Hemodynamic Response in Lung Transplantation as a Model of Total Lung Denervation

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FUJIMURA, S., KONDO, T., SOHARA, Y., YAMAUCHI, A., KAWAKAMI, M. and NAKADA, T. Hemodynamic Response in Lung Transplantation as a Model of Total Lung Denervation. Tohoku J. exp. Med., 1979, 127 (1), 71-79 — As a means to approach the question regarding the exact effect of lung denervation, hemodynamic studies were carried out in 49 dogs which had undergone either unilateral or bilateral lung autotransplantation. In 14 chronically survived animals of 20 with unilateral lung reimplant, unilateral pulmonary artery occlusion test was carried out. In the 29 with either one-stage or two-stage bilateral lung reimplants, serial hemodynamic studies were performed along with histologic examinations of the transplanted lung at autopsy. In the chronic survivors with the bilateral transplants, rapid and continuing infusion of 3,000 ml of plasma expander was performed within 10 min through intratraial catheter and various hemodynamic values were measured simultaneously. The animals with one-stage bilateral lung reimplants showed a varying degree of pulmonary edema in both lungs in the early postoperative period, and some of them succumbed to respiratory failure with a gradual decease in PaO₂ but the other animals recovered from these pathologic states within 10 postoperative days and survived chronically. Hemodynamics of those long-term survivors showed high pulmonary vascular resistance early after surgery but this value returned nearly to the preoperative level in a distant postoperative period. On occlusion of contralateral pulmonary artery in unilateral lung reimplantation an increase in pulmonary arterial pressure was invariably observed. Their relationship was steep and almost linear against a given increment of cardiac output when cardiac output vs. pulmonary arterial pressure was plotted in each animal. These facts suggest that transplant differs from the normal lung in tolerance of the vasculature in an event of an increase in pulmonary blood flow. In the plasma expander infusion test, the dog with bilateral lung autotransplants demonstrated that pulmonary arterial pressure showed a parallel and linear increase with an increase in cardiac output until lung transplant became edematous, while in the control animal total pulmonary vascular resistance decreased with an increment in pulmonary arterial pressure during the course of increasing cardiac output. It can be interpreted from these results that changes have occurred in mechanism of pulmonary circulation of the transplant; the transplanted lungs cannot vasodilate totally with an increase in blood flow.

lung transplantation; lung denervation; pulmonary circulation

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Pulmonary transplantation has been established as technically feasible and capable of sustaining life (Alican et al. 1971; Derom et al. 1971; Fujimura et al. 1972; Kondo et al. 1972). However, there have been only less than 40 clinical cases of lung transplantation performed in the world (Hardy 1976), because there have been many critical and basic problems preventing its clinical application. Among them the acute and chronic physiologic and pathologic changes noted after surgery have not been clearly defined in relation to their etiology. Studies of autotransplants have been undertaken by some investigators as a means of delineating those effects which are attendant to the procedures of transplantation and those which results from rejection.

Previous studies (Fujimura et al. 1972a,b, 1973, 1977) suggested that hemodynamic alterations after surgery were due to denervation, anatomic status of the vascular anastomoses and/or structural changes occurring at the alveolar-capillary level.

The purpose of the present studies is to determine the role of lung denervation in changes in pulmonary hemodynamics in view of the results obtained from unilateral pulmonary occlusion test in animals with unilateral lung autotransplantation and from acute and chronic hemodynamic studies in bilateral lung auto- and allotransplantation.

**Materials and Methods**

*Lung transplantation*

All experiments were carried out in mongrel dogs weighing 10-32 kg, under general, intravenous anesthesia (sodium pentobarbital, 25 mg/kg). The animals were intubated and maintained on a Bird (Mark 8) or a Harvard respirator. Forty-nine dogs used in this study were divided into three groups according to operative procedures.

*Unilateral lung autotransplantation (20 dogs).* This was performed on the left or right side. For left lung reimplantation, the pulmonary veins were transected in continuity with a cuff of left atrium. The right pulmonary veins were divided separately at the orifices. The excised lungs were perfused with cold heparinized 6% dextran 70 solution through the pulmonary artery. The venous and pulmonary arterial anastomoses were completed with continuous 4-0 Tefdek suture technique. The bronchus was reconstructed with continuous CO-chromic catgut. Ischemic time varied from 40 to 70 min. Lung function of chronic survivors were studied by means of contralateral pulmonary occlusion test within 7 weeks after lung autotransplantation.

