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Yoshihiko Katayama
Katsumoto Hatanaka
Takashi Hayashi
Isao Yada
Shoji Namikawa
Hiroshi Yuasa
Minoru Kusagawa

The effects of single lung transplantation in rats with monocrotaline-induced pulmonary hypertension

Y. Katayama · K. Hatanaka · T. Hayashi
P I. Yada · S. Namikawa · H. Yuasa
M. Kusagawa
Department of Thoracic Surgery,
Mie University School of Medicine,
Japan

Y. Katayama (✉)
Department of Respiratory Physiology,
Papworth Hospital, Papworth Eveard,
Cambridge CB3 8RE, UK

Abstract Acute haemodynamic change after single lung transplantation for primary pulmonary hypertension was evaluated using a rat transplantation model. Inbred Fisher 344 rats were administered with 40 mg/kg monocrotaline in order to induce pulmonary hypertension. The rats whose mean pulmonary arterial pressure (PAP) was over 30.0 mm Hg received a left lung isograft from a normal donor after right heart catheterization. In the control group, PAP increased after single lung transplantation. On the other hand, in the pulmonary hypertensive group, PAP was significantly decreased 60 min after the transplantation, but 3 and 6 h after the transplantation, the PAP significantly increased again. On the day after the operation, it again decreased significantly. Left-to-right lung blood flow ratio was significantly increased in rats with pulmonary hypertension compared to rats with normal pulmonary pressure on both the 1st and 3rd postoperative days. The oedema of the grafted lung was more severe in the pulmonary hypertensive group than in the control group in the acute phase. In conclusion, single lung transplantation for pulmonary hypertension shifted pulmonary blood perfusion to the grafted lung and this shift made pulmonary oedema of the grafts more severe in the acute phase. These oedematous changes, which were more pronounced in the grafts in the pulmonary hypertensive rats, might have contributed to the transient rise in PAP in those rats after single lung transplantation.

Key words Primary pulmonary hypertension · Monocrotaline Single lung transplantation

Introduction

Single lung transplantation (SLT) for primary pulmonary hypertension (PPH) has been recognized as an effective option to improve haemodynamic disturbances [1–3]. However, preoperative haemodynamic conditions are different from other patients receiving SLT because of the elevated pulmonary arterial vascular resistance [2]. In this experiment, we studied the difference between SLT for PPH and for other lung diseases in which pulmonary arterial pressure (PAP) is not so severely increased. In particular, the acute haemodynamic change after SLT for PPH was evaluated using a rat transplantation model.

Materials and methods

All animals received humane care in compliance with the "Principles of laboratory animal care" formulated by the National Society for Medical Research and the "Guide for the care and use of laboratory animals" prepared by the National Academy of Science and published by the National Institute of Health (NIH publication no. 86-23, revised 1985).

Induction of pulmonary hypertension in rats

Before starting the experiment, a preliminary study was done to test the induction of pulmonary hypertension in rats. Inbred F344 rats were used in this study. In order to induce pulmonary hypertension, 40 mg/kg of monocrotaline was administered subcutaneously at the age of 8 weeks [4]. Then right heart catheterization (RHC) was performed weekly to measure the pulmonary arterial pressure. Rats were anaesthetized by an intraperitoneal injection of sodium pentobarbital (35 mg/kg). A catheter was inserted through the jugular vein using a modification [5] of a closed-chest technique previously described [6] and PAP was measured intermittently. The position of the catheter was confirmed at sacrifice. Three weeks after the monocrotaline administration, the PAP (mean PAP = 17.6 ± 1.89 mm HG; $n = 12$) was significantly increased compared to the baseline (mean PAP = 36.7 ± 8.0 mm Hg; $n = 6$); $P < 0.01$). The rats were used as pulmonary hypertensive rats, 3 weeks after the monocrotaline administration.

