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The Research Progress of Kidney Ischemia-Reperfusion Injury on Mechanism and Its Influencing Factors

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Abstract

Ischemia-reperfusion injury (IRI) occurs when the blood flow to the particular organ is obstructed, followed by the restoration of blood to the ischemic organ. In the kidney, IRI contributes to pathological conditions called acute kidney injury (AKI) that is a clinical syndrome with rapid kidney dysfunction and high mortality rates. Although the pathophysiology of IRI is very complicated and is not completely understood, several important mechanisms resulting in kidney failure have been mentioned. IRI usually is associated with an inflammatory reaction, oxidative stress, intracellular Ca^{2+} overload, renin-angiotensin activation and microcirculation disturbance. Better understanding of the cellular pathophysiological mechanisms underlying kidney injury will hopefully result in the design of more targeted therapies to prevent and treat the injury. In this review, we summarize some important potential mechanisms and therapeutic approaches in renal IRI.

Keywords

Ischemia-Reperfusion Injury, Kidney Injury, Free Radical, Ca^{2+} Overload, Inflammation

肾脏缺血再灌注损伤机制及其影响因素的研究进展

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摘 要

缺血再灌注损伤(IRI)是指在缺血的基础上恢复血流后组织损伤反而加重的现象。肾脏缺血再灌注损伤引起的急性肾功能损伤(AKI)在临床上具有很高的死亡率。其机制非常复杂，涉及多种因素共同作用，且目前对于IRI的具体作用机制尚不十分明确，目前认为与缺血再灌注后的炎症反应、氧化应激、细胞内钙超载、肾素-血管紧张素激活、微循环障碍等有关。更好的理解肾缺血再灌注损伤的机制才能找到有效的防治措施。这篇综述我们总结了缺血再灌注损伤可能的机制及防治措施。

关键词

缺血再灌注损伤，肾损伤，自由基，钙超载，炎症

1. 引言

1955 年 Sewell 等首次报道在心脏冠状动脉结扎解除后，恢复血流引发的损伤现象[1]。这种在缺血基础上恢复血流后组织损伤反而加重，甚至发生不可逆性损伤的现象称为缺血再灌注损伤(IRI)。常见原因有：休克后微循环的再通、心脏骤停后的复苏、冠脉搭桥术、溶栓疗法、体外循环下心脏手术、断肢再植和器官移植等。IRI 严重程度与缺血时间，组织器官功能结构、代谢特点，再灌注的条件等因素有关。组织器官对氧需求程度越高，侧枝循环形成越少、越晚，IRI 越重，故而肾脏成为易受 IRI 的器官之一。肾脏缺血再灌注损伤表现为血肌酐升高，严重者可导致急性肾小管坏死进而引起急性肾功能衰竭[2]。

2. 病理生理学改变

缺血再灌注损伤病理生理学机制很复杂，涉及多因素共同作用，具体发生机制至今尚未完全阐明，而研究也多集中在心肌缺血再灌注损伤方面，肾脏缺血再灌注损伤研究较少。IRI 包括缺血和再灌注两个阶段。首先，组织缺血缺氧会引起能量代谢的变化，表现为由葡萄糖的有氧氧化转变为糖酵解，糖酵解产生过量乳酸，引起细胞内酸中毒，同时缺氧和能量代谢的变化导致细胞内 ATP 水平下降，两者为引起缺血再灌注损伤的始动环节[3]。

2.1. 钙超载

IRI 缺氧阶段导致 ATP 减少，抑制钠-钾-ATP 酶活性，同时为了缓解细胞内酸中毒，H^+-Na^+交换蛋白激活，两者引起细胞内钠离子浓度升高，进而导致钠/钙交换蛋白反向转运增强，引起细胞内钙超载[4]。ATP 减少同样会抑制内质网对钙离子的重吸收，加重细胞胞浆钙超载[5]。再灌注时 PH 的恢复，细胞外液氢离子浓度迅速下降，激活 H^+-Na^+交换蛋白，促进细胞内氢离子排除，细胞外钠离子内流，进一步加重细胞钙超载[4]。

2.2. 自由基产生增多

自由基是指含有单个不成对电子的原子、原子团、分子的总称，主要包括活性氧(ROS)、活性氮(RNS)，

可引起氧化应激反应[6]。缺血再灌注时因线粒体电子传递链受损、黄嘌呤氧化、细胞呼吸爆发、一氧化氮合酶等作用产生过量的自由基。自由基通过氧化反应损伤细胞内大分子，包括膜脂质、蛋白质和 DNA [7]。