*One-stage bilateral lung autotransplantation (20 dogs).* This was performed in 20 animals by the previously described technique (Fujimura et al. 1972a). Right lung reimplantation was carried out first. Perfusion was carried out in both lungs as in the unilateral experiments. Heparinized Ringer’s lactate solution, heparinized 6% dextran 70 in normal saline, heparinized 5% dextran 40 (Rheomacrodex) or modified Collins solution was used in this group. Methylprednisolone (250 mg/liter) was added to the latter two solutions and pH of solutions was adjusted to pH 7.40. Right lung ischemia was 50-80 min and left lung ischemia was 50-60 min.

*Two-stage bilateral lung autotransplantation (9 dogs).* Thirteen days to 6 months following the unilateral lung reimplantation, the contralateral lung was removed, perfused and immediately replaced. The longer was the interval from initial operations to the second, the more difficult was the second surgery.

All animals were treated with intramuscular penicillin or carbenicillin and streptomycin for five days after the surgery.
Measurements

Of 20 animals 14 survived the left lung reimplantation and underwent unilateral pulmonary artery occlusion test according to the methods described in the previous paper (Kawakami 1967). After intravenous general anesthesia with pentobarbital sodium, respiration was spontaneous through the respiratory valve, and a double lumen cardiac catheter with a balloon at the distal opening was indwelled in the pulmonary artery of the contralateral lung. The contralateral pulmonary artery was occluded by the inflated balloon. Pulmonary artery pressure was measured continuously and cardiac output was determined on the basis of Fick’s principle, and the oxygen uptake was measured from collected expired gas.

On animals which survived bilateral lung reimplantation, various preoperative and postoperative examinations were made. They included serial arterial blood gas analysis, frequent chest x-ray examination and serial right heart catheterization. In the latter experiment, a flow-directed balloon tip catheter was used and cardiac output was determined in duplicate by dye-dilution techniques, with indocyanine green injected into pulmonary artery and sampling from the aorta. The techniques were described previously (Fujimura et al. 1972a).

In order to define changes of pulmonary vascular beds in response to abrupt alteration of pulmonary blood flow in denervated lung, 3,000 ml of plasma expander was infused rapidly within 10 min via intraatrial catheter (14 F cournard cardiac catheter).

Pulmonary artery pressure, aortic pressure and cardiac output were measured simultaneously. Cardiac output was measured with the use of indocyanine green ear piece dye-dilution techniques. This experimental protocol is illustrated in Fig. 1.

All animals which died in the postoperative period underwent histologic examinations; the lung specimens obtained from those animals were fixed in 10% neutral formalin and embedded in paraffin. Sections were stained with hematoxylin and eosin for light microscopy.

Fig. 1. Scheme of rapid intravenous infusion experiments in bilateral lung reimplantation. 
PA, pulmonary artery; VCI, inferior vena cava; AO, aorta; PPA, pulmonary arterial pressure; PAO, aortic pressure; CO, cardiac output.
RESULTS

Results of lung reimplantation and its histologic findings

Of 20 animals which underwent unilateral lung reimplantation 6 died of pulmonary venous thrombosis within a week postoperatively, in other words, they succumbed to technical failures. In the simultaneous bilateral lung autotransplantation, however, pulmonary congestion and/or edema albeit patent and smooth pulmonary vascular anastomoses were one of the most prominent findings in early postoperative period. The survival rate is summarized in Fig. 2. Of 20 animals with one-stage bilateral lung reimplants 17 died of pulmonary edema within 10 days postoperatively. They showed gradual but persistent decrease in PaO₂ until death. After 10 days postoperatively some long-term survivors showed an improvement in both arterial blood gas analysis and hemodynamic examinations with the value of approximately preoperative levels.

![Fig. 2](image)

Fig. 2. Survival time after one-stage bilateral lung autotransplantation. Of 20 animals with bilateral lung reimplants 17 died of pulmonary edema within 10 days postoperatively.

![Fig. 3](image)

Fig. 3. Changes in cardiac output and pulmonary arterial pressure immediately after one-stage bilateral lung autotransplantation. Pulmonary arterial pressure tended to be increased despite decreased cardiac output. ○, control; ●, one stage bilateral lung replantation.