Experimental protocol

At the age of 8 weeks, 40 mg/kg of monocrotaline was administered subcutaneously. Three weeks after monocrotaline administration, RHC was performed to assess PAP as described before. PAP was measured intermittently. One day after RHC, PAP was measured and those rats with a PAP of more than 30 mm Hg received a left lung isograft from a normal donor. Left lungs were orthotopically transplanted under a surgical microscope, as described previously [7]. This group was named the PHLT group ($n = 12$). In the CLT group ($n = 12$), 11-week-old rats received a left isograft 1 day after the RHC. PAP was monitored from the end of the operation until the 5th postoperative day.

Measurement of the left to right pulmonary blood flow (L/R) ratio

In order to determine the L/R ratio at 1 and 3 days after SLT, radiolabelled microsphere ^{51}chromium (15 μCi, NEN^R) and ^{109}cadmium (15 μCi, NEN^R) were injected. To evaluate the L/R ratio of normal rats, ^{51}chromium (15 μCi, NEN^R) was also injected into normal rats ($n = 6$). After sacrifice, both lungs were removed and radioactivity of both lungs was counted by well scintillator (Aloka Inc., Auto Well Gamma System, JDC755) and then the L/R ratio was calculated.

Histology

In each group, six rats were sacrificed for histopathological examination 6 h, 24 h and 3 days after SLT and those pressure data were excluded from statistical evaluation. Other rats were sacrificed on the 5th postoperative day (POD).

Data analysis

All results are expressed as the mean ± standard error. Statistical comparisons were made using the ANOVA test (Fisher PLSD test).

Results

Change in PAP

In the CLT group, PAP increased after SLT as shown Fig. 1. On the contrary in the PHLT group, PAP was significantly decreased 60 min after SLT but 3 and 6 h after SLT, PAP significantly increased again. One day after the operation, PAP again decreased significantly, whereas it was continuously increased in the CLT group (Fig. 1).

Left to right pulmonary blood flow ratio

Figure 2 shows the L/R ratio. In normal rats, the L/R ratio was 0.61 ± 0.03. In the PHLT group, the L/R ratio was 0.46 ± 0.12 on POD1 and 0.48 ± 0.09 on POD3. In the CLT group, the L/R ratio was 0.14 ± 0.02 on POD1 and 0.14 ± 0.03 on POD3. This ratio was significantly

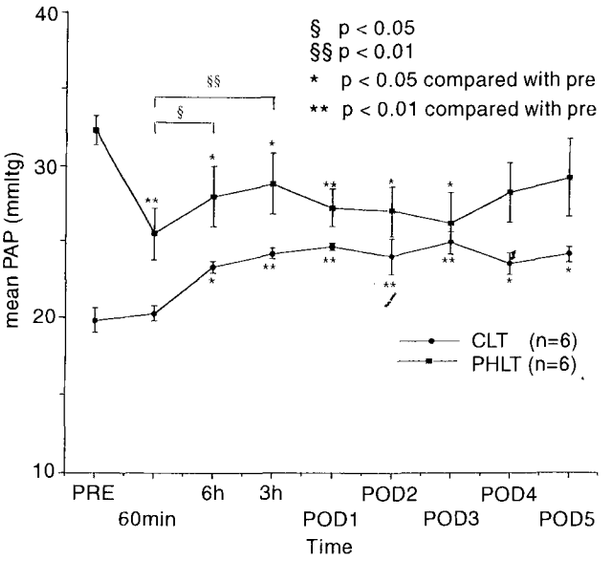

Fig. 1 The changes in pulmonary arterial pressure (PAP) after left lung transplantation. In the CLT group, PAP increased after single lung transplant (SLT). On the other hand, in the PHLT group, PAP significantly decreased 60 min after the transplantation but 3 and 6 h after the transplantation, it significantly increased again (*Pre* pretransplant)

