厚生労働科学研究費補助金（難治性疾患政策研究事業）
分担研究報告書

水素含有臓器保存液による肺保存の有用性

Protective effects of a hydrogen-rich preservation solution during cold ischemia in rat lung transplantation

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研究要旨

肺移植において虚血再灌流障害を軽減することが、急性期の死亡率および慢性期の拒絶を減少させるために重要である。分子状水素には酸化ストレスに対する細胞保護効果が報告されている。そこで、我々は肺移植時の肺保存における水素含有臓器保存液の有効性をラット冷肺虚血モデルを用いて検討した。保存液に水素水を添加することにより、ガス交換能の改善、肺水腫の軽減、TNF-α mRNA の発現抑制を確認した。以上から水素含有保存液はラットを用いた肺移植モデルにおいて、移植後の呼吸機能の低下ならびに肺水腫の抑制と抗炎症作用による障害抑制効果を認めると結論した。

A. 研究目的

移植医療において、臓器保存中の障害を軽減することは、その後に生じる虚血再灌流障害の軽減につながり、移植後の予後に影響を与える重要な因子となる。分子状水素には酸化ストレスに対する細胞保護効果が報告されているが、今回我々は肺移植時の肺保存における水素含有臓器保存液の有効性を検討した。

B. 研究方法

Lewis ラット(12 週齢、雄)→Lewis ラット(12 週齢、雄)の同所性片肺移植モデルを用いた。保存液への水素添加なし群（コントロール群）と水素添加あり群（水素群）の 2 群にわけ検討した（各 n=6)。ドナーより心肺ブロックを取り出し、 6 時間冷保存した後、レシピエントに左肺移植を行った。再灌流後 120 分経過時に、動脈血液ガス分析、肺機能検査を行った。さらに、犠牲死させた後、肺組織を乾湿重量比、生化学検査、組織学的評価に用いた。

C. 研究結果

コントロール群に対して水素群では動的肺コンプライアンスおよび血中酸素分圧が有意に良好であった(各 $p<0.05$)。乾湿重量比は水素群で有意に小さく($p<0.05$)、組織学的検査においても血管周囲の浮腫が軽減されていた。Real Time PCR 法では、水素群で有意に TNF-α mRNA の発現が抑制されていた($p<0.05$)。

D. 結論

水素含有保存液はラットを用いた肺移植モデルにおいて、移植後の呼吸機能の低下ならびに肺水腫の抑制と抗炎症作用による障害抑制効果を認めた。

E. 研究発表

1. 論文

Saito M, Chen-Yoshikawa TF, Takahashi M, Kayawake H, Yokoyama Y, Kurokawa R, Hirano S-I, Date H. Protective effects of a hydrogen-rich solution during cold ischemia in rat lung transplantation. J Thorac Cardiovasc Surg 2020;159:2110–2118.

Protective effects of a hydrogen-rich solution during cold ischemia in rat lung transplantation

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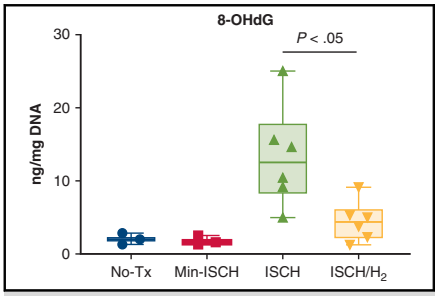
ABSTRACT

Background: Molecular hydrogen can reduce the oxidative stress of ischemia-reperfusion injury in various organs for transplantation and potentially improve survival rates in recipients. This study aimed to evaluate the protective effects of a hydrogen-rich preservation solution against ischemia-reperfusion injury after cold ischemia in rat lung transplantation.

Methods: Lewis rats were divided into a nontransplant group (n = 3), minimum-ischemia group (n = 3), cold ischemia group (n = 6), and cold ischemia with hydrogen-rich (more than 1.0 ppm) preservation solution group (n = 6). The rats in the nontransplant group underwent simple thoracotomy, and the rats in the remaining 3 groups underwent orthotopic left lung transplantation. The ischemic time was <30 minutes in the minimum-ischemia group and 6 hours in the cold ischemia groups. After 2-hour reperfusion, we evaluated arterial blood gas levels, pulmonary function, lung wet-to-dry weight ratio, and histologic features of the lung tissue. The expression of proinflammatory cytokines was measured using quantitative polymerase chain reaction assays, and 8-hydroxydeoxyguanosine levels were evaluated using enzyme-linked immunosorbent assays.

Results: When compared with the nontransplant and minimum-ischemia groups, the cold ischemia group had lower dynamic compliance, lower oxygenation levels, and higher wet-to-dry weight ratios. However, these variables were significantly improved in the cold ischemia with hydrogen-rich preservation solution group. This group also had fewer signs of perivascular edema, lower interleukin-1β messenger RNA expression, and lower 8-hydroxydeoxyguanosine levels than the cold ischemia group.

Conclusions: The use of a hydrogen-rich preservation solution attenuates ischemia-reperfusion injury in rat lungs during cold ischemia through antioxidant and anti-inflammatory effects. (J Thorac Cardiovasc Surg 2020;159:2110-8)



The use of hydrogen rich preservation solution reduced the level of 8-OHdG in lung tissue.

Central Message

A hydrogen-rich preservation solution alleviated lung ischemia-reperfusion injury by suppressing oxidative stress and inflammation.

Perspective

The addition of hydrogen to the preservation solution attenuated ischemia-reperfusion injury, and the solution is potentially suitable for organ storage and transportation.

See Commentary on page 2119.

Lung transplantation is currently the only viable treatment for end-stage respiratory disease. However, the survival rate after lung transplantation remains lower than that of other organs.[1] The main causes of death in lung transplant recipients are primary graft failure, infectious diseases, acute rejection, and chronic lung allograft dysfunction. As primary graft failure is frequently the result of ischemia-reperfusion injury (IRI), the prevention or attenuation of IRI can help to improve patient survival after lung transplantation.[2-5]

Harvested donor lungs are commonly immersed in organ preservation solution and kept at low temperatures during transport to recipients.[6,7] Various methods for organ

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Received for publication June 10, 2019; revisions received Sept 9, 2019; accepted for publication Sept 9, 2019; available ahead of print Nov 25, 2019.

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0022-5223/$36.00

https://doi.org/10.1016/j.jtcvs.2019.09.175

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