

·综述·

脑死亡供体肾脏保护的相关研究进展

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摘要: 肾移植是治疗终末期肾病的有效治疗方式, 可以提高患者的生存率和改善生活质量。肾移植涉及多个复杂的环节, 如可行性、适应症、禁忌症和移植后并发症的防治等方面。重视对DBD供肾的保护、革新保存方式、良好的围手术期管理和减少相关并发症等是当今的研究重点。本文主要综述脑死亡供体肾脏的相关研究进展。

关键词: 肾移植; 脑死亡器官捐献

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Research Progress on Kidney of Donation After Brain Death

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ABSTRACT: Renal transplantation is an effective treatment for end-stage renal disease, which can improve the survival rate of the related patient and their life quality. Renal transplantation includes a complex of issues, such as feasibility, indications, contraindications, and prevention of complications after transplantation. To attach importance to the protection of the donor kidney, the innovation of preservation technique, the management during the perioperative period of renal transplantation and the prevention of complications is the key point in the field of Renal transplantation. We reviewed the current research of DBD kidney.

KEY WORDS: Renal transplantation; Donation after brain death

0 引言

随着临床及科研技术的不断进步, 器官移植已取得了极大的进展, 但供体器官短缺仍然是制约其发展的瓶颈。目前, 我国公民逝世后器官捐献途径主要包括以下三类: 脑死亡器官捐献(donation after brain death, DBD)、心脏死亡器官捐献(donation after cardiac death, DCD)和脑-心双死亡标准器官捐献(donation after brain death awaiting cardiac arrest, DBCD)^[1]。研究表明, 脑死亡所引起的诸多病理生理改变对供体器官有显著影响^[2-3]。本文就脑死亡供体肾脏的病理生理改变和器官保护等相关方面的最新进展综述如下。

1 脑死亡供体肾脏的病理生理变化

脑死亡患者多存在脑缺血导致脑组织膨胀, 引起颅内压增高, 进一步加重脑组织水肿。较高的颅内压可使颅内血流停止, 导致垂体的分泌功能受限, 进而促使大量儿茶酚胺瞬间入血, 从而使内皮细胞受到广泛的损伤, 最终导致各种细胞因子的释放和各器官的缺血。相关研究表明, DBD初期患者肾脏可出现肾小球充血、内皮细胞增生、肾小球周围炎症等一系列病理生理改变^[4]。

1.1 补体系统

补体系统作为先天免疫系统的组成部分, 在移植后肾损伤方面起到重要作用^[5]。补体系统主要通过3种途径进行激活, 包括经典途径、旁路途径和凝集素途径。经过上述途径激活后可导致C3、C5及相应膜复合体的形成, 最终造成对机体的损伤。研究表明, 敲除模型相应的补体, 可在一定程度上避免肾移植缺血再灌注损伤(ischemic reperfusion injury, IRI), 同时, 供体肾脏局部表达的补体C3可增强移植排斥反应并导致功能的减退^[6]。此外, 甘露聚糖结合凝集素相关丝氨酸蛋白酶(mannose-binding lectin-associated serine protease 1, MASP1)可直接激活C3, 进而介导损伤^[7]。但是, 在脑死亡诊断之前和1小时内应用可溶性补体受体1型(soluble complement receptor 1, sCR1)可有效改善移植后肾脏功能^[8]。同时, 一些补体激活抑制剂如C1酯酶抑制剂已广泛应用于血管水肿等方面治疗中^[9]。由此可见, 补体系统的激活和抑制在肾脏移植方面具有巨大的研究价值。

1.2 Toll样受体

Toll样受体(Toll-like receptors, TLRs)是一种跨膜受体, 可以被病原相关分子模式和危险相关分子模式所激活, 进而引发下游信号通道, 从而导致细胞因子和趋化因子的表达增加, 最终使先天免疫和适应性免疫连接起来^[10]。相关动物试验敲除TLR2, 发现炎症反应的发生减少, 移植后再灌注损伤的程度较轻, 同时, 应用TLR2反义寡核苷酸可有效预防肾缺血再灌注损伤^[11]。补体和Toll样受体可被同样的配体激活, 但没有相关研究证实二者在肾损伤中的相互联系^[12]。研究猜测丝裂原活化蛋白激酶可能是二者联系的关键点, 这种联系在肠道的缺血再灌注损伤中被体现^[13]。因此, 这些领域可能成为今后研究的重点, 并且可能会对器官移植方面起到一定的推动作用。

