

A Review:

The Association between Oxygen Consumption of the Liver Graft and Post-transplant Outcome

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Abstract

The association between oxygen consumption of the liver graft after reperfusion and post-transplant outcome has been studied from 1950s. The lack of significant progress is because oxygen consumption of the liver graft is determined by various factors, including the donor condition, status of the graft preservation, cold ischemia time, and hepatic blood flow after reperfusion. However, metabolic alterations, such as oxygen consumption and glucose metabolism in the liver grafts are reliable predictors of subsequent the liver graft function, and may help the decision of re-transplantation for the patients with failed liver graft. Appropriate organ preservation reduces oxygen consumption of the liver grafts, and low oxygen consumption might reflect less histological damage after preservation and reperfusion. In contrast, systemic oxygen consumption after reperfusion in patients with successful liver transplantation was higher than systemic oxygen consumption in those with primary non-function and graft dysfunction. This review summarizes association between oxygen consumption of the liver graft and post-transplant outcome.

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Introduction

Liver transplantation has become important in the management of patients with end-stage liver disease (ESLD), because advances in organ preservation, surgical technique and immunosuppressive agents have resulted in improved outcomes following liver transplantation (1). In spite of these recent improvements primary non-function (PNF) and graft dysfunction (GDF) occur in 2-4 % (2, 3), and 13-36% (4, 5) of liver transplant recipients, respectively. Therefore, an early assessment of liver graft function during and after liver transplantation is important for determining graft outcome, and making the decision for re-transplantation early, when the liver graft fails to PNF or GDF. Metabolic alterations, such as oxygen consumption and glucose metabolism (6-8) in liver grafts have been reported as reliable predictors of subsequent liver graft function, and are known to influence graft outcome (9-11). Because oxygen cannot be stored intra-cellularly, oxygen consumption of the liver graft after reperfusion could be a reliable predictor of the post-transplant graft function, which reflects the status of organ preservation, ischemic-reperfusion injury, and hepatic blood flow after reconstruction of the vessels (12-14). In fact, association between high oxygen consumption of the liver grafts

after reperfusion and poor prognosis have been reported in a small retrospective clinical study (15). This review summarizes association between oxygen consumption of the liver graft and post-transplant outcome.

Oxygen consumption of the liver graft during and after reperfusion

Kupper cells and ischemic reperfusion injury

Under resting conditions, the normal liver requires a blood supply of about 800 - 1,200 mL/min, which is about 20–25% of cardiac output (16), and consumes about 20-25% of systemic oxygen consumption (17, 18). Kupper cells constitute the liver sinusoids together with sinusoidal endothelial cells, hepatic stellate cells, natural killer cells, and dendritic cells, and these cells play an important role in the development of ischemic reperfusion injury (19). Phagocytosis of bacteria and sequestering of endotoxin by Kupffer cells impose a high metabolic demand on the reticuloendothelial system (20). Moreover, Kupper cells when activated, change their metabolic behavior, and generate a lot of reactive oxygen species in early reperfusion (21). Lemasters reported that flushing liver grafts after storage with Carolina rinse solution containing antioxidants, adenosine, calcium

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blocker, energy substrates, and glycine at pH 6.5 decreases endothelial cells death, reduces Kupffer cells activation, and improves graft survival (22). Appropriate organ preservation reduces oxygen consumption and ischemic reperfusion injury of the liver grafts.

Temperature of organ preservation

The conditions, including temperature, of donated preserved liver are associated with the graft metabolism after reperfusion (23, 24). Several investigators conclude that hypothermia results in a decreased metabolism and oxygen consumption (25). Fujita et al studied the effect of temperature on isolated rat liver perfusion model (26). Livers were perfused for 12hours with oxygenated Krebs-Henseleit solution at 5, 10, 15, 20, 25, and 30°C, followed by one-hour normothermic reperfusion. Oxygen consumption of the preserved liver at 5°C reduced to 8.2% of that at 37°C (27). During one-hour normothermic reperfusion, bile production of preserved livers at 5 and 10°C was well maintained as compared to those at other temperatures. In addition, released liver enzymes of preserved livers at 5, 10, 15 and 20°C were fewer than those at 30°C. In microscopic findings of the preserved livers at 5°C after normothermic reperfusion, most sinusoidal cells showed normally elongated appearance lining the

regulatory arranged cords of hepatocytes, and histological damages at the centrilobular zone were rare as compared to those at 25 and 30°C. These results suggested that low oxygen consumption of the liver graft might reflect less histological damage after preservation and reperfusion.

