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REIMPLANTATION RESPONSE IN CANINE LUNGS+

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Summary: The function of the transplanted lungs may crucially impaired in the early postoperative period by the reimplantation response. Several factors of the transplantation procedure, such as hilar stripping, stenotic anastomoses, and graft ischemia, are deliberated to cause this reimplantation response.

In our study the inseperable contributions of these factors have been ananalyzed in dogs, after reimplantation or hilar stripping of the lungs. An 60 percent postoperative survial rate was accomplished. Transplanted and hilar-stripped the lungs were investigated by chest roentgenography, arterial blood gases and pulmonary arterial pressures at regular intervals up to 30 days operation. Macroscopic and histologic morphology was examined at corresponding intervals.

Our results show that perfusion and ventilation of the lung grafts are independently affected by distinct factors of the transplantation procedure. Hilar stripping did decrease graft perfusion transiently. Hilar stripping also impaired ventilation, by causing interstitial and alveolar edema. After transplantation, edema and consequent impairment of ventilation were aggravated by graft ischemia. Consequently, it was found that in hilar stripping group reimplantation response was less whereas it was more serious in reimplantation group.

Key words: Reimplantation response, pulmonary transplantation, hilar stripping.

Transplantation of the lungs has not reached the same succes as transplantation of the kidney, heart, and liver. The disappointing results of clinical lung transplantation have been attributed to surgical complications, particularly of the bronchial anastomosis (12), to ventilation/perfusion imbalance of the transplanted lung caused by the remaining lung (15), and the rejection of the transplanted lung and complications secondary to rejection (11). However even in technically and immunologically uncoplicated transplantations, the function of the transplanted lung may be transitorily but crucially deranged in the early postoperative period. This disarrangement, which also occurs in dogs (8) after reimplantation (i.e., autotransplantation) of the lungs, is ascribed to as the reimplantation response and is defined as the complex dearangement of perfision and ventilation caused by excision and replacement of the lung, with no im-

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munologic rejection phenomena.

Although improvements in the transplantation procedures have reduced the severity of the reimplantation response, they heve not eliminated the response, they have not dislodged the response. Several factors of the transplantation procedure are considered to contribute to the reimplantation response. These factors, related directly to technical aspects of transplantation, are functional stenosis of the vascular and bronchial anastomoses, ischemia of the transplanted lung, and dissection of the lung by hilar stripping. However, the degree to which the individiual factors contribute to the remiplantation response has been poorly investigated (7).

In our study, the individual contribution of these factors to the reimplantation response was analyzed in dogs. Therefore, we compared reimplanted lungs to hilarstripped lungs in regard to function and morphology.

MATERIALS AND METHODS

Dogs. Spesific pathogen-free mongrel dogs, weighing 18 to 20 kg, were caged in a laminar air-flow cabined separately from other dogs. The dogs were randomly allocated to tow groups. Ten dogs underwent hilar stripping (Group I). Reimplantation of the lung was also carried out in ten dogs (Group II). Some of these dogs were sacrified within 30 days after the operation for histologic investigation. The function of all left lungs was regularly determined by the chest roetgenography and arterial blood gases and pulmonary artery pressures for periods up to 30 days.

Transplantation and hilar stripping.

Preoperative care and anesthesia.

Recipients of a left lung graft and the dogs for hilar stripping were prepared for identically: 1 mg/kg of meperidine HCl was injected intramuscularly before one hour the operation. Each dog was anesthetized by 10-15 mg/kg penthotal sodium intravenously and 20-25 mg/kg ketamine intramuscularly, intubated by an endotracheal tube (28 Fr 6 oral 8.7 Rüsch W. Germany) and ventilated by a mechanical respirator (Ohio Medical Products A Div. o Air Reduction Co., Inc.) (tidal volume 10-20 ml at a frequency of 60 to 40 breaths/min and inspired oxygen fraction was kept at 0.2 throughout the experiment). If necessary, mucus was aspirated endotracheally by introducing a thin catheter through the endotracheal tube. The dogs were infused with Ringer's lactate solution into a superficial vein, to prevent dehydration and base excess and electrolytes were continuously corrected.

Operation. The transplantations and hilar strippings were performed under aseptic conditions and without the aid of an operating microscope.

In group I, at thoracotomy through the left fifth intercostal space gave the best access to the hilus of the left lung. After ligation and resection of the postcaval lobe of the right lung, the surrounding tissue was dissected from the left pulmonary veins and artery and the bronchus, so that the lymphatics, the branches of the vagal nerve, and the bronchial arteries were disrupted. In the hilar stripping series the thorax waas closed at this stage.

