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氧化应激引起精索静脉曲张男性不育的认知与治疗

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摘　要

精索静脉曲张是一种以精索及睾丸静脉丛异常扩张和迂曲为特征的泌尿生殖系统疾病，其与男性不育之间的密切联系已得到广泛认可。约有15%的男性人口受到精索静脉曲张的影响，其发病机制主要与静脉瓣膜的结构缺陷或功能障碍有关。精索静脉曲张可能导致睾丸组织缺氧、阴囊温度升高及有害代谢物回流，通过不同途径触发活性氧的产生，从而引发氧化应激，对精子的形态、运动能力和遗传物质完整性造成损害从而引起不育。在临床治疗方面，手术疗法包括传统的精索静脉曲张结扎、腹腔镜手术、显微手术技术和介入栓塞治疗是目前主要的治疗选择。这些治疗方法旨在改善精液参数，提高生育率，并可能对氧化应激产生缓解作用。此外，抗氧化治疗作为一种新兴的治疗手段，通过补充抗氧化剂来对抗由精索静脉曲张引起的氧化应激，展现出改善精子质量和提升生育能力的潜力。未来的研究需进一步阐明精索静脉曲张的病理生理过程，并探索更为有效的治疗方法，以优化患者的生殖健康和生育预后。

关键词

精索静脉曲张，活性氧，氧化应激，不育症

The Understanding and Treatment of Male Infertility Caused by Varicocele Due to Oxidative Stress

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Abstract

Varicocele, a significant urological and reproductive condition, is defined by the anomalous dilation and tortuosity of the spermatic cord and testicular venous plexus, whose etiology is predominantly associated with structural anomalies or functional impairments of venous valves. This condition is estimated to affect approximately 15% of the male population, resulting in testicular hypoxia, increased scrotal temperature, and the regurgitation of noxious metabolites, which collectively precipitate the generation of reactive oxygen species (ROS), thereby initiating an oxidative stress response. The oxidative stress induced by varicocele is implicated in the detrimental alteration of sperm morphology, motility, and genomic integrity, which collectively contribute to male infertility. Therapeutically, surgical interventions, including conventional varicocelectomy, laparoscopic surgery, microsurgical approaches, and interventional embolization, represent the principal modalities for the management of varicocele. These interventions are aimed at ameliorating semen quality, enhancing fertility potential, and potentially mitigating oxidative stress. Moreover, antioxidant therapy, as a novel therapeutic modality, has demonstrated the potential to rectify the oxidative stress induced by varicocele and to improve sperm quality and fertility outcomes through the administration of antioxidants. Future scholarly endeavors are required to delineate the pathophysiological underpinnings of varicocele and to investigate more efficacious treatment strategies for optimizing the reproductive health and procreative prognosis of affected individuals.

Keywords

Varicocele, Relative Oxygen Species, Oxidative Stress, Infertility

1. 引言

精索静脉曲张是是由精索及睾丸静脉丛的异常扩张和迂曲引起的男性泌尿生殖系统的一种常见病症。随着对该疾病研究的深入，人们发现精索静脉曲张和男性不育有着密切的关系。在原发性不育症患者中，精索静脉曲张发病率约为 25%~35%，在继发性不育症患者中，其发病率可高达 45%~80% [1]。由于解剖结构或静脉功能的问题引起的精索静脉曲张可能通过热损伤、活性氧(ROS)释放、氧化应激等途径引起睾丸生殖细胞损伤进而引发男性不育，目前已被认为是男性不育的主要原因[2] [3]。本文拟对精索静脉曲张的病理生理及引起不育的机制以及目前主要的治疗方案选择进行综述。

2. 流行病学

根据欧洲泌尿外科协会发布的指南[4]，在人群中大约有 15%的男性患有精索静脉曲张，其中左侧的发病率显著高于右侧。而在世界卫生组织 WHO1992 年的一项包含 9000 多名男性的调查研究中，在精液参数指标异常和正常的男性中，精索静脉曲张的发病率分别为 25.4%和 11.7% [5]。而在年龄方面，Levinger U.和 Akbay E.的研究均揭示了精索静脉曲张的发病率随着年龄的增加而增加，每十年发病率上升约 10%，