1.3 凋亡相关基因和酶的表达

在DBD肾脏中, 细胞凋亡受多种活化或者抑制基因调控, 影响细胞凋亡通道的一些酶发生变化, 并且与移植后肾功能的恢复密切相关。研究发现, DBD肾脏的下列物质均高于活体肾脏: 白细胞介素-18、高迁移率族蛋白、CASP3、分化群95和肿瘤p53基因等^[14]。同时, p53、CASP3和Bcl-2在移植延迟肾功能恢复的肾脏中表达有所增加, 并且与冷缺血时间的长短有密切关联^[15]。Bcl-2是与细胞凋亡密切相关的基因家族, 家族成员中包括抗凋亡和促凋亡的成员, 正常情况下各成员的表达保持平衡。研究表明, 冷保存可增加供体肾脏抗凋亡基因的表达, 进而减少近端小管上皮细胞的凋亡^[16]。蛋白酶caspase可专一、高效地水解一系列蛋白质底物, 使相应蛋白质的功能发生改变或者丧失。在缺血导致的肾小管间质损伤中, CASP3的表达增加^[17]。Fas(CD95)是存在于细胞表面的死亡受体, 是细胞凋亡的信号分子, 参与诱导细胞凋亡, 下调FASL可能减轻肾移植排斥反应, 但具体机制尚未明确^[18]。

2 肾脏移植及保护

2.1 术前供者管理

目前, 改善DBD供肾的质量是临床科研工作者面临的重大挑战, 对供者进行合理的管理和治疗可对器官移植起到积

极的作用。近期,目标导向的液体治疗(Goal-directed Fluid Therapy, GDFT)日益受到临床工作者的重视。GDFT可在一定程度上减少心脏负荷,保证器官灌注,减少并发症的发生,对患者的预后有积极的意义^[19-21]。研究表明,脑死亡时间的长短可影响DBD供肾移植疗效,如移植术后移植肾的肾功能延迟恢复(delayed graft function, DGF)和术后急性排斥发生率^[2]。DBD供者应用药物可减少肾功能受损程度,如在低血压和低灌注期应用缩血管药物。S-亚硝基试剂亚硝酸乙酯可增加NO生物活性,对改善移植肾的功能起到积极的作用^[22]。相关动物实验应用促红细胞生成素预处理发现促炎症基因表达减少,中性粒细胞浸润减少^[3]。此外,研究表明DBD供者应用羟乙基淀粉可独立增加肾脏发生DGF的风险^[23]。同时,低温治疗作为一种干预措施可对供肾起到积极的保护作用,进而减少DGF的发生^[24-25]。

2.2 摘取供肾的手术方式

目前,摘取供肾的手术方式分为传统开腹手术和腹腔镜供肾取出术。手术麻醉方式多采用全身麻醉及椎管内麻醉,与单纯全身麻醉相比,全麻复合硬膜外麻醉可有效降低术后的应激反应^[26]。相关研究表明,开腹手术与腹腔镜手术对于供肾的移植及术后并无明显差异^[27-28]。此外,快速获取法作为传统的供肾获取法,多用于可控性的DCD^[29]。供肾原位保存法,是一种微创手术,多应用于非可控的DCD。相关学者通过对原位保存法和供肾快速获取法进行对比,发现后者的热缺血时间较短,肾存活率较高,PNF发生率和肾废弃率较低^[30]。随着医学技术的不断进展,腹腔镜供肾取出术发展越来越快,手术时间逐渐缩短,并发症也逐渐减少,越来越被广大临床工作者所青睐。

2.3 供肾保存

DBD供肾的保存会产生不同程度的缺血损伤,这对于器官移植的预后起到较大的影响。目前, DBD供肾的保存方式主要包括:低温机械灌注(hypothermic machine perfusion, HMP)和冷保存(static cold storage, CS)。相关学者通过对上述两种方法进行对比,发现HMP可在一定程度上降低DGF的发生率,提高了移植植物生存率^[31-32]。HMP对改善肾移植效果有重要的作用,这可能与改善微循环和清除代谢产物相关^[33]。到目前为止,没有详实的报道对上述两种方式的机制做出具体的解读。笔者认为, HMP和CS二者协同合作可能会对器官的保存起到积极的作用,研究其机制可能是今后的研究方向之一。此外,相关试验表明类细胞培养基灌注液可对保存液的保护效应有一定程度的改善,在一定程度上提升了移植效果^[34]。

3 展望

随着医学科研技术的不断发展与进步,使得与DBD供肾的相关研究成果逐渐被认可并应用于临床。但是,肾脏移植涉及诸多较为复杂的环节,如供肾来源、供者与受者机体病理生理变化、供肾离体前后的损伤与保护等方面。关于供肾损伤的具体机制尚未明确,仍需进一步探索。同时,如何更大限度的减少供肾的损伤将会成为广大学者的今后努力的方向之一。

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