线粒体在自由基产生过程中起重要作用，缺血时，细胞 ATP 减少，钙离子进入线粒体增多，细胞色素氧化酶系统功能失调，电子传递链受损，使细胞内氧经单电子还原生成 ROS 增多，此外钙离子进入线粒体内使 SOD 对氧自由基清除能力下降，ROS 产生与清除失衡，ROS 增多[8]。

缺血时，细胞内 ATP 代谢为次黄嘌呤，导致次黄嘌呤在组织中大量堆积；细胞内钙超载导致细胞内黄嘌呤脱氢酶(XD)转化为黄嘌呤氧化酶(XO)。再灌注后，大量氧进入组织，次黄嘌呤在 XO 催化下氧化为黄嘌呤并进一步氧化形成尿酸，此过程中产生大量的超氧阴离子及羟自由基[7]。

缺血再灌注时大量炎症介质释放、补体系统激活，使中性粒细胞、巨噬细胞等向缺血组织趋化、浸润，激活细胞内 NADPH/NADH 氧化酶系统，在再灌注时大量涌入的氧分子作用下，产生氧自由基，此过程称为呼吸爆发[9]。

血管内皮细胞内的一氧化氮合酶(eNOS)催化 L-精氨酸产生少量的 NO 维持血管正常功能，四氢生物蝶呤(BH4)是 eNOS 的必要辅助因子。缺血后再灌注时，内皮细胞受损，eNOS 催化产生的 NO 减少，而超氧阴离子增多[10]。

2.3. 肾素-血管紧张素系统

肾素-血管紧张素系统的激活和血管紧张素 II 含量的增高[11]是 IRI 的重要危险因素。血管紧张素 II 通过收缩肾血管、提高血管对交感神经刺激敏感性[12]、引起氧化应激反应[13]、促进肾间质纤维化和介导凋亡[14]损伤肾脏。血管紧张素 II 可直接收缩血管并能通过增加交感神经张力，降低肾血流量；通过增加 NADPH 氧化酶的表达，产生过量的 ROS [15]；而其介导凋亡可能与 Bcl 家族蛋白表达有关[16]。同时血管紧张素 II 通过 Smad 通路促进肾上皮细胞向间质细胞分化转移，促进肾间质纤维化，导致肾脏慢性纤维化[17]。

3. 病理改变

3.1. 细胞死亡

3.1.1. 坏死和坏死性凋亡

细胞非程序性死亡是指细胞受到环境中的物理或化学刺激发生的细胞被动死亡，这通常被认为是坏死。而研究表明，并非所有的坏死都是非程序性的，而在信号通路转导下的坏死，称之为坏死性凋亡。细胞坏死后会释放细胞内容物和促炎症因子，引起炎症。

如前所述，缺血及再灌注两个阶段均会引起细胞内 Na^+与 Ca^+浓度升高，升高的渗透压与细胞膜损伤共同引起细胞肿胀、坏死。

细胞内钙超载、ROS、再灌注后 PH 的恢复会导致线粒体渗透性钙转运通道(mPTP)的开放，进而引起 ATP 的减少、ROS 增加、细胞肿胀坏死[18]。mPTP 的开放可能是在受体相互作用蛋白介导下进行的[19]。

3.1.2. 凋亡

TNF 是由活化巨噬细胞产生的细胞因子，是介导凋亡的重要外源性因素。TNF 与 TNF 受体(TNFR1 和 TNFR2)结合后，通过中间媒介蛋白—TNF 受体相关联的死亡结构与(TRADD)和 Fas 相关死亡结构域(FADD)启动凋亡蛋白酶(Caspase)活化的信号通路，产生 Caspase-8，后者可以直接活化 Caspase 家族其他

成员，触发凋亡执行(execution of apoptosis) [20]。

缺血再灌注后自由基及细胞内钙超载损伤线粒体膜，通过不同方式诱导细胞凋亡。① 线粒体膜损伤，释放内部的核酸内切酶 G 进入细胞核切割 DNA，造成细胞凋亡。② Bcl 家族蛋白表达，作用于线粒体外膜的线粒体凋亡诱导通道(MAC)，释放 Cyto-C，Cyto-C 一方面影响氧化呼吸链，使 ATP 生成减少，另一方面形成凋亡复合体，后者裂解产生 Caspase-9，进而激活 Caspase-3。③ 线粒体通透性增加后，释放 SMAC/Diablo，与凋亡蛋白抑制因子(IAP)结合并使其失活，从而抑制 IAP 阻遏凋亡的过程[20] [21] [22]。