在 80 到 89 岁的男性中，其发病率可增加到 75% [6] [7]。

3. 机制研究

3.1. 病因及病理学

精索静脉曲张病因学的研究在 1967 年 Kohler 的研究中就有所讨论，他们对尸检标本的左肾静脉进行造影剂注射造影，结果显示造影剂显影停止在左侧精索静脉近端，说明其存在瓣膜结构。而其对一名精索静脉曲张男性的尸检标本进行造影剂注射，则没有发现静脉中的瓣膜结构，这提示了精索静脉曲张的可能病因是患者的静脉瓣膜缺如或者功能障碍引起的精索静脉压力增高、回流受阻从而引起静脉曲张。此外，精索静脉曲张的形成还与某些患者瓣膜机制的异常有关[8]。

Ahlberg 及其同事的一项研究中，对 30 名正常男性的尸检结果进行分析，发现 40%的左侧精索静脉和 23%的右侧精索静脉完全没有瓣膜。在他们的后续研究中，通过对精索静脉曲张患者和直立位对照受试者的选择性静脉造影，证实了 22 名左侧精索内静脉和 10 名右侧精索内静脉患者的逆行充盈现象。他们报告称这些患者中有些没有瓣膜，而有些患者的瓣膜功能不全[9]。

基于精索静脉曲张的流行病学特征，我们知道左侧的发病率超过了右侧，这一现象可以通过泌尿系统的解剖结构来得到解释。右侧的精索静脉是倾斜地流入下腔静脉，而左侧的是垂直汇入左肾静脉，并且左侧精索内静脉的长度比右侧大约 8 至 10 厘米，由于上述两种原因，左侧精索静脉的静水压往往更高，且可能会影响部分男性的瓣膜功能，引起精索静脉的扩张和扭曲。Shafik 和 Bedeir 的研究工作进一步阐明了这一现象[10]，他们对 32 名左侧精索静脉曲张患者和 30 名对照者的精索静脉的静脉张力模式进行了研究。结果显示，左侧精索静脉曲张患者在休息和瓦氏动作期间的静脉张力显著高于对照组，分别平均增加了 19.7 毫米汞柱和 22 毫米汞柱。

值得一提的是，由于左侧精索内静脉是垂直流入左肾静脉的，因此它更容易受到左肾静脉内压力的影响，而左侧肾静脉穿行于腹主动脉和肠系膜上动脉之间，若两动脉的夹角较小，可能会挤压左侧肾静脉进行导致静脉静水压增高，临床上常称为胡桃夹综合征(Nutcracker syndrome)。

3.2. 引起不育的机制

人类精子具有产生活性氧(ROS)的特性，这是精子获能所需要的，但这一特性在某些条件下可能导致产生的 ROS 引起精子质膜中的不饱和脂肪酸发生过氧化反应，这在男性不育的发病机制中有重要地位[11]。精索静脉曲张可能引起睾丸组织缺氧、阴囊过热及代谢物回流等，从而通过细胞内各种不同的通路导致 ROS 的释放引起氧化应激(OS, Oxidative Stress) [2] [12]。

在 Kilinc 的研究中，他们建立了大鼠精索静脉曲张模型，在手术诱发精索静脉曲张的大鼠中，缺氧和血管生成的各种标志物，缺氧诱导因子-1α (HIF-1α)和血管内皮生长因子的水平对比假手术组和对照组均有显着升高[13]。在 Lee *et al.*的研究中，他们通过检测 HIF-1α 的表达来检查精索静脉曲张患者精索内静脉是否发生组织缺氧。与对照受试者相比，精索静脉曲张男性中精索内静脉中的 HIF-1α 表达是对照组的接近 7 倍[14]。这两项研究都证实精索静脉曲张与缺氧增加有关。