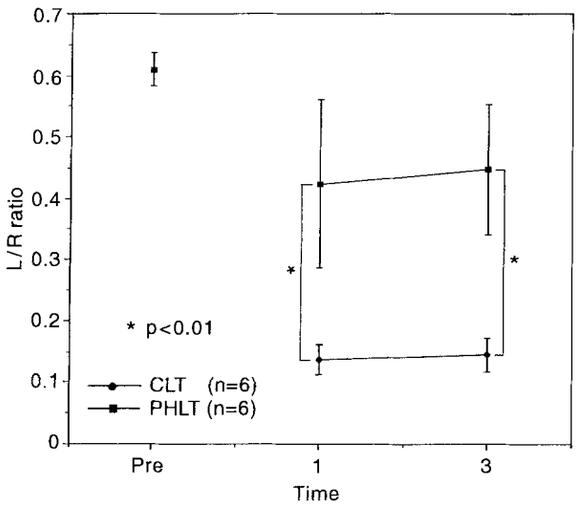

Fig. 2 The left to right pulmonary blood flow (L/R) ratio was significantly increased in the PHLT group on both 1st and 3rd postoperative days

increased in the PHLT group on both POD1 and POD3 ($P < 0.01$). At sacrifice, the pulmonary arterial anastomosis and the pulmonary vein anastomosis were examined and no stenosis was found.

Histology

Figure 3a is a photomicrograph of the grafted lung in the CLT group 24 h after SLT. Perivascular oedema and peribronchial oedema can be seen on histology. These changes were most significant at 24 h after SLT. Figure 3b is a photomicrograph of the grafted lung in the PHLT group 24 h after SLT. In addition to perivascular oedema and peribronchial oedema that was seen in the control group, inflammatory cell infiltration into the alveolar septum and alveolar oedema were also present. This change was most severe at 24 h after the transplantation. On the 3rd postoperative day, these oedematous changes were slightly reduced.

Discussion

Transplantation in patients with end-stage pulmonary hypertension has previously been limited to heart lung transplantation [8, 9]. Although achieving success to some extent, this procedure has been limited by the shortage of donors. Recognizing its success in end-stage lung disease, SLT has also been used in patients with pulmonary hypertension [2, 10]. It has been reported that SLT decreases PAP and pulmonary arterial resistance and increases cardiac output, arterial oxygen saturation and quality of life in patients with PPH [1]. This procedure has several advantages over heart-lung transplantation. The surgical procedure of SLT is simpler than heart-lung transplantation and can be performed without cardiopulmonary bypass [11]. This option also increases donor organ supply. However, in the case of SLT for pulmonary hypertension, intensive care is needed in some cases due to donor lung dysfunction [2]. Because the preoperative pulmonary vascular resistance of patients with PPH is different from that of other patients, the acute haemodynamic changes after SLT for PPH is different from the changes after SLT for other lung diseases in which PAP are not so severely increased. In this experiment, we evaluated the acute haemodynamic changes after SLT for PPH using a rat transplantation model. PAP increased after SLT in the CLT group. The reason PAP increased was not apparent. The reduction of compliance due to the operation may have contributed to this increase. Inflexibility of the vascular anastomotic site may also have been responsible to some extent. In the PHLT group, PAP was first significantly decreased 60 min after SLT but it showed a transient significant rise at 3 and 6 h after SLT (Fig. 1). The L/R ratio was significantly increased in the PHLT group on both POD1 and POD3 (Fig. 2). This blood flow shift was not due to the operative procedure but was due to the elevated pulmonary resistance of the native lung. Histology revealed that the lung oedema was more severe in the PHLT group than in the CLT group in the acute phase. This difference may be due to a massive blood shift to the grafted lung after SLT. The pulmonary oedema was induced by reperfusion injury. This difference in severity of lung oedema must be due to the difference in blood shift to the grafted lung after SLT. The lung oedema of the graft makes the haemodynamic state and the blood oxygenation worse in the acute phase after SLT. To avoid this situation, strong vasodilation of the pulmonary artery of the native lung may be effective.

In conclusion, these results suggested that SLT for pulmonary hypertension shifts pulmonary perfusion to the grafted lung and this shift makes pulmonary oedema of the grafts more severe in the acute phase. We also suggest that the histological changes, which were more pronounced in the lung grafts in pulmonary hypertensive rats, might have contributed to the transient rise in PAP in those rats after SLT for pulmonary hypertension.