细胞内钙超载既能增强 Caspase-3 的活性，又能激活该依赖性的蛋白酶(如 Calpain [23])，进而诱导凋亡。

3.1.3. 自噬

细胞自噬是指细胞利用溶酶体降解自身成分的过程，被降解的成分包括细胞质及细胞器。正常情况下生长因子能激活哺乳动物雷帕霉素靶蛋白(mTOR)，活化的 mTOR 能抑制诱导细胞自噬的关键信号分子 Atg1，从而抑制细胞自噬的发生，而在应激及氧供缺乏的情况下，mTOR 失活，启动细胞自噬[21]。

3.2. 炎症反应

缺血再灌注损伤涉及的炎症反应主要与缺血组织细胞因子、趋化因子产生和白细胞浸润有关。

炎症介质的产生与多种因素有关。自由基损伤会释放炎性介质并减少 NO 产生[24]。同时细胞坏死会导致细胞内容物及促炎症因子的释放，引起炎症。肾小管上皮细胞和活化的 T 细胞也会产生多种细胞因子、趋化因子，如 TNF-α，白介素-1，白介素-8 等[25]。Toll 样受体(TLR)尤其是 TLR2 和 TLR4 的激活在这些介质产生中具有重要作用[26]。补体系统激活释放 C5a 和 C5b-9 也可以刺激内皮细胞表达选择素和细胞间粘附分子-1 (ICAM-1) [27] [28]。

炎症因子促进白细胞浸润。趋化因子促使白细胞等炎症细胞向缺血区域移动，而粘附分子会促进白细胞与血管内皮细胞的粘附、聚集，而白细胞和内皮细胞的相互作用是导致肾缺血再灌注损伤的重要原因[29]。

3.3. 微循环障碍

炎症反应会在清除坏死组织细胞的同时产生 ROS，并会导致缺血区的微循环障碍，甚至导致再灌注后缺血区无复流现象[7]。微循环障碍主要与白细胞浸润、游走，血管收缩-舒张功能障碍，血管通透性增高，血栓形成和新生血管有关[24]。无复流现象是指当缺血原因去除血流重新恢复后，缺血区很多毛细血管并没有得到充分的血流灌注。微循环障碍甚至无复流现象导致血供恢复后，组织仍处在缺血缺氧的状态，导致损伤不能减轻反而继续加重。

3.4. 间质纤维化

如前所述，血管紧张素 II 通过 Smad 通路促进肾上皮细胞向间质细胞分化转移，促进肾间质纤维化，导致肾脏慢性纤维化[17]。同时，肾缺血再灌注后促炎因子、生长因子、基质金属蛋白表达上调，都会导致肾纤维化。并且，微循环障碍导致的缺氧也会促进肾间质纤维化[2]。

4. 防治措施

4.1. 尽快恢复血流灌注

肾缺血再灌注损伤与组织缺血的时间与程度有很大关系，目前观点是肾脏常温状态下缺血 30 分钟以内并不会引起永久性损伤[30]；而动物实验证实，肾脏缺血 75~90 分钟以上会出现肾功能的损伤[31]。尽

可能早的恢复血流灌注是防治缺血再灌注损伤的关键。

4.2. 抗炎

炎症反应是由多条信号转导通路参与的复杂调控网络，发生机制负载，涉及其中的炎症因子和细胞繁多，针对不同靶点，研究发现很多药物通过抗炎起到减轻肾 IRI 损伤的作用。

JAK/STAT 信号通路是细胞因子信号转导的重要通路，小鼠中应用 JAK 抑制剂[32] (如右旋美托咪啶[33])再灌注后肾功能损伤、肾小管上皮细胞的凋亡都明显减轻。

抗胸腺细胞球蛋白(ATG)可以抑制树突细胞功能[34]，同时于再灌注之前应用可以减少 ICAM-1，E-选择素，血小板内皮细胞粘附分子、CD11b 等粘附分子，从而减轻炎症反应[35]。

可溶性的 P 选择素可以通过抑制 p 选择素和白三烯聚合体的结合减轻缺血后组织中性粒细胞浸润[36]，白三烯受体阻滞剂(孟鲁司特[37]，扎鲁司特[38])通过抑制白细胞浸润、粘附分子表达和脂质过氧化保护肾脏。

胆碱能受体激动剂(烟碱)可以通过 $\alpha 7$ 烟碱型乙酰胆碱受体(α7nAChR)通路抑制中性粒细胞浸润和细胞因子释放，从而减轻炎症反应[39]。

如前所述，TLR 在炎症反应中具有重要作用，动物实验表明，通过单克隆抗体 OPN-305 抑制 TLR2 可以显著减轻心肌缺血再灌注损伤[40]，TLR4 阻断剂 eritoran 也可以减轻肾缺血再灌注损伤[41]。同时，阻断 TLR 通路的 IRAK-4 [42]和 MYD88 [43]同样可以减轻肾脏缺血再灌注损伤。