There were no consistent histologic abnormalities in the lung specimens obtained from chronic survivors of one-stage bilateral lung reimplantation. Histologic findings of pulmonary emboli, pneumonitis, atelectasis, perivascular collections of mononuclear cells, and bronchial muscle hypertrophy were present in limited areas but they were negligible in their degree.

Of 9 dogs with two-stage bilateral lung autotransplant 3 animals survived chronically, the other dogs died of pulmonary edema and/or pneumonia within one week postoperatively.

Hemodynamic characteristics of the lung autotransplants in early postoperative period

For this purpose, measurements for hemodynamics must be done either on the animals with ligation of the contralateral pulmonary artery immediately after
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unilateral lung reimplantation or on those with the both lungs replanted in one-stage.

Hemodynamically, the latter showed various degrees of impairment in function immediately after surgery and some cases showed critical values; pulmonary arterial pressure tended to be increased despite decreased cardiac output. Therefore, calculated pulmonary vascular resistance was increased (Fig. 3). However, these values were within normal range. Six to seven weeks after operation the impaired hemodynamic values returned to near the preoperative values. The results of follow-up studies of hemodynamic alterations after bilateral lung reimplantation have been described elsewhere (Fujimura et al. 1972b).

Hemodynamic characteristics of the lung autotransplants in chronic survivors in view of unilateral pulmonary artery occlusion test

On complete occlusion of the contralateral pulmonary artery, total cardiac output necessarily flows through the pulmonary artery of the lung transplant. In this situation, there was a consistent increase in pulmonary arterial pressure. The cardiac output tended to decrease, with a considerable rise in calculated total pulmonary vascular resistance. The relationship between cardiac output and pulmonary arterial pressure at steady state during unilateral pulmonary arterial occlusion test is summarized in Fig. 4. In control, before unilateral pulmonary artery occlusion test, pulmonary arterial pressures showed a narrow range distribution against a wider distribution of cardiac output. When unilateral pulmonary artery was occluded, pulmonary arterial pressure showed a marked increase in distribution while there was the same distribution of cardiac output as in control. In the animals with narrowed hilar vascular anastomoses, there were

![Fig. 4. Cardiac output (CO) and pulmonary arterial pressure (P_PA) on occlusion of contralateral pulmonary artery in the dog with unilateral lung reimplant. In control or before unilateral pulmonary artery occlusion, pulmonary arterial pressure distribution showed one of narrow ranged against a wider distribution of cardiac output, whereas the former showed a marked increase in distribution after occlusion of contralateral pulmonary artery while there was the same distribution of the latter values as in control. o, control; •, occlusion of contralateral pulmonary artery.](image-url)
a considerable increase in pulmonary arterial pressure and decrease in cardiac output during the occlusion test.

**Pulmonary hemodynamic characteristics of chronic survivors from the results of rapid plasma expander infusion test in bilateral lung autotransplantation**

Six months after completion of bilateral lung reimplantation, a rapid infusion of 3,000 ml of plasma expander (Hemacel) was performed within 10 min in the animal with bilateral lung autotransplantation. During the procedure, cardiac output, pulmonary arterial pressure and systemic pressure were measured simultaneously. Results are illustrated in Figs. 5 and 6.

![Graph](image.png)

**Fig. 5 (upper).** Pulmonary arterial pressure ($P_{PA}$) and total pulmonary vascular resistance (TPVR) to different cardiac output (CO) in the control animal. Note the calculated TPVR was decreased despite increased CO and $P_{PA}$.

**Fig. 6 (lower).** Pulmonary arterial pressure ($P_{PA}$) and total pulmonary vascular resistance (TPVR) to different cardiac output (CO) in the transplanted animal. TPVR was increased in parallel with increase in CO and $P_{PA}$ during the infusion test.

Cardiac output and pulmonary arterial pressure were increased both in control and the animals with bilateral lung autotransplants. On the other hand, calculated total pulmonary vascular resistance was decreased in the former but increased in the latter in parallel with increases in cardiac output and pulmonary arterial pressure.

There was a limitation in increase in cardiac output despite a further infusion of plasma expander; the animal showed symptoms of pulmonary edema when cardiac output level reached as much as 10.8 ml/min. However, it was a temporary phenomenon and the animal survived throughout and after the whole procedure.
DISCUSSION

It has been known that a unilaterally transplanted lung can sustain total lung function if it was rendered to carry the entire pulmonary blood flow by ablation of the function of the contralateral lung (Kawakami 1967; Veith and Richards 1969). Recently it has been established that bilateral lung transplantation is possible and can support the life of the host chronically though there is a critical impairment in cardiopulmonary function during the early postoperative period which leads to high postoperative mortality.

