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Double and Sequential Lung Lobe Transplantation

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SUMMARY : To maintain an adequate pulmonary function for alleviating the patients with respiratory distress by means of lung homotransplantation, this study was aimed as to whether improved surgical technique of lung transplantation could overcome immunologic handicaps by double or sequential lobe transplantations.

In double lobe transplantation from indifferent two donors, this study drew the fact that when one lobe had been rejected, the other also became aggravated almost at the same time.

On the other hand, in sequential lobe transplantation, the second lung grafts became aggravated in far shorter period after one lobe had been rejected. In conclusion, as to the reasons for early rejection of graft in double or sequential lobe transplantations it appears that immunologic hypersensitivity after a rejection of the first graft may play an important role in rejecting second double or sequential lung lobe grafts.

INTRODUCTION

Technique for lung transplantation has been established with the use of left atrial cuff anastomosis for the pulmonary vein by Metras¹⁾. However, since DAVIS²⁾ reported in 1952 that a key of successful lung allotransplantation should be related to the immune response, it has become concentrated on solving the problems concerning rejection by the immune reaction³⁾⁴⁾.

Much has been reported concerning the function of transplanted lungs.

First of all, denervation is a great concern. It has been reported that the transplanted lung function is mainly affected as a presence of vasospasm caused by the ensuing denervation and vascular stenosis in anastomotic sites to some extent⁵⁾⁶⁾.

The previous work^{7)~13)} corroborate the concept of the possibility of life-support by unilateral transplanted lung alone.

Fresh light has been shed upon relief of vari-

ous states of respiratory distress by clinical application of lung transplantation. However, the wide clinical use of lung transplantation necessitates overcoming serious problems on procurement of the donor lung and potent suppression of the immune response to grafts.

The purpose of this study is to search the possibility as to whether double lobe transplantation is able to keep pulmonary function properly, if one lobe is rejected, the other would functionally compensate for the rejected one.

MATERIAL AND METHOD

1) Transplantation procedure

a) Double lobe transplantation

Mongrel dogs, weighing 10 to 15 kg in body-weight, were selected at random for recipient and two donors from whom upper and lower lobes were provided.

Each dog was anesthetized with 25 mg/kg of pentobarbital sodium, intubated intratracheally and connected with the respirator (HARVARD).

Left thoracotomy was made at the same time in the selected three dogs in whom the body weight were almost equal. In recipient, the left lung was removed and in the two donors, the lower and the upper lobes were separately procured after heparization (1 mg/kg of heparin intravenously given). Technique of transplantation is almost the same as that of left lung transplantation except for the use of fine atraumatic needle for vascular and bronchial anastomoses.

The pulmonary vein was first anastomosed with 7-0 proline and the bronchus with 4-0 dextron, finally the pulmonary artery was done with 6-0 proline respectively. All these anastomoses were made with the use of interrupted sutures. Immediately after completion of lobe transplantation, the transplanted lung had become well aerated and reddish, reflecting good ventilation and perfusion. The transplanted lobes with poor aeration and perfusion by stenosis at anastomotic sites were excluded from this study.

b) Sequential lung transplantation

Mongrel dogs, weighing 10 ~ 15 kg, were at random selected as a donor and a recipient respectively. These were matched in body weight as far as possible. Left thoracotomy was performed in both dogs at the same time. Left upper lobes were removed and these were transplanted on the other side.

The anastomosis techniques of the bronchus, the pulmonary artery and vein were quite similar to those of double lobe transplantation. Poorly aerated and perfused lobes were excluded from this study.

2) Evaluation of the transplanted lobe function

The degrees of aeration of the transplanted lobes on chest xp were evaluated by the grade of radiopacity on daily chest xp as follows. grade I: it shows less aeration but still visible pulmonary marking. grade II: it becomes dark and no visible pulmonary marking with localized consolidation. grade III: it shows increased radiopacity with underdefined margin.

The grades of blood perfusion in the transplanted lobes were also analyzed by staining on ^{131}I -MAA scintigram, which was made by using intravenous injection of 155mc ^{131}I -MAA.