氧化应激(OS)是指由于活性氧(ROS)的过量产生或抗氧化剂的不足而导致的生理氧化还原平衡失调。在不育男性中，其精浆中的活性氧水平有所增加，同时抗氧化剂的浓度却有所下降。对许多 VCL 患者的血浆及精液进行分析提示其血浆 ROS 水平高于正常男性，而精液中总抗氧化能力(TAC, Total Antioxidant Capacity)水平明显低于正常男性。Hendin 及其合作者证明，与对照组相比，精索静脉曲张患者的活性氧(ROS)水平显着升高[15]。对于活性氧增多引起的氧化应激中，抗氧化酶系统及其相关基因通路调控发挥着重要作用。许多研究表明，例如 NRF2、SOD、CAT、GPX、PRX、GRX、TRX 和 NOS 等相关抗氧化

调控基因，其编码的酶在精子发生过程中的抗氧化反应、合成、谷胱甘肽还原和还原硫醇的氧化还原循环中发挥作用。对上述基因进行动物模型构建敲除或降低表达水平，均出现模型内的活性氧水平增高，诱发了氧化应激引起细胞凋亡，DNA 碎片化等损伤睾丸及生精细胞，影响精子的生成，从而导致不育[11] [16]-[23]。

精子中高水平的 ROS 水平可以影响精子染色质的完整性。鸟嘌呤(G)是 DNA 分子结构中最常见的碱基，其比较容易受到自由基的氧化作用，进而转化为 8-羟基鸟嘌呤(8-OHG)。有研究对不育男性和正常男性的 DNA 进行比较，结果显示不育男性的 8-OHG 含量大约是正常男性的 100 倍。精子中存在 8-OHdG DNA 糖基化酶，参与碱基切除修复(BER)过程，能够主动移除 8-OHdG 并将其释放到细胞外。但精子缺乏该途径的后续分子，导致 DNA 修复不完整，引起 β-消除或核糖循环反应，最终引起 DNA 链断裂引起 DNA 片段化[24] [25]。

4. 临床治疗

目前精索静脉曲张的临床治疗主要是手术治疗，包括传统的精索静脉曲张结扎(varicocelectomy)，腹腔镜精索静脉结扎术(laparoscopic varicocelectomy)，较新的运用显微手术技术的精索静脉结扎术(microscopic varicocelectomy)以及介入栓塞治疗(embolization)。手术入路的选择也可以分为腹股沟入路(inguinal)或腹股沟下入路(subinguinal)以及 Palomo 式的腹膜后入路(retroperitoneal)。1994 年 Schlesinger 及其同事回顾了早期文献，发现接受精索静脉曲张切除术的生育能力低下的男性精液参数有所改善。根据 Agarwal，Marmar 及 Abdel-Meguid 等人的不同研究，精索静脉曲张切除术，精子的浓度和活力等精液参数都有显著增加，手术后实现自然妊娠的可能性[26] [27] [28] [29]。同时，精索静脉曲张的手术矫正可能与氧化应激减少有关[30] [31]。Mostafa 报告说，精索静脉曲张切除术可显着降低不育男性的 ROS 水平，同时提高精液的抗氧化能力[32]。但是目前的临床指南指出，虽然手术治疗是精索静脉曲张的首选方案，但不同的手术方式治疗精索静脉曲张并没有体现出很大的优越性[4]。

基于氧化应激这一重要机制，近年来也有研究在关注精索静脉曲张的抗氧化治疗。机体的抗氧化系统包括各种氧化物歧化酶、非酶类物质以及例如如谷胱甘肽、维生素 A、C 和 E、辅酶 Q10 等小分子化合物[33]。在上述物质在体内呈低水平或其他病理过程引起相应物质减少而引起的氧化应激时，可以通过补充抗氧化剂进行缓解。目前已有部分泌尿外科或男科医生予以患者口服抗氧化剂来治疗不孕症[34]。Alahmar 的一项研究表明，对少弱精症(oligoasthenoteratozoospermia)的患者，予以辅酶 Q10 (200 mg/day)或硒口服治疗可以改善其精子浓度、活力和抗氧化状态[35]。

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