Some investigators (Benfield and Coon 1967; Veith and Richards 1969) have stressed that perfect vascular anastomoses are essential for the transplant to resume normal function. A varying degree of pulmonary edema is also a contributing factor of postoperative lung dysfunction (Alican et al. 1971; Isawa et al. 1971). Alican et al. (1971) and Hardy (1976) suggested that pulmonary edema was due to anoxic and mechanical injury to the pulmonary vasculature. In the present study, histologic examinations have been made in one-stage bilateral lung autotransplants with normal hilar anastomoses who died with pulmonary edema early after surgery. These dogs demonstrated extensive pulmonary vascular congestion and intra-alveolar edema. These histologic changes were associated with progressive and irreversible blood gas deterioration, elevated pulmonary artery pressure and normal capillary wedge pressure.

These morphologic changes by light microscopy are strikingly similar to those documented in the post-pump perfusion lung (Bear and Osborn 1960) and in shock (Wilson et al. 1970). Experimental observations with the unilateral transplants and clinical experience with patients manifesting posttraumatic pulmonary insufficiency suggest that these changes are potentially reversible. However, this histologic deterioration might lead to one of the causes of changes in nature of pulmonary vascular wall during the course of chronic period.

Even though lung replantation has been used as an experimental model for functional studies, the characteristic features regarding the function of transplanted lung has not been fully elucidated. It still remained a matter of controversy and interest how to explain the rise in pulmonary arterial pressure in reimplanted lung, although some investigators attributed it to spasm of pulmonary vessels as a consequence of denervation (Nigro et al. 1964). The pulmonary vessels retained their ability to respond to intrapulmonary injections of acetylcholine and tolazoline, with a subsequent decrease in pulmonary arterial pressure. It is not clear whether this response was mediated by a neurogenic reflex or by a direct smooth muscle relaxant effect.

Recently, Alican et al. (1971) and Fujimura et al. (1972a, b) reported hemodynamic results after simultaneous reimplantation of both lungs in the dog. The present study also showed normal pulmonary arterial pressures during the entire postoperative course in chronic survivors, though magnitude of changes were present in early postoperative period.

The hemodynamic changes in totally dependent autograft with contralateral
pulmonary artery occlusion and in bilateral lung transplantation have been clearly
defined in relation to lung denervation.

By examining the hemodynamic response to unilateral pulmonary artery
occlusion and to rapid infusion of plasma expander via intraatrial catheter in
bilateral lung transplantation, the present study was designed to assess the effects
of denervation.

It has been known that occlusion of one pulmonary artery by ligation or
occlusion with intraatrial balloon does not give rise to elevated pulmonary arterial
pressure in a normal subject. This shows that the vessels of the other lung
bearing total cardiac output can dilate with an increase in blood flow. On occluding
the contralateral pulmonary artery with an intraluminal balloon, a consistent increase
in pulmonary arterial pressure was observed which was accompanied by a little
or no changes in cardiac output in animal with normal vascular anastomoses.
From Fig. 4 where cardiac output vs. pulmonary arterial pressure during steady
state of each animal was plotted, pulmonary arterial pressure did not increase
despite the increment of cardiac output until this value reached 200 ml/min/kg
respectively in control, while in the occlusion test a sharp increase in pulmonary
arterial pressure was noted. The relation between them was almost linear. These
results suggest that there is difference in behavior of pulmonary vasculature in
responses between normal and transplanted lungs to tolerate an increased intra-
luminal blood flow, though each experiment was carried out in different material.

In order to clarify the cause underlying these phenomena, plasma expander
was infused to the animal with bilateral lung replantation continuously via
intraatrial catheter. During the course of increased cardiac output both pulmonary
arterial pressure and total pulmonary vascular resistance were getting higher
and higher and became linear until the transplant became edematous, while in the
control animal the total pulmonary vascular resistance showed a decrease despite
the increase in cardiac output and pulmonary arterial pressure. It can be assumed
that these results indicate the change in mechanism of pulmonary circulation in
the transplanted lungs; vessels of transplanted lungs could not dilate with increased
blood flow neurogenically.

Further studies are being conducted in an attempt to elucidate the etiology of
increased pulmonary vascular resistance in the transplanted lung.

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