The degrees of blood perfusion were graded as follows: GI: homogenous and no different staining from the intact lobe, GII: poorly and unhomogenous staining, GIII: apparently poorly or scattering staining respectively.

3) Immune adherence test (IA)

2×10^6 target cells were prepared from the mesenterial or hilar nodes. Antiserum was used by dilution to $2 \times$ to $4 \times$ with glucose-KGVB. Complement was the commercial product (Kyokuto Pharma. Co.) of 150 to 180 CH₅₀/ml and also human O type blood was prepared from those who were previously tested to be highly sensitive to the IA response^{10) 14)}.

In this study, IA test was made in the condition as described by HONDA²⁷⁾.

4) Ia-positive cell in bronchoalveolar lavage (BAL)

BAL was prepared from the transplanted lobes at sacrifice. Expression of Ia antigens in the monocytes of BAL was made by using OK-Ia₁ antigen¹⁵⁾ (Ortho-mune) in contrast with IgG of mouse.

Monocytes in BAL were analyzed on the cytochrome by using spectrm III.

The Ia positive rates were calculated. When the Ia positive rate exceeded 30%, it was realized that lung grafts would fall to rejection rather than infection. The staining grade of Ia cells were microscopically compared between lung grafts. The greater the staining grade of Ia cells, the easier the discrimination between rejection and infection in non-functioning lung grafts.

RESULT

Survival period

Survival period following double lobe transplantation ranged from 6 to 16 days with an average of 10.8. It was superior to that of the control (7.0 days) that was received unilateral lung homotransplantation without any immunosuppressive drugs. Functioning time interval of the transplanted lobes.

The function of the transplanted lobes were evaluated by means of chest xp and RI scintigram. It is assumed that radiopacity on chest xp indicates ventilatory failure and accumulation defect on lung scintigram implied pulmonary

circulation failure, in particular, in the pulmonary vascular beds.

At double lobe transplantation, functioning time interval of these lobes were shown in Fig. 1. It was shown that function of both lobes kept during almost the same period if ventilatory function of one lobe had become aggravated, that of the other lobe also would have lost within at least three days.

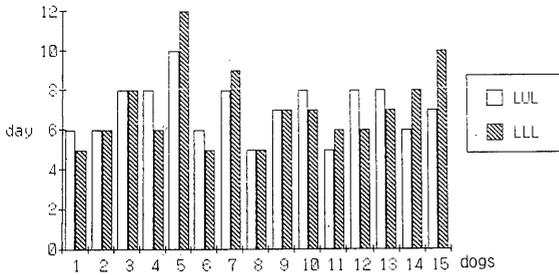


Fig. 1. function time of transplanted lobes evaluated by radiopacity on chest xp

On the other hand, as for perfusion on the scintigram of the transplanted lobes, the results were indicated in Fig. 2. It was shown that both the lobes lost their function at the same time and failed to maintain proper pulmonary function so as to compensate for loss of the function of the rejected one lobe by the other lobe.

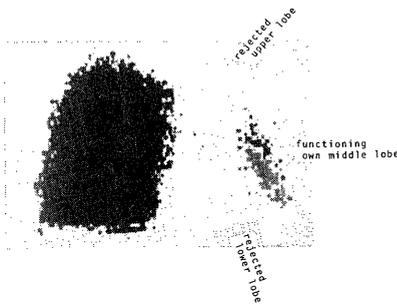


Fig. 2. function time of transplanted lobes evaluated by scintigram

Assessment of immune response regarding feasibility of sequestial lobe transplantation to maintain pulmonary function

Fig. 3 showed changes in the IA titer that presented antigen-antibody complex following left lung homotransplantation. The IA levels were gradually increased with time. Even in re-

moving the transplanted lung graft, those were still remaining high until at least 10 days, thereafter those were gradually reduced to the prior levels in a 15 days or more duration.