Hepatic blood flow

Status of oxygen delivery is tightly related to organ oxygen consumption and utilization, and the monitoring of oxygen delivery is crucial important in many critical situations (28-32). Splanchnic blood circulation should improve after liver transplantation, because removing of the cirrhotic liver decreases the hepatic resistance and portal hypertension. However, surgical modifications of the hepatic artery and portal, and hepatic veins, might cause new resistance of the splanchnic blood flow and make an abnormal hepatic blood circulation. Moreover, the liver graft tissue edema as seen in PNF produces increased graft resistance. Impaired blood supply of the liver graft causes decrease of oxygen delivery and utilization in the liver graft. In our experimental study, intra-operative hepatic arterial flow (HAF) after reperfusion in low oxygen consumption recipients tended to be greater than that in high oxygen consumption recipients, and intra-operative portal venous flow was similar

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in both groups (14). We concluded inadequate HAF might increase oxygen utilization of the liver grafts and lead to poor graft function and outcome from results of our previous experimental study. We previously reported that intra-hepatic arterial perfusion of adenosine restores the hepatic arterial buffer response (33-36), increase HAF in a clinical pilot study (37), and improves survival in a porcine model of small-for-size syndrome (13, 38, 39). Intra-hepatic arterial perfusion of adenosine may be one of the possible therapeutic strategies for decreasing oxygen consumption of the liver graft, and improving graft function after liver transplantation.

Oxygen consumption of the whole body during and after reperfusion

Systemic oxygen consumption has also been reported as an early predictors of PNF and GDF (8, 17, 28, 40-42). In contrast, high oxygen consumption of the liver grafts after reperfusion was associated with a poor outcome after liver transplantation in the retrospective clinical study (15) and our experimental study (14), systemic oxygen consumption after reperfusion in patients with successful liver transplantation was higher than systemic oxygen consumption in those with PNF and GDF. In non-transplant patients

with severe liver damage, such as ESLD and after major hepatectomy, hemodynamic changes and a decrease in oxygen consumption of the liver and systemic organs have been reported (41, 43-45). During an anhepatic phase, cross-clamp results in dramatic alteration of the hemodynamics and oxygen transport (46). The decreases of the cellular oxygen pressure and the oxygen delivery may lead decrease of the oxygen consumption in the liver graft and other organs. In addition, the severe hepatic dysfunction due to post-transplant graft failure may lead changes in systemic hemodynamics and metabolism, including oxygen consumption, which is similar to the changes seen in non-transplant patients with severe liver injury.

Several investigators concluded that the decrease in systemic oxygen consumption reflects the decrease in the metabolism and the reduced hepatic arterial blood flow in the failed liver grafts (40, 47), because the value of cardiac index, arterial pressure, and oxygen delivery were similar in the both patients with better and poor prognosis after liver transplantation in contrast to oxygen consumption. However, actual oxygen consumption of the liver graft after reperfusion is lower in patients with better liver graft condition as compared to those with PNF or

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GDF (14, 15). Therefore, we think that systemic oxygen consumption includes and more reflects oxygen consumption in the other organs than that in the liver graft, and oxygen consumption of the liver graft probably more reflects the status of the liver graft after reperfusion.

Conclusions and future aspects

Early detection of surgical and metabolic abnormality of the liver graft may allow for diagnosis and correction of the abnormality before the damage of the liver graft becomes irreversible. It is very difficult to establish the normal range of the oxygen consumption of the liver graft after reperfusion, because the oxygen consumption of the liver graft may be composed of various factors, including the donor condition, status of the graft preservation, cold ischemia time, and hepatic blood flow after reperfusion (48-50). Monitoring and assess the changes in metabolism of the liver graft including oxygen consumption may help to establish the normal range, and understanding of the mean of oxygen consumption of the liver graft after reperfusion.

In conclusions, lower oxygen consumption of the liver graft after reperfusion is associated with better graft function, and oxygen consumption of the liver graft is one of possible predictors of therapeutic outcome after liver transplantation.

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