Acta Med. Nagasaki 35 : 225−227

Graft Function Associated with Oxygen Free Radicals Immediately after Transplantation

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Received for publication, June 25, 1990

ABSTRACT : Free radical formation on lung allografts was estimated in macrophages of the bronchoalveolar space, and monocytes of the pulmonary artery and pulmonary vein in terms of the different immunosuppressive drugs of cyclosporine and azathioprine. It is elucidated that free radical formation is facilitated by macrophages of the bronchoalveolar space.

It is of interest to emphasize that cyclosporine plays a cytoprotective role in prevention of free radical formation.

INTRODUCTION

Since cyclosporine (CsA), a hydrophobic, fungal endecapetide of novel chemical structure, has been introduced over the past few years as a potent immunosuppressive agent in the field of various organ allotransplantations, the results of organ allotransplantations were improved to get the long survivors with satisfactory graft function.

The purpose of this study is to clarify the reasons for improving the results of lung allografts by using cyclosporine and to elucidate the validity of the use of cyclosporine.

MATERIALS AND METHODS

Mongrel dogs were used for this study. A pair of dogs with almost the same body weight were selected at random. The dogs were given twenty-five mg/kg of nembutal sodium intravenously, endotracheally intubated and connected with a Havard respirator (10ml/kg in tidal volume and 16/min in respiratory cycle).

Each dog underwent thoractomy at the 5th intercostal space. The donor lung was prepared to pose the atrial cuff, where the pulmonary veins anchored.

A lung graft was orthotopically transplanted in the following order, first suturing the left atrial wall, anastomosing the bronchial stumps and then the left main pulmonary artery edges.

The dogs that underwent left lung allotransplantation were divided into two groups. One received 20mg/kg/day of cyclosporine every day group, the other of 5 dogs 5mg/kg/day of azathioprine every day.

Oxygen free radicals were measured as a mean values 6 hours following transplation as compared with those prior to transplantation by using DCFHDH according to Bass' Method[1]. Blood samples from the pulmonary artery and vein were collected from the catheters intraoperatively introduced to the pulmonary artery and vein. At the same time as drawing blood samples from each catheter, bronchial alveolar lavage (BAL) was made with 100ml saline, pumping 3 times to allow the collecting rate of over 70 per cent.

RESULTS

Oxygen free radical formation in macrophages was compared in accordance with the immunosuppressive agents of cyclosporine (Group I) and azathioprin (Group II) as shown in **Fig. 1.**

The generation of oxygen free radicals after transplactation in BALF was enhanced as compared to that prior to transplatntation. Oxygen radicals in Group II was inhibited rather than that in Group I, reflecting the action of cyclosporine.

Meanwhile oxygen free radical formation in monocytes of the pulmonary artery after transplantation did not vary as compared with that before transplantation and was almost the same between Goup I and II as shown in **Fig. 2.**

On the other hand, oxygen free radical formation in monocytes of the pulmonary vein following transplantion was apparently and suppressed as compared with that before and it was prominent in Group I as shown in **Fig. 3.**