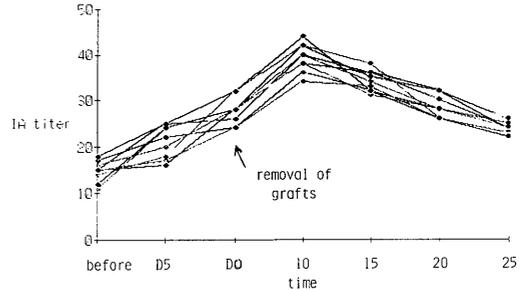


Fig. 3. Changes in IA-titer with time following lung transplantation and removal of lung grafts

Sequential lobe transplantation after removal of the lobe that acute rejection occurred had the IA titer increased as shown in Fig. 4. An increase in the IA-titer in a short period was much more augmented in sequential lobe transplantation rather than in double lobe transplantation. The functioning time intervals of the lobes sequentially transplanted were compared between the first and the second grafts.

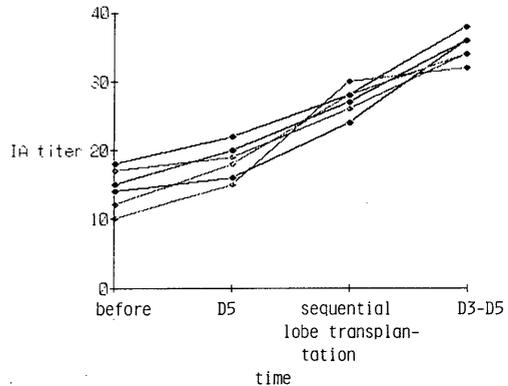


Fig. 4. Changes in IA-titer in accordance with sequential lobe transplantation

The functioning time was regarded as the time intervals from performing transplantation to appearing grade II radiopacity on chest film daily taken as shown in Fig. 5. In this series, sequential lobe transplantation technique did not frequently succeed because of fragil vessel wall and bronchial stump at the time of

transplantation for the second graft. The six grafts with satisfactory transplantation technique were subjected to this study. The functioning time of the second graft was about half as long as that of the first one.

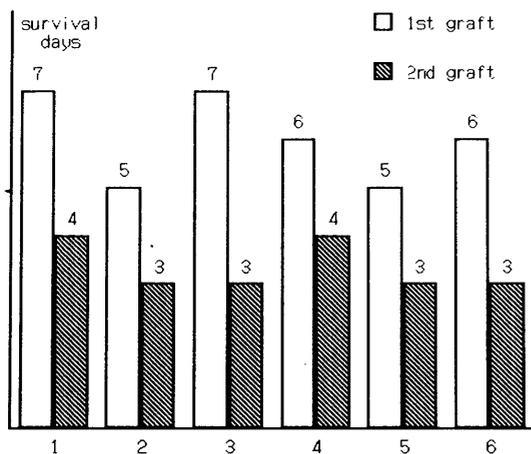


Fig. 5. Functioning time of sequentially transplanted lobes between the 1st and the 2nd grafts before appearing grade II radiopacity on chest XP.

The function-losing lobes following double and sequential lobe transplantation were histologically examined. The lobes that demonstrated histologic finding of inflammation by bronchial stenosis at anastomosis were excluded from this study. The key findings in the function-losing lobes were of perivascular and peribronchial cuffing as shown in Fig. 6.

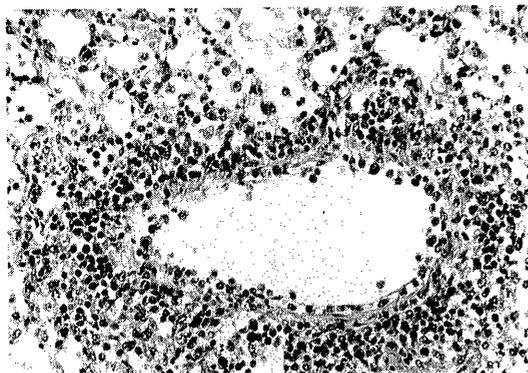


Fig. 6. Histologic pattern of perivascular cuffing which represents the immune response

Furthermore, it was confirmed by means of staining Ia positive cell as to whether failure of transplanted lobe function was based on acute rejection or not. Ia-positive cells were presented in most of the transplanted lobe at the time of losing their function, as shown in Fig. 7. However, stained Ia-positive cells were distributed with varying variety, some were scattering, others were dense. It did not correlate with functioning time.