而对于补体介导的炎症反应，实验表明选择性的 C5a 受体拮抗剂[44]、沉默 C3 补体基因和凋亡基因[44]可以减轻肾脏缺血再灌注损伤[45]。C1 抑制剂可以显著减少肾小球和肾小管毛细血管 C4d 和 C5b-9 沉积，减少缺血再灌注后肾小管损伤和肾小管上皮细胞凋亡[46]。

4.3. 抗氧化

IRI 与自由基产生的损伤作用有很大关系，减少自由基产生或者清除自由基可以起到保护缺血组织、器官的作用。

缺血再灌注时因线粒体电子传递链受损、黄嘌呤氧化、细胞呼吸爆发、一氧化氮合酶等作用产生过量的自由基。XO 抑制剂[24]、给予 BH4 和 L-精氨酸[47]可以减少自由基产生可以起到保护作用。

清除自由基是抗氧化的重要方式，超氧化物歧化酶(SOD) [48]、褪黑素[49]、异丙酚具有清除自由基和抗氧化的作用。同时，褪黑素减轻缺血再灌注损伤还可能与抑制交感神经、减少儿茶酚胺释放有关[50]。异丙酚通过增加骨形态生成蛋白 2 (BMP 2)表达、增加 SOD 含量、减少炎症因子释放减轻肾缺血再灌注损伤[51]。

4.4. NO

CO、NO、硫化氢、氢气等气体已经被应用于减轻 IRI [4]，研究表明肝移植过程中吸入 NO 有利于提高肝功能并减少肝细胞的坏死[52]。动物实验亦表明，摄入亚硝酸盐产生的 NO 通过多种通路调节肾脏对缺血和炎症的反应，有利于移植后肾功能的恢复[53]。

4.5. 缺氧诱导因子

缺血缺氧状态下，能量代谢由有氧氧化转变为无氧糖酵解，缺氧诱导因子 1 (HIF-1)是缺氧基因表达重要转录因子。常氧状态下，脯氨酸-4-羟化酶(PHD)使 HIF-1α 亚基羟化，而缺氧时 PHD 羟化作用降低，HIF-1α 降解减少，HIF 增强多种基因的表达，促进细胞对缺氧的适应性反应。PHD 抑制剂可以增强肾脏对缺血的耐受性[54]，促红细胞生成素(EPO)可以提高 HIF-1α 从而减轻肾小管缺氧损伤[55]。

4.6. 肾素-血管紧张素系统抑制剂

肾素抑制剂[56]、血管紧张素Ⅰ转化酶抑制剂[57] [58]可以通过减少血管紧张素Ⅱ的含量，减轻氧化应激反应、白细胞浸润及细胞凋亡，从而减轻肾缺血再灌注损伤。绝大多数动物实验证实，血管紧张素受体 1 (AT1)阻断药可以通过阻止血管紧张素Ⅱ与 AT1 的结合起到减少肾 IRI 的作用[11] [59] [60]。但是 Pazoki 等通过对比应用不同剂量卡托普利、依那普利、洛沙坦后肾缺血 30 min 肾细胞坏死程度发现，不同于卡托普利和依那普利，洛沙坦并不具有减轻肾 IRI 的作用[58]。ACRI 类药物及 ARB 类药物对于肾 IRI 的作用是否通过 AT1，或者通过作用于 AT2 以及其他途径尚需进一步明确。

4.7. 缺血预处理

1986 年，Murry 等在心肌缺血-再灌注动物模型中发现：预先反复、短暂施与缺血预处理(IPC)可以减轻心肌缺血再灌注损伤[61]。后来人们发现其他部位缺血预处理也可以对未行预处理的缺血器官产生相同的保护作用，这种处理方式被称之为远程缺血预处理(rIPC) [62]。其细胞保护机制尚未完全阐明，考虑与 rIPC 上调腺苷、缓激肽等内源性保护介质，通过 G 蛋白偶联受体激活 ATP 依赖钾离子通道，抑制 mPTP 的开放，从而减少细胞凋亡[63]。神经通路也可能在其细胞保护机制中具有重要作用[64]。

