发生缺血缺氧时,视网膜表达 HIF-la 及 VEGF 明显增加,说明 HIF 可上调 VEGF 的表达。VEGF 被认为是促进全身特别是视网膜组织新生血管形成的重要因子,VEGF 与糖尿病性视网膜血一视网膜屏障损害有密切关系[16]。VEGF 能特异性的促使内皮细胞激活,与其受体结合后使之增殖、迁移、管腔形成,破坏血－视网膜屏障,显著地增加微血管的通透性加速眼部血视网膜屏障的破坏[17]。氧是 HIF 最佳的抑制剂,而提高缺血组织氧含量正是 HBO 治疗疾病的最显著特点。应用高压氧可以提高组织氧分压、改善缺血组织乏氧,成功抑制了 HIF 的活化及下游蛋白的表达,改善 DR 病情。

高压氧治疗的研究进展

高压氧治疗(hyper baric oxygen therapy,HBOT)已经有四十多年的历史,广泛的应用于临床,已成为现代医学的一部分[18]。高压氧治疗是将病人置于标准或高于标准大气压的高压氧舱内,进行加压、吸氧,以达到治疗疾病目的的一种方法。高压氧治疗是一种无创伤治疗方法,以物理方式改善微循环障碍,有效地纠正组织的缺氧,在临床上获得良好的疗效。在眼科领域,已有大量证据表明,高压氧治疗对视网膜静脉阻塞及黄斑囊样水肿、缺血性视神经病变、中心性浆液性脉络膜视网膜病变等眼病安全有效[19]。

近年来已有大量试验研究表明高压氧在治疗糖尿病微血管并发症方面取得显著的疗效。Chang 等[20]通过实验发现,治疗剂量 HBO 作用于 SD 糖尿病大鼠模型,可以不同程度的改善破坏的血 - 视网膜屏障,达到治疗糖尿病视网膜病变的目的。1、高压氧治疗能提高氧分压[21]。通过增加物理溶解氧的幅度,提高全身组织氧含量和储氧量[22],使氧的有效祢散范围扩大、毛细血管端的氧分压提高,纠正眼底低氧,改善有氧代谢,恢复血管壁功能,从而减少渗出有效缓解了视网膜的缺氧状况。2、高压氧能降低血液粘稠度,提高吞噬细胞功能。由于高压氧提高了组织供氧,迅速改善缺氧缺血所致的红细胞变形能力降低,增强红细胞通过毛细血管的能力[23],降低红细胞压积,加快红细胞电泳,同时恢复血栓素和前列环素的平衡,减轻血小板聚集有利于改善组织灌注,从而可纠正糖尿病患者的血液的高粘滞状态。同时高压氧能够激发吞噬细胞及纤维蛋白溶解酶的活性,加快眼底渗出物的吸收,纠正视网膜的瘀血状态改善微循环,减少渗出和水肿[24,25]。3、高压氧可提高机体的抗氧化能力。高压氧治疗可改善全身血流量,提高机体的抗缺氧能力,同时加强组织对于自由基的清除能力,减轻组织的炎症反应,促进 NO 的合成有效地扩张血管改善微循环,改善机体的缺血缺氧[26]。

小结

糖尿病视网膜病变是糖尿病特征性并发症,高血糖是糖尿病视网膜病变公认的始动因素,高血糖导致视网膜血管周细胞选择性丧失,刺激基底膜增厚;内皮细胞增生,导致血－视网膜屏障的破坏,通透性增加;血液粘度增高、异常血小板粘附和凝集等引起毛细血管闭,血流量下降,血栓形成及组织低氧,诱发一系列血管生长因子增生,致使微血管瘤、新生血管形成[27],视网膜结构和功能发生改变,最终致使糖尿病视网膜病变的发生发展,因此需要早期的干预治疗。HIF 是调控细胞氧气平衡以及缺氧应答反应中的核心调节因子,是维持机体氧稳态的主要因子。在糖尿病视网膜病变早期阶段,多种信号通路通过调控 HIF 活性,上调 VEGF 的表达,加重糖尿病视网膜病变的发生发展。在对 HIF 途径的干预将成为治疗糖尿病视网膜病变的新靶点[28]。高压氧医学在我国已经有几十年的历史,越来越广泛的应用于临床,在治疗视网膜病变方面发现其潜在的治疗价值。高压氧治疗可以成功抑制 HIF 的活化及下游蛋白的表达,减少 VEGF 等细胞因子的生成,同时高压氧治疗还可以提高眼底视网膜血液中氧含量,增强眼底微循环的血液流变功能,增加视网膜血流量,加速氧自由基的清除,减轻组织的炎症反应从而纠正视网膜组织缺血、缺氧,从而达到预防治疗糖尿病视网膜病变的疗效。

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