

The role of trimetazidine in lung transplantation

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Abstract

Lung transplantation is an established therapeutic procedure for end-stage pulmonary disease. Ischaemia-reperfusion (I/R) injury after lung transplantation continues to present a potentially life-threatening problem and has been the focus of much research during the last 20 years. Despite improved strategies, as many as 10-15% of the transplanted pulmonary allografts might experience severe graft dysfunction immediately after implantation. Trimetazidine (TMZ) has been shown to be an effective anti-ischaemic drug in cultured cells, isolated organs and animal models of ischaemia. Although it has been reported that it affects both metabolic functions and ion permeabilities in mitochondria, its mechanism of action is not fully understood. The preventive effect of TMZ in post-transplant lung I/R injury is observed in a single lung transplant model in rats as well. Our experimental experience is compared with the literature.

Key words: lung transplantation, reperfusion injury, trimetazidine.

Introduction

Over the last 20 years lung transplantation has become a therapeutic option for selected patients suffering from various types of end-stage lung disease refractory to medical treatment. This type of surgical treatment gained increasing success with better early and late survival rates [1]. However, lung transplantation is still hampered by persisting problems such as donor organ shortage, early graft dysfunction (ischaemia-reperfusion injury), late graft dysfunction (bronchiolitis obliterans syndrome), and morbidity related to long-term immunosuppression [2].

Pulmonary ischaemia-reperfusion injury is characterized by increased pulmonary vascular resistance, poor oxygenation, worsened compliance, and increased capillary permeability leading to oedema formation. This clinical syndrome usually occurs within 72 hours of surgery. The ischaemic insult to the lung results in cytokine production and increased expression of adhesion molecules by hypoxic lung cells. The injury cascade is mediated mostly by neutrophil-endothelial adherence and subsequent neutrophil-mediated organ injury. Activated neutrophils secrete reactive oxygen species and proteolytic enzymes which results in structural and functional injury of the lung parenchyma. Several studies have shown that agents such as prostaglandins; the oxygen free radical scavengers superoxide dismutase, catalase, glutathione, allopurinol, dimethylthiourea, lazaroids and melatonin; aprotinin; platelet factor antagonists; and the angiotensin-

converting enzyme inhibitor captopril, are effective in protecting the lung against ischaemia-reperfusion injury [3-7].

Mechanism of action

In anaerobic metabolism, instead of 38 mol of ATP, only 2 mol is produced, representing a 94% reduction of energy production for essential cellular processes. Failure of ion pumping with rapid loss of electrochemical gradients results in translocation of ions, notably Ca^{+2} . Free Ca^{+2} rapidly accumulates and triggers many adverse effects including phospholipase activation [8, 9]. Another consequence of failed ion pumping is that intracellular Na^{+} accumulates and K^{+} is lost to the extracellular fluid. Cell swelling and interstitial fluid accumulation produce oedema and increase diffusion distances, further compromising oxygen and substrate delivery [8]. The production of oxygen-derived free radicals is considerably increased during tissue ischaemia due to dissociation of oxidative phosphorylation, which results in univalent reduction of oxygen, catabolism of ATP into hypoxanthine and uric acid, and infiltration of damaged tissues by PMN and phagocytosis [9].

Trimetazidine (1-(2,3,4-trimethoxybenzyl) piperazine dihydrochloride) (TMZ) is an anti-ischaemic agent known to improve exercise tolerance and cardiac function in patients with ischaemic heart disease [9]. Its anti-ischaemic effect has been experimentally assessed in various models including cell cultures, isolated and perfused organs, and in-vivo [9-15].

Various experimental studies have shown that trimetazidine preserves the intracellular concentrations of ATP and inhibits the extracellular leakage of potassium during cellular ischaemia. Additionally, it prevents excessive release of free radicals, which are particularly toxic to phospholipid membranes and are responsible for both the fall in the intracellular ATP concentration and the extracellular leakage of potassium [16]. It also reduces intracellular accumulation of sodium and calcium [16]. Its mechanism of action is not fully understood but data indicate that it affects both metabolic functions and ion permeabilities in mitochondria [17]. It has been shown that TMZ restores ATP synthesis in isolated mitochondria previously exposed to Ca^{+2} overload [18]. The formation of a giant pore, called a mitochondrial transition pore, might be involved, allowing the exchange of small solutes (<1500 Da) across the inner membrane [19]. It has been stated that TMZ acts on mitochondrial function in at least two different ways, as a mitochondrial Ca^{+2} releaser when the giant pore is closed, and by inducing its closure when it is open [17].

Experimental experience in lung transplantation

In a recent study from our laboratory we determined the protective effect of TMZ on post-

transplant lung ischaemia-reperfusion injury which was assessed by blood oxygenation, peak airway pressure, lung tissue ATP content, lipid peroxidation and neutrophil accumulation [20]. In that study, using a rat single-lung transplant model, we showed that donor and recipient treatment with TMZ, 5 mg/kg intravenous 10 min before harvest and reperfusion, resulted in significantly improved graft function. Energy status was protected and lipid peroxidation was reduced after 18 hours of cold storage and 2 hours of reperfusion. A marked decrease in lung ATP level was observed in the ischaemic control, confirming that this index of function is rapidly and seriously affected by ischaemia-reperfusion. Lung grafts of animals treated with TMZ and stored for 18 hours showed ATP contents similar to lung grafts without storage. We assume that the higher ATP content is not only the result of better protected tissue by lesser ischaemia reperfusion injury but a direct effect of ATP utilization itself. Although TMZ is not known to have a direct effect on neutrophils, the number of infiltrating neutrophils was significantly lower in TMZ treated rabbits in a myocardial ischaemia-reperfusion model [21]. Additionally, in a rat intestinal ischaemia-reperfusion injury model, decreased MPO activity after TMZ therapy has been reported [22]. In contrast, in our study we were not able to show a difference in MPO activity among our study groups.

We have also shown that lipid peroxidation of the TMZ treated group was significantly less than that of the non-treated ischaemic control group. This reduction in MDA levels is consistent with the powerful antioxidant effect of TMZ. Significant reduction of lipid peroxidation has also been reported by other investigators [22-25].

In another study we evaluated the protective effect of recipient treatment alone with TMZ on post-transplant lung ischaemia-reperfusion injury [26]. We compared the effects of recipient treatment alone with donor treatment (5 mg/kg intravenous) and TMZ added to flush solution alone. We found that recipient treatment with TMZ resulted in significantly improved graft function, protection of the energy status and reduced lipid peroxidation after 18 hours of cold storage and 2 hours of reperfusion.

Recipient treatment with TMZ and addition of the drug into the flush and preservation solution significantly preserved the lung ATP content compared to other study groups. We have also shown that recipient treatment with TMZ decreased the lipid peroxidation significantly, which reflected the dominant antioxidative effect of this regimen compared to only donor treatment or only adding this drug into the flush solution.

We were not able to show a difference of MPO activity, an index of neutrophil accumulation, among the study groups.

In conclusions the problem of experimental studies concerning ischaemia-reperfusion injury is to transfer these agents into clinical lung transplantation. However, TMZ has been used by cardiologists for ischaemic heart disease for many years without any side effects [27]. Therefore, the transfer of TMZ to clinical lung transplantation might be easier. In conclusion, TMZ may be an important adjunct to prolong ischaemic time safely and prevent ischaemia-reperfusion injury after lung transplantation.

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