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Present Situation and Progress of Small Intestine Graft Preservation

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Abstract

In all abdominal donor organs, small intestine grafts need the shortest preservation time limit for cold ischemia, but cold static preservation technology has been used for almost 30 years and could not meet the clinical needs anymore. Aggravated ischemia-reperfusion injury and subsequent intestinal mucosal barrier damage can directly lead to bacterial displacement, reperfusion syndrome, and fluid and electrolyte metastasis, which could increase the risk of acute rejection post transplantation. Nowadays, the preservation of the small intestine still depends on cold perfusion and static preservation, which didn't involve the treatment and preservation of the small intestine cavity. Early studies have confirmed that UW low temperature static preservation of small intestine grafts within 9 h, the damage is lighter, but this time limit is difficult to meet the actual needs of most transplant centers. There are few researches on the clinical preservation and IRI of small intestine grafts, and more experimental research, which provides an important reference for the practical application of clinical practice. This article will present the progress of small intestine graft preservation in recent years.

Keywords

Small Intestine Transplantation, Organ Preservation, Ischemia-Reperfusion

小肠移植物的保存现状及展望

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摘　要

在所有腹部器官移植供体器官中，小肠移植物对冷缺血时限要求最严格，目前低温静态保存技术已经沿

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用近30年，已经无法满足不断提高的临床需求。进行性加重的缺血－再灌注损伤以及其后伴随的肠黏膜屏障破坏，会直接导致菌群移位、再灌注后综合征以及液体与电解质转移，并增加器官移植术后急性排斥反应风险。时至今日，小肠的保存仍然依靠低温灌注及静态保存，小肠内腔的处理与保存技术仍停留在实验阶段。UW低温静态保存小肠移植物在9 h以内，损伤较轻，但是这个时限难以满足大多数移植中心的实际需要。本文就近年来的相关进展，以及小肠移植物保存改进策略，进行简要介绍。

关键词

小肠移植，器官保存，缺血再灌注

1. 引言

在所有腹部器官移植的供体器官中，小肠移植物对冷缺血时限要求最严格，一般认为保存时间必须要在 9 h 以内，才能进行移植。低温静态保存技术已经沿用了近 30 年，已经无法满足不断提高的临床需求。进行性加重的缺血－再灌注损伤以及其后伴随的肠黏膜屏障破坏，会直接导致菌群移位、再灌注后综合征以及液体与电解质转移[1] [2]，增加器官移植术后急性排斥反应风险[3]。时至今日，小肠的保存仍然依靠低温灌注及静态保存，未涉及小肠内腔的处理与保存[4]。UW 器官保存液(University of Wisconsin solution)低温静态保存小肠移植物在 9 h 以内，损伤较轻，但是这个时限难以满足大多数移植中心的实际需要[5]。本文就近年来小肠移植物的相关保存进展以及改进策略，进行简要介绍。

2. 小肠移植物主要损伤机制为缺血－再灌注损伤

在小肠移植物体外保存过程中、植入受体后，分别存在冷保存损伤以及缺血－再灌注损伤，导致小肠粘膜及实质细胞的破坏以及后续的炎症反应。然而，小肠移植物存在旺盛的代谢活动，肠腔内容物作为潜在的巨大感染源，肠腔为特殊的空腔结构，这与其他器官均不相同。由于存在缺氧及低温保存环境，小肠能量产生会逐渐耗竭甚至停止，导致能量供应匮乏[6] [7]，这些特点均是小肠移植物的缺血-再灌注损伤的特殊性。缺血－再灌注损伤影响肠粘膜的正常结构及其功能，破坏细胞骨架的完整性，影响小肠移植物的跨膜转运，影响蛋白质的合成，破坏内质网结构，破坏线粒体及呼吸链的完整性及正常功能，从而导致小肠黏膜细胞凋亡[8]。

小肠黏膜细胞间存在紧密连接，在结构上属于跨膜蛋白复合体，具有信号传输的重要功能。在体外低温保存过程中，由于无氧及低温环境，造成能量供应匮乏，导致肌动蛋白解聚，破坏细胞骨架结构，造成细胞膜通透性增加，肠粘膜水肿及肠道上皮细胞破坏[9] [10]。在小肠移植血流开放后，缺血-再灌注损伤生成许多活性氧自由基，直接导致细胞破坏，导致炎症因子(例如热休克蛋白、白介素-1 等)大量释放，并与 TLR-4 受体结合，激活受体体内的 DAMP 信号通路(包括 NF-κB 通路、p38 丝裂原活化蛋白激酶及等 ERK1/2 通路通路) [11]，形成瀑布级联效应，导致嗜中性粒细胞聚集[12]，造成严重的再灌注损伤。

3. 目前临床常用保存方式：低温保存

目前临床小肠移植常用保存方式包括，原位低温灌注及静态低温保存。其中，灌注保存除了快速降温及持续去除残余血液的作用外，还有利于减轻缺血缺氧期间细胞水肿，维持小肠移植物的代谢平衡。

目前用于临床保存小肠移植物的主要是 UW 液，近年来 HTK 保存液(Histidine Tryptophan Ketoglutarate solution)使用也有增加趋势[13] [14]，前者被视为最经典的器官保存液，但是粘滞度较高。尽管大家对于 HTK 保存液的小肠移植物保存效果存在质疑，但是由于缺乏与 UW 液系统性的对比研究[15]，仅有一项研究涉及两种保存液的效果对比，两组平均保存时间 8.5 h，比较术后 90 d 的生存率，其结果并无统计学差异[16]。