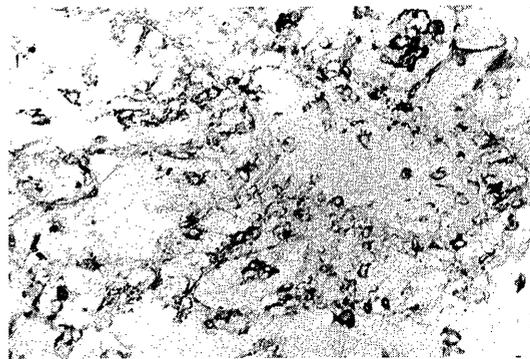


Fig. 7. Ia-positive cell staining

DISCUSSION

Since lung homotransplantation was clinically used in 1963¹⁷⁾, clinical cases have been reported in Japan. However, the outcome was not satisfied yet including the cases experienced in all over the world.

It is attributed to direct communication by air way by which the lung is susceptible to infection and rich containing lymphocytes of the lung where the immune response is strengthened. Surgical technique regarding lung transplantation is already established enough to carry out with safety in clinical use. To develop clinical application of lung transplantation, there are many troubles to solve, how to procure a donor lung, preserve a donor lung for a long time and suppress the immune response effectively.

It has been confirmed that lung transplantation is effective in overcoming functional defect to alleviate respiratory distress in spite of influence of denervation^{18) 19)} on the trans-

planted lungs which cause vasospasm and absence of Hering-Breuer-reflex. However, it is also well known that bilateral lung transplantation enables the animals to survive^{9)~13)}.

Since the potent immunosuppressive drug of cyclosporine A was developed, the results to have the survival period prolonged following organ transplantations have been much more improved. However, it was not completely satisfactory because of side effects such as nephrotoxicity and hepatotoxicity by using for a long time.

At present, there is nothing to compensate for maintaining function by means of repeated transplantation with use of improved technique in order to enhance the effectiveness of organ transplantation. It, however, was defined that double lobe or sequential lobe transplantation could not continue to maintain pulmonary function properly.

Cross immunologic reaction and immunologic memory to the other lobe is a great barrier to expect the function of not yet affected lobes.

Even the immunologically less affected one lobe become susceptible to acute rejection very soon when the other lobe was rejected immunologically. The functioning loss of the other lobe affected was attributed to immunologic response in spite of some part of infection originated from the rejected lobe. It was confirmed to some extent by changes in IA titer in serum and a presence of Ia-positive cell. This facts seemed to be derived from immunologic sensitization of the recipient in whom the graft of one lobe as rejected. Needless to say, when histocompatibility could be completely matched between donor lobes and recipient, the function of transplanted lobes should be expected to maintain satisfactorily. In this study it was defined that the function of one lobe become deteriorated in a short period of 2 or 3 days after the other lobe would be fallen in rejection.

As a result, it implied that improved technique regarding organ transplantations could not overcome the immunologic barrier even in performing double and/or sequential lobe transplantation. It is well known that graft rejection is attributable to damage to the endothelium of graft vessels by humoral antibody where platelet adheres easily to form thrombus

that causes interruption of blood flow to result in organ destruction²³⁾²⁴⁾.

ROCHER *et al.*²⁵⁾ reported that the patients who received prior renal transplants could scarcely have immediate graft function and required prolonged post-transplant dialysis. It suggests that prior transplants affect the second graft survival and its function. COOPER²⁶⁾ also reported that non-functioning grafts did not represent a special hazard to the recipient as long as minimal dosis of anticoagulants were used. In fact, if anticoagulants were used for prevention from thrombus formation in rejected grafts, it might help not to cause the second grafts rejection to some extent.

It is of interest to document from the results of this study that sensitization of the recipients evolved by prior transplants may play a key role in rejecting double or sequential grafts transplanted.

Surgeon should be aware of a barrier of a great immunologic problem with all far improved surgical technique.

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