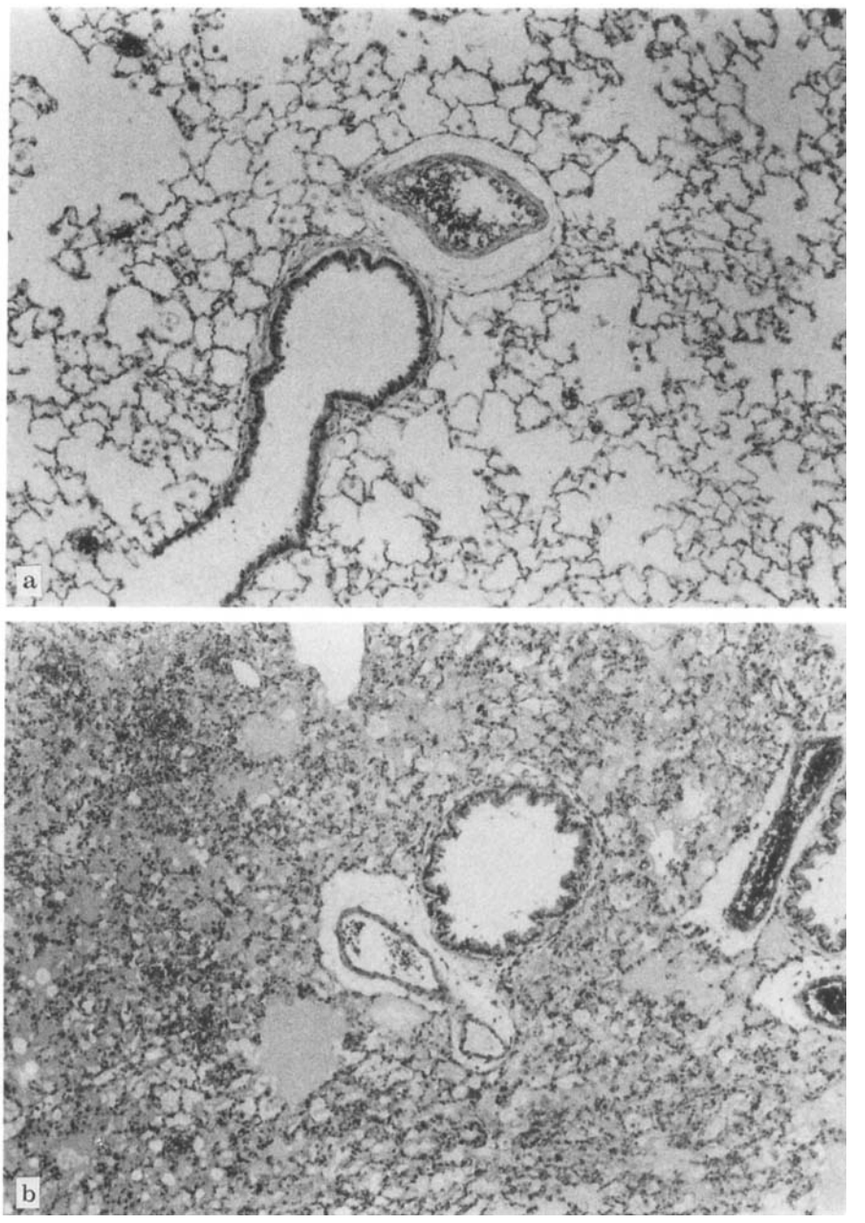

Fig. 3a, b Photomicrographs of grafted lungs 24 h after SLT stained with haematoxylin and eosin. **a** Grafted lung of a control. Perivascular oedema and peribronchial edema can be seen on histology (×155). **b** Grafted lung of a PHLT. In addition to perivascular oedema and peribronchial oedema, inflammatory cell infiltration into the alveolar septum and alveolar oedema were also present

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