Olson 等研究发现，UW 液保存小肠移植物 4 h 后开始出现小肠上皮水肿，其后逐渐加重，保存至 12h 后，细胞水肿严重，粘膜下层亦开始水肿，而肉眼形态并无明显改变[17] [18]。Roskott 等研究证实，小肠移植物的冷保存损伤程度取决于供体类型，如果供体符合 OPTN (Organ Procurement and Transplant Network)标准，冷保存损伤程度较轻，供体不符合 OPTN 标准则结果相反，冷保存损伤严重[19]。研究证实，小肠移植物经历 8 h 的 UW 低温保存之后，血流开放后出现明显渗血、上皮细胞及粘膜的破坏等再灌注损伤表现。UW 液保存小肠移植物最长时间为 17 h [13]，HTK 液为 14 h [16]。

小肠移植进行性的缺血-再灌注损伤的早期临床表现是再灌注后综合征(post-referfusionsyndrome, PRS)，具体表现为术中低血压，全身血管阻力及心输出量降低，肺动脉压升高，可导致肾功能衰竭及术后早期死亡[2]。冷保存时间延长还会导致肠粘膜屏障破坏，菌群移位风险增加，如果冷保存时间在 7 h 之内，菌群移位发生率为 14%，而如果延长至 9 h，则菌群移位发生率明显增加至 76% [20]。在部分动物实验研究中，使用其他保存液替代 UW 液及 HTK 保存液，结果证实保存效果接近，但是保存 12 h 之内小肠黏膜超微结构及炎症因子水平无明显变化[21] [22]。但是这些研究均停留在动物试验阶段，损伤发生时间以及灌注压力与临床实际均不不同[23]，动物品种也会对实验结果产生影响[24]。

4. 小肠移植物保存方法改进的策略

4.1. 肠腔内保存

小肠是人体摄取营养物质、水及电解质的重要通道，跨膜蛋白形成细胞间紧密连接，直接调节小肠黏膜通透性[25] [26]。与肝、肾等实质器官保存原理不同，小肠属于空腔脏器，单纯血管灌注并不能满足小肠保存的需要，因此需要同时进行小肠腔内保存。其原理基于通过保存液进行肠腔内浸泡，提供给肠粘膜细胞及上皮直接的保护。大动物实验证实，对照组仅进行血管灌注保存，小肠移植物开放后会出现粘膜明显渗血，所有动物均死亡，实验组同时进行血管灌注及腔内保存，术后 7 d 所有动物均存活良好[29]，其机制与谷氨酰胺相关，它是肠细胞主要能量来源，细胞存活重要保证[30] [31] [32] [33]。使用含谷氨酰胺的聚乙二醇溶液进行小肠移植物肠腔内保存，冷保存 14 h 后小肠细胞形态基本正常，肠腔内保存液谷氨酰胺水平迅速降低[32] [33]。这些研究均证实冷保存期间，对小肠移植物进行肠腔内保存的意义及重要性。最佳的小肠腔内保存液尚未明确，但是研究已经证实，选择 UW 液同时进行血管灌注及腔内保存，明显降低小肠保存损伤[27] [28]。小肠移植物冷保存损伤导致进行性的黏膜上皮水肿及破坏，粘膜与粘膜下层分离。

以往研究证实，为防止细胞肿胀，保存液渗透压需要维持在 110 ± 140 mOsm/Kg，因此使用聚乙二醇替代羟乙基淀粉。Oltean 等研究证实，含有低分子聚乙二醇成分(3350a)的腔内保存液可减轻小肠移植物冷保存损伤[34]，聚乙二醇可以形成保护性涂层，防止小肠移植物细胞间紧密连接蛋白的破坏。而高分子的聚乙二醇(15-20000Da)也有相同保护作用[35] [36] [37] [38]。

4.2. 气体保存

缺血－再灌注损伤的病理生理学机制主要涉及缺氧，那么提供充足的氧气有助于减轻缺血－再灌注损伤，改善能量供应，促进恢复[39] [40] [41]。肠腔内氧弥散也有助于改善小肠移植物的能量供应，减轻

肠黏膜破坏[42]。但是有研究指出，长时间的肠腔内氧弥散会增加脂质过氧化作用，1 h 时间的氧弥散足够[43]。而相应的脂质过氧化作用，可在腔内含复合氨基酸的溶液中，添加水溶性维生素拮抗[44]。

除氧气之外，外源性的低浓度一氧化碳可以产生明显的肠粘膜细胞保护作用[45] [46] [47]。因此在小肠移植物低温保存期间，向充满 UW 液的肠腔内缓慢输送一氧化碳，可以减轻肠黏膜屏障破坏，减少促炎因子的表达，提高受体生存率[48]，一氧化碳吸入的安全性会导致争议，但是通过体外输注，由于避免血红蛋白的干扰，不仅可提高安全性，还会提高利用效率。氢气与氮气也被用于类似研究，研究证实，肠腔内给予富氢的 UW 液，可以维持肠黏膜完整性，减轻脂质过氧化作用，减轻炎症反应，提高受体生存率。而氮气保护作用不明显。

5. 小结

综上所述，小肠移植物保存技术进展缓慢，其损伤机制主要是缺血－再灌注损伤。与肝、肾等其他实质器官相比，有其特殊性，需要同时进行血管灌注及肠腔内保存，其保存方法的改进策略多停留在动物实验阶段，其临床意义需要未来的临床研究加以证实。

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