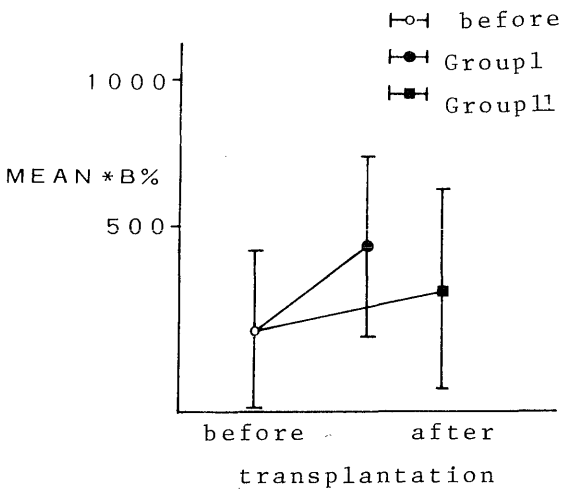

Fig. 1. O_2 production in macrophages of BALF

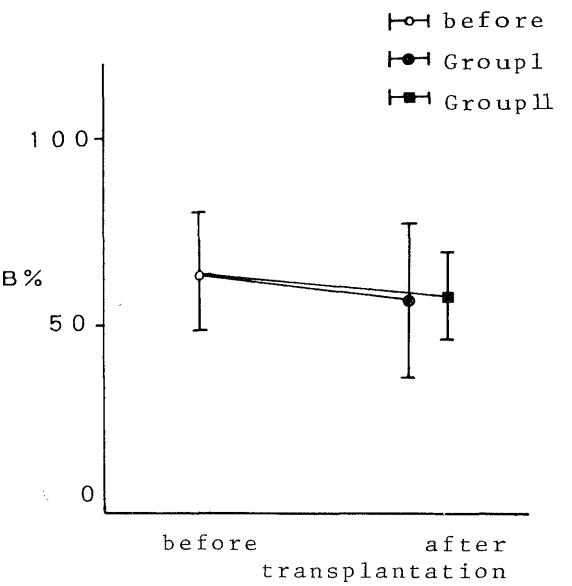

Fig. 2. O_2 production in neutrophiles of PA

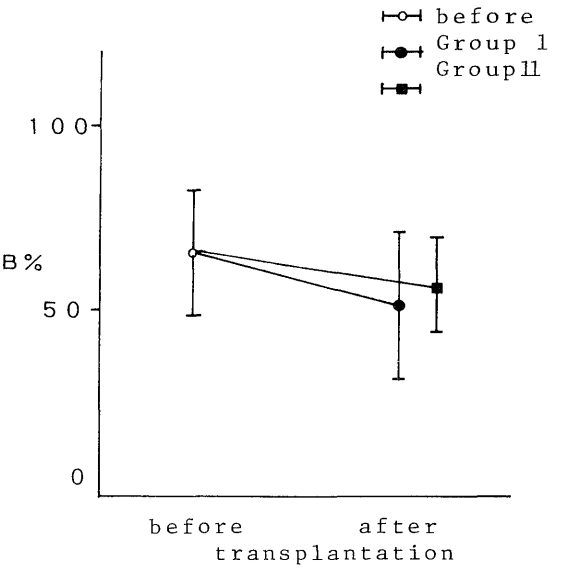

Fig. 3. O_2 production in neutrophiles of PV

DISCUSSION

A graft function is mainly associated with a shortage of preservation time and warming ischemic time. Furthermore, it is well known that reperfusion injury is one of the main causes to lead to a failure of graft function. The present investigation focuses on the injury to a graft at the time of restarting blood circulation[2]. The blood urgently perfused into cells at ischemic state makes it possible to facilitate cell membrane permeability[3]. Eventually it is accepted that rapid influx of calcium into the cell is induced[4]. Recent studies indicate that oxygen

free radical plays an important role in the injury associated with ischemia[3,5~7].

Rapid generation of free radical may cause reoxygenation of lipoprotain which is composing the cell membrane. It mainly occurs in the endothelium of the vessels. As hyperoxygenated lipoprotein enhances the action of thromboxantine, so this evolves platelet-aggeregation in the vessel and ensuing vasospasm. Consequently ischemic damage with subsequent recirculation will be aggravated.

The lung is mostly susceptible to oxygen toxicity because of direct exposure to inspired oxygen and large volume of the blood which is one of the major cause of free radical farmation arising from monocytes.

This study indicates that cyclosporine itself prevents free radical formation in transplanted lung allografts.

It is stressed that cyclosporine provides a great benefit to keep a lung graft from the injury associated with oxygen free radicals. And also this study clarified that cyclosporine plays a cytoprotective role in suppression of oxygen free radicals formation in transplanted lung allografts, and helps a graft to minimize reperfusion injury.

ACKNOWLEDGEMENT

The authors appreciate for kindness of animnal supply from the Labolatory Animal Center for Biomedical Research of Nagasaki University School of Medicine.

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