In group II 'i.e., in the transplantations series), left lung reimplantation in dog was caried out as follows: the left thorax was entered through the left fifth intercostal incision. The heart, the great vessels, and the left lung were exposed. The hilar structures were isolated and divided and then individualy anastomosed. After administration of heparin, the left pulmonary artery was occluded and vascular clamps were applied to the pulmonary veins and to the left atrium. After incision of the inferilor and anterior wall of isolated portion of the atrium, posterior aspect was carefully divided under direct vision, leaving a cuff of 4 to 5 mm on the atrial side. The left atrial anastomomsis was begun well on anterior aspect of the inferior angle as a single-layer, running everting mattres stitch of 6-0 Prolene. After completion of the atrial anastomosis, the left pulmonary artery was divided between vascular clamps and was reapproximated in a single layer using a double-stay running over-and-over suture of 6-0 Prolene. After completion of the vascular anastomosis, all occlusive vascular clamps were removed and blood flow was re-established to the left lung. The left main-stem bronchus was divided with scalpel close to origin of the left upper-lobe bronchus. By advancing the single-lumen endotracheal tube intro the right main-stem bronchus, the potential large air-leak present after division of the left bronchus was prevented. Preferably, a singel row of continuous 4-0 polypropylene (Prolene) suture material was used to approximate the membraneous bronchus and interrupted sutures of 4-0 Prolene were used to close the cartilaginous part. When all anastomosed were completed, the chest was thoroughly irrigated with salin solution and all suture lines were checked for leaks (Figure 1-5).

The thorax was closed in the same way after reimplantation and after hilar stripping. A drain was left in the pleural cavity, the ribs were joined by four sutures of 1-0 Prolene, and the muscles and the skin sutured by 3-0 Vicryl. The dog was disconnected from the respirator and started breathing room air spontaneously. As soon as the dog awoke from anesthesia the chest drain was removed.

Postoperative care. For 24 hours after the operation the dogs were ventilated by a pressure-controlled respirator (Bird, Mark 7, Products Corp, Palmsprings, Calif.). 1 g/daily of cephaperasone was given intravenously up to 5 the day. The dogs were weighed at least twice a week to monitor their recovery.

Function of the lung. For monitoring the functions of the lung, arteriel blood gases, pulmonary artery pressures, and chest roetgenograms were recorded, just postoperative, immediately postoperative, and third, fifth, seventh, fourteenth, and thirtenth days after the operation, with the dogs under penthotal+ketamine anesthesia.

Blood gases and hemodynamic determinations. Arterial blood gases analyses were carried out. Pulmonary artery pressures were measured in the anesthetized during occlusion of the contralateral pulmonary artery with a ballon catheter.

Chest roentgenographies. Chest roetgenograms were taken in the anteroposterior projection with the dog supported in the upright position.

Morphology. The dogs were put to death with overdosaged penthotal for histologic investigation. After in situ fixation for 20 minutes, the lungs were dissected, embedded in paraffin, cut in sections 6 um thick,and stained with hematoxylene and eosin for examination under the light microscope. Histological analysis was performed by a single pathologist.

Statistical analysis. All data were expressed as mean ± standart deviation. Levels of significans between the towo groups were calculated by Student's t test of independent data. A value of $p<0.05$ was regarded as significant.

RESULTS

Operation. Seven animals died before the end of the experiment: three in group I (i.e., in hilar stripping series) after 2,72 and 120 hours because of bleeding of bronchial artery, respiratory faliure, and septicemia

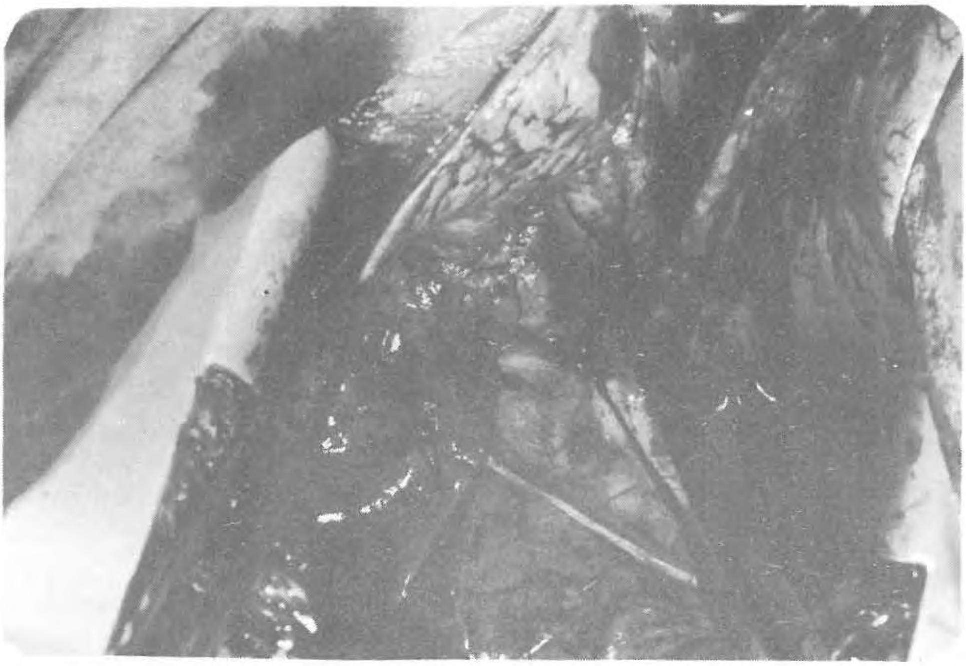

Figure 1a. Left thoracotomy. In the first step of the operation the left pulmonary vens are encircled with a tape.

Figure.1b. Then, the left pulmonary artery is also encircled with another tape.

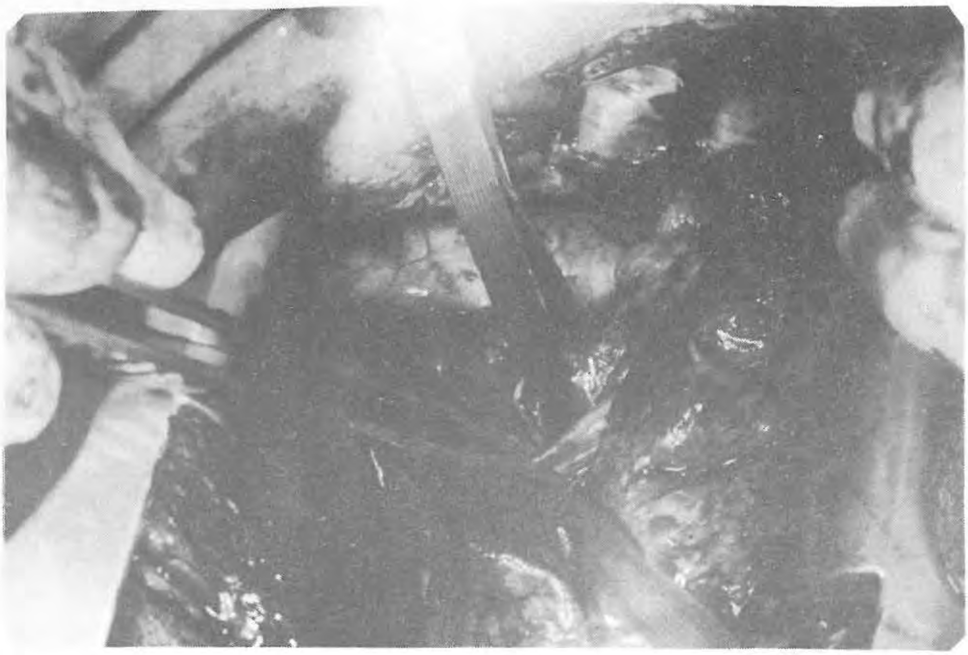

Figure 1c. Left thoractomy. The left main-stem bronchus is isolated and encircled with a tape.

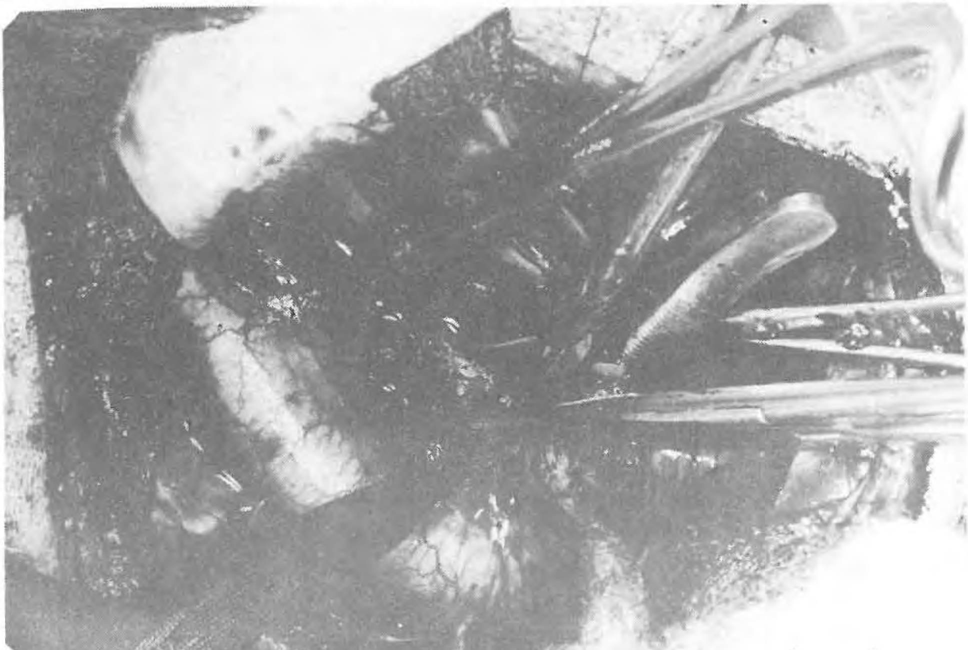

Figure.2. Left thoracotomy. In the second step of the operation the pneumonectomy is completed. Note the Potts' clamp on the artery, the Satinsky clamp on the bronchus, and another Satinsky clamp on the left atrial cuff.

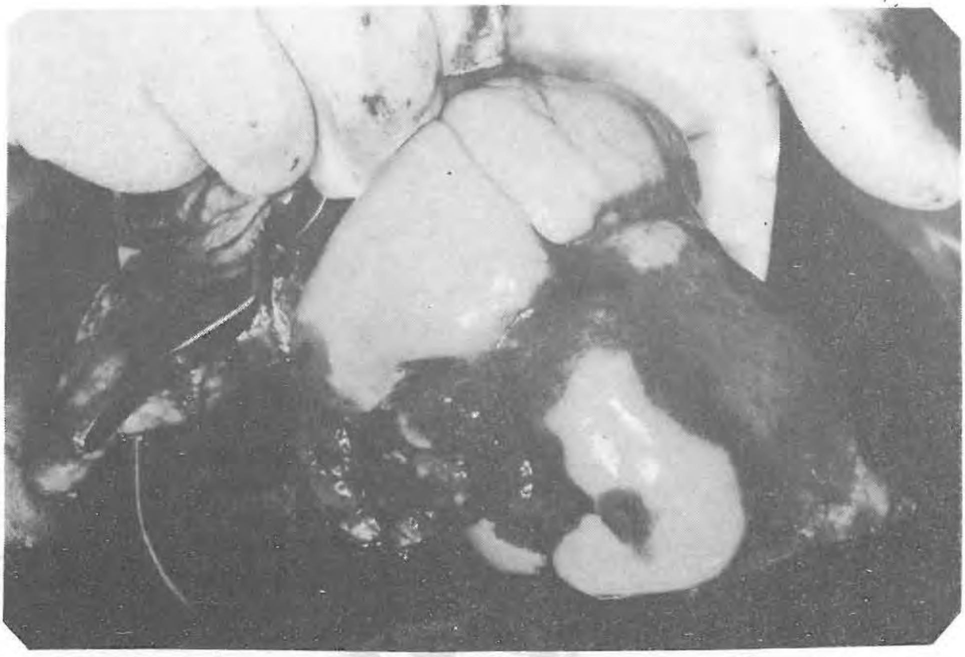

Figure 3. In the third step of the operation the excised lung, is inflated with a 15 cmH_2O of positive pressure, is holded in saline solution containing 5000 U/L of heparine for minutes.

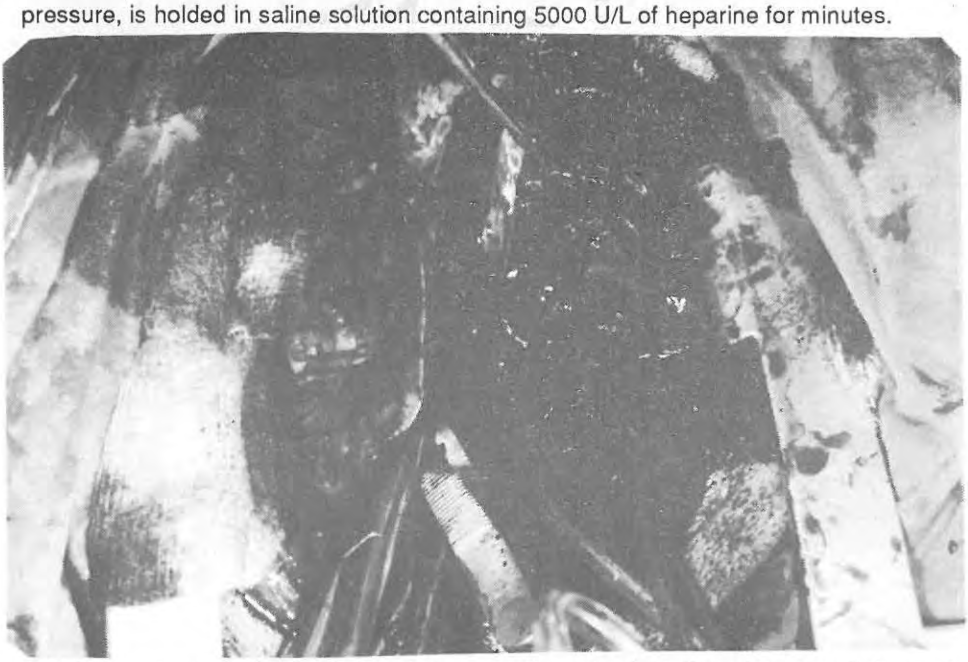

Figure 4a. Left thoracotomy. In the final step of the operation reimplantation of the lung is begun by anastomosing the atrial cuff. The posterior wall will be sutured first with a continuous over-and-over suture.

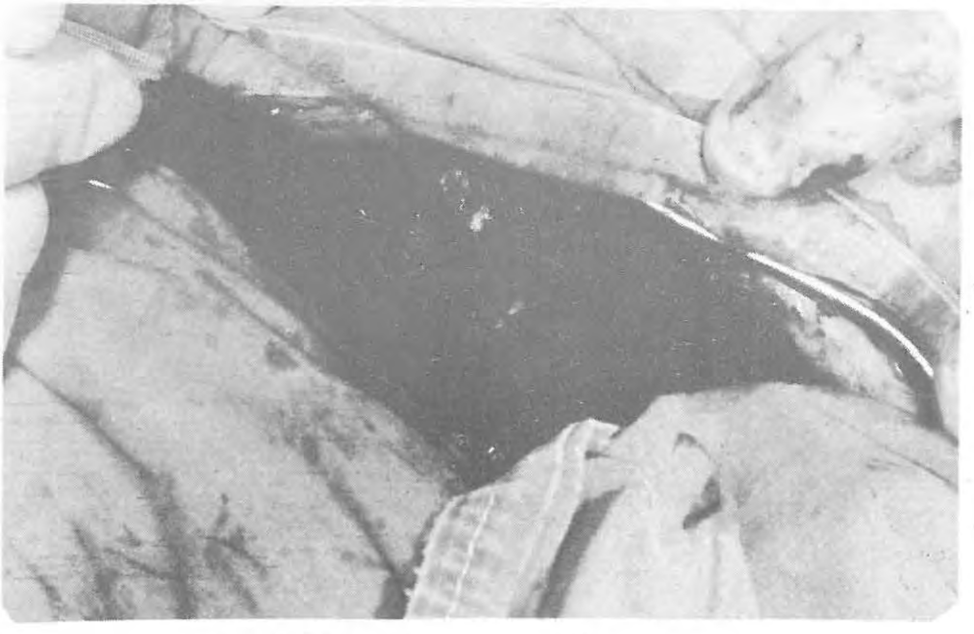

Figure 4b. The atrial cuff anastomosis is completed.

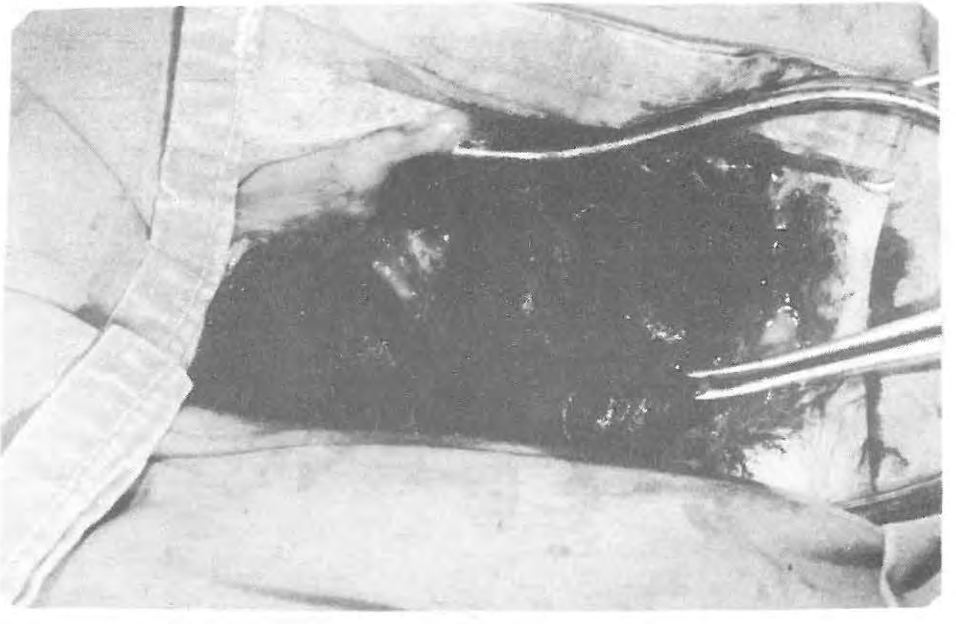

Figure 5. Left thoracotomy. The pulmonary arterial and bronchial anastomoses are completed, and the blood flow of the nonventilated lung is restored.

respectively, and four in group II (i.e., in reimplantation series) after 24, 25, and 72 hours because of pneumothorax, from a pulmonary artery anastomosis, and pulmonary artery stenosis in two dogs, respectively. The postoperative survival rates of the group I and II was 70 % and % 60, respectively.

Function of the lung. Blood gas and hemodynamic measurements were calculated preoperatively as the following: Po_2 = 137.5 ± 1.3 mmHg, Pco_2 = 28.2 ± 0.45 mmHg, pH = 7.29 ± 0.005, and Ppa = 22.44 ± 0.20 mmHg, Ppaw = 9.95 ± 1.0 mmHg. These results were insignificant when compared with the groups (both Group I and II, separately) ($p>0.05$), It found that, in both groups, pH values increased in first three days when compared with preoperative values. This increasing was insignificant in fifth day. The difference in between groups was insignificant when they compared for pH outcomes ($p>0.05$) (Figure 6).

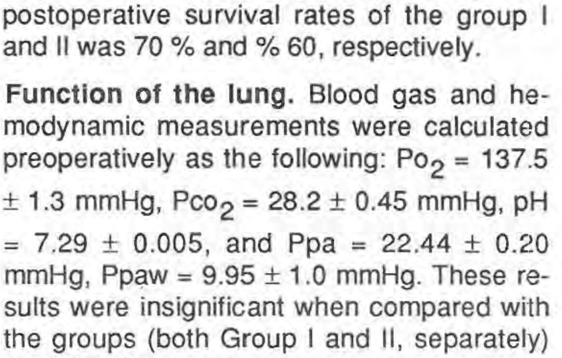

Figure 6. Mean pH values in both groups. It showed that the increase was marked in first third day but decreased gradually from fifth day. The difference between groups was insignificant statistically ($p>0.05$).

In both groups, Po_2 values were significant in third day when compared with the preoperative values ($p<0.05$). In addition, the difference in between groups also was significant ($p<0.05$). In postoperative fifth day, arterial oxygen presures in group I and II of 101.94 ± 2.90 and 85.97 ± 10.20 mmHg, respectively, were found significantly lower than in the preoperative values ($p<0.05$). However, there was no statistically significant difference between the two groups in postoperative fifth day (Figure 7).

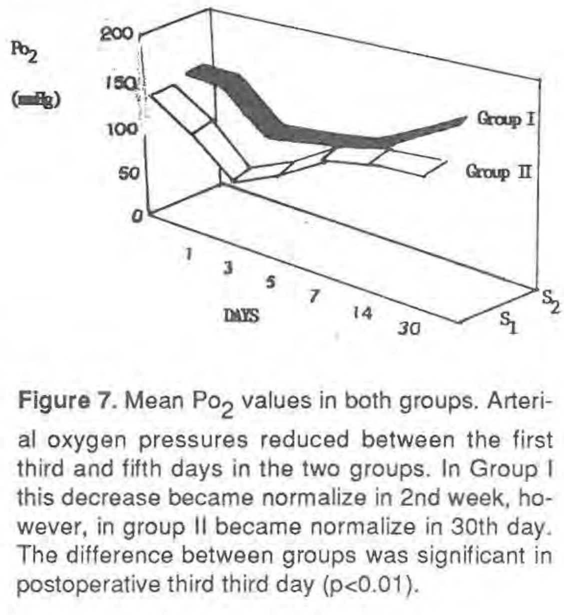

Figure 7. Mean Po_2 values in both groups. Arterial oxygen pressures reduced between the first third and fifth days in the two groups. In Group I this decrease became normalize in 2nd week, however, in group II became normalize in 30th day. The difference between groups was significant in postoperative third third day ($p<0.01$).

Measurement of arterial carbondioxide pressure showed that there was no significant differences between the two groups at any time points.

Measurement of PA pressure showed that PA mean pressure in both groups was significanty increased in third day when compared with preoperative values ($p<0.01$) but there was no significant differences between the two groups. In fifth day, PA pressure in group II of 24.58 ± 0.66 mmHg was found significantly higher than in preoperative values ($p<0.05$), whereas PA pressure in group I was insignificant when compared with preoperative values ($p>0.05$). There was statistically significant differences between the two groups ($p<0.05$). In postoperative 7th, 14th, and 30th day, there was no statistically significant

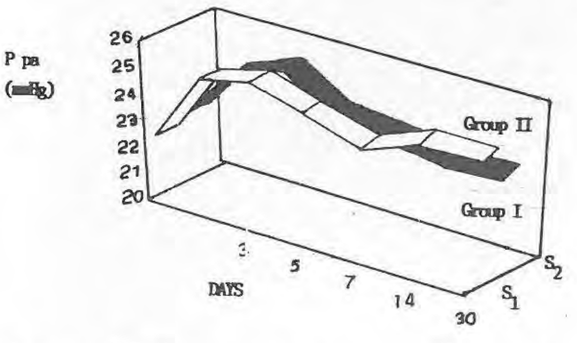

Figure 8. Pulmonary artery mean pressures in group II continued highly than group I. In group II normal values were not still obtained in postoperative 30th day. The difference between groups was insignificant statistically.

differences between the two groups (Figure 8).

PA wedge pressure in two groups increased significantly when compared with the preoperative values ($p<0.01$), however, there was no significant differences between both groups ($p>0.05$). PA wedge pressures in both groups elevated maximally in third day and it decreased from fifth day. The pressures normalized at 30th day (Figure 9).

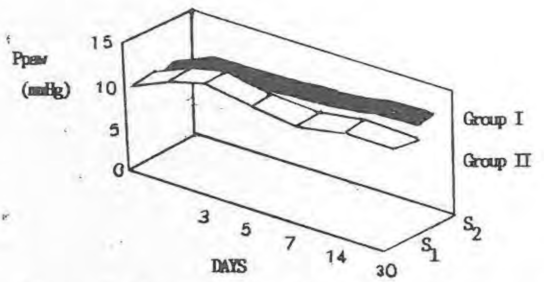

Figure 9. Mean Ppaw values. PA wedge pressures in both groups increased significantly when the preoperative values ($p<0.01$), whereas there was no significant difference between groups ($p>0.05$). The difference between preoperative Ppaw and postoperative Ppaw has lost the fifth day in group I but the seventhy day in group II.

Chest roentgenograpies. Chest roetgenograms in early postoperative period revealed that there were usually atelectasis associated with a mediastinal shift to the left, and a pneumothorax (10a) After the third day, chest roentgenograms improved rapidly: the atelectasis areas were cleared but an increased density, became dense around the hilar region, remained in the left surface (10b). In group I,

Figure 10a. Roentgenogram obtained first day following reimplantation of left lung. Atelectasis, pneumothorax, and mediastinal shift is observed on the operated side.

Figure 10b. Same dog, third postoperative day. Atelectasis is still continued, and a remarkable hilar opacity in the left hemithorax is observed.

Figure 10c. Same dog fifth postoperative day. It persisted in atelectasis and opacification.

chest roetgenograms were normalized in postoperative fifth day (11) but a mild increased densitiy remained in group II (10c). In about 30th day the roentgenograms in the two groups were almost normal (10d).

Morphology.

Macroscopic aspect. There was no difference macroscopically between hilarstripped and transplanted lungs. Many of the left lungs had some atelectatic areas, often corresponding to the overlying thoracotomy incision. The atelectalic, hemorrhagic, and edematous areas were most remarkable in the early period but were absent or replaced by scar tissue in late period. The anastomoses of the vein and the bronchus were completely patent, but the artery was narrowed in two dogs which they had died postoperatively in third day. In a dog of group II, diffuse thrombus around the atrial cuff anastomosis was found postoperatively in fifth day.

Microscopic aspect. The two groups had the same aspect in early period: There was vasculer congestion, intra-alveolar bleeding and edematous formation (Figure 12). In the late period, group I looked almost: Edema and hemorrahges had disappeared (Figure 14), however, in group II alveolar septal thickeninig, mild vascular congestion, and alveolar macrophages and epitelial cells in alveolar spaces were present (Figure 13).A mild inflamatory reaction and edema was seen on both bronchial and vascular anastomotic lines in early period, whereas, in late period chronic inflamatory cells and fibrosis were present (Figure 15).

Figure 10d. Same dog 1 month postoperatively. Both sides of chest appear essentially normal.

Figure 11. Roentgenogram obtained fifth day following hilar-stripping of left lung. It appears to be fully aerated.

DISCUSSION

Although Demikhov (Moscow, 1947) asserted post facto have performed the first lung transplantation, Metras (Paris, 1950) is commonly believed with demonstrating in dog model in 1950 that single lung transplantation is possible (6,10).

The pulmonary reimplantation response consist roentgenologicaly of a mixing alveolar infiltrate which is generally associated with and probably due to the presence of edema fluid within the air spaces. The proces embraces the central parts of the lung and extends into the pulmonary paranchyma along a peribronchial and perivascular patlway. The pulmonary peripheral parts are not involved. The maximum expression occurs by the thidr postoperative day. This is followed by a variable improvement between the fourth and seventh postoperative days and a slow disappearance of the infiltrate which is complete between the seventh and twenty-first days. The edema and resultant alveolar infiltrate are probably due to an allianece of factors, the most important of which are operative-trauma, ischemia and lymhatic interruption. During the clearing phase, the infiltrate withdraws centrally so that the pulmonary peripheral parts are the earliest to be restored to a normal appearance. The phenomenon of peripheral sparing and central regression may clarify the discepancy observed between the lung biopsies and the chest films. In some animals the lung biopsies acquired from the outer third of the lung were wholly normal whereas the chest radiograms comprised evidence of residual central pulmonary infiltrate (8).

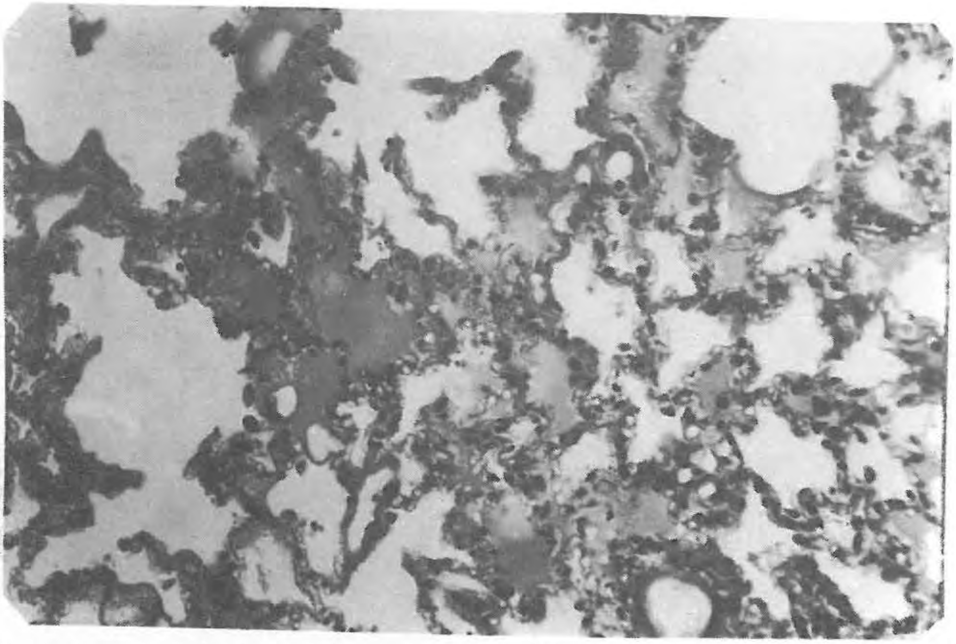

Figure 12. Photomicrograph of canine lung in early period following reimplantation. Note foci of alveolar edema and hemorrhages, and marked vascular congestion (HEX200).