动物实验证实，rIPC 在 IRI 中对肾脏有保护作用。但是 rIPC 在临床应用中效果尚有争议。在成人心脏手术中，9 项临床试验中，4 项[65] [66] [67] [68]表明 rIPC 有保护作用，而 5 项[69] [70] [71] [72] [73]单中心随机对照试验则没有发现显著差别。Zimmerman [65]进行了一项单中心随机对照试验，118 例病人入组，rIPC 组 3 周期阻断下肢 5 分钟，手术后 48 小时 AKI 定义为：sCr > 0.3 mg/dL 或者大于基线 50%。结果是，rIPC 组术后 AKI 发生率显著降低。Candilio [69]等最近进行的一项单中心随机对照试验，178 例病人入组，rIPC 通过同时阻断上臂和大腿 5 分钟，再灌注 5 分钟，重复两周期，手术后两组病人 AKI 发生率无明显统计学差异。

rIPC 在肾移植手术的应用较少，Wu [74]等进行了一项尸体供肾肾移植的随机对照试验，研究选取 48 例患者，随机分为两组，一组接受 rIPC，一组对照。rIPC 组在移植过程中钳夹暴露的髂外动脉 5 min，反复 3 次。对比移植后 2 小时、12 小时、1~7 天、14 天、30 天的血肌酐和肾小球率过滤，发现肾移植后 12 小时、1~7 天、14 天 rIPC 组较对照组血肌酐低，肾小球率过滤高。肾移植后 12 小时、24 小时，rIPC 组尿 NGAL 明显低于对照组。然而移植后两组在组织病理学上没有明显区别，并且这项试验没有检测 30 天后两组的情况。值得一提的是这个试验过程中 rIPC 的实施并不精确，阻断时间为 10.4 ± 1.4 分钟而不是精确的 5 分钟。MacAllister [75]等进行了一项活体供肾肾移植的大样本、多中心三期随机对照试验。试验选取 406 名大于 18 岁患者，随机分为四组：近期 rIPC (手术前 30 分钟)，远期 rIPC (手术前 24 小时)，双期 rIPC (早期与晚期)与对照组。rIPC 施行方式：供体与受体同时施行，阻断上肢 5 min 放开，重复 4 次。早期组在 3 月和 12 月在肾小球率过滤上较对照组明显升高。晚期组与对照组没有明显差异。结果表明，早期 rIPC 对于肾 IRI 的肾脏有保护作用，可以延长患者预期寿命 2~3 年。

然而，各项临床试验中，对于急性肾脏损伤的定义并不一致，rIPC 的施行方案也没有统一标准，有多个方面存在不同：阻断位置(上肢、下肢)、阻断时间与周期、阻断方式(止血带和直接钳夹血管)。

一项 58 个动物实验的荟萃分析显示，长时间持续和短时间多周期缺血刺激的 rIPC 效果一致[76]，目前尚没有这方面的临床试验数据。同时研究显示，上下肢阻断位置的不同在 AKI 的发病率上并没有不同[77]。麻醉用药、合并症甚至性别等都是影响结果的因素。

研究试验表明，虽然心脏手术中关于 rIPC 对于肾功能的保护作用尚有争议，但是在肾移植中 rIPC 对肾脏是有保护作用的。因此，尚需要更多的临床实验和更长期的随访结果来更好地定义 rIPC 在肾 IRI 中的作用。

5. 总结

肾缺血再灌注损伤(IRI)是急性肾损伤的重要原因。其机制非常复杂，涉及多种因素的共同作用，且目前对于 IRI 的具体作用机制尚不十分明确，目前认为与缺血再灌注后自由基损伤、细胞内钙超载、炎症作用、肾素-血管紧张素激活进而引起的细胞死亡、微循环障碍、间质纤维化等有关。

肾移植后肾功能损伤进而需要透析的发病率很高，尽快找到能有效减轻肾移植过程中的缺血再灌注损伤而提高移植肾功能的措施意义重大。

尽快恢复肾血流灌注是防治肾缺血再灌注损伤的关键。因肾 IRI 机制多种多样，针对不同靶点，药物干预也多种多样，这些药物作用在动物实验中已经得到证实，但是绝大多数尚未应用于临床，值得一提的是，关于 ACEI 及 ARB 类药物作用途径的作用需要进一步研究。

rIPC 因为无创、容易操作且患者容易耐受，已经应用于临床试验，但是效果尚有争议，不同临床实验结果迥然，而且绝大多数临床试验于心脏手术，肾移植、保留肾单位手术等肾脏手术临床试验较少，而且目前来说对于 rIPC 的施行方式，术后检测指标并没有统一的方案。探索有效、易耐受、微创、标准的 rIPC 方案及 AKI 评价标准需要进一步研究，需要进行多中心大样本的随机对照试验，同时，rIPC 的机制也需要进一步揭示。分子机制的阐述有利于选择实施方案及预测哪类人群可以从 rIPC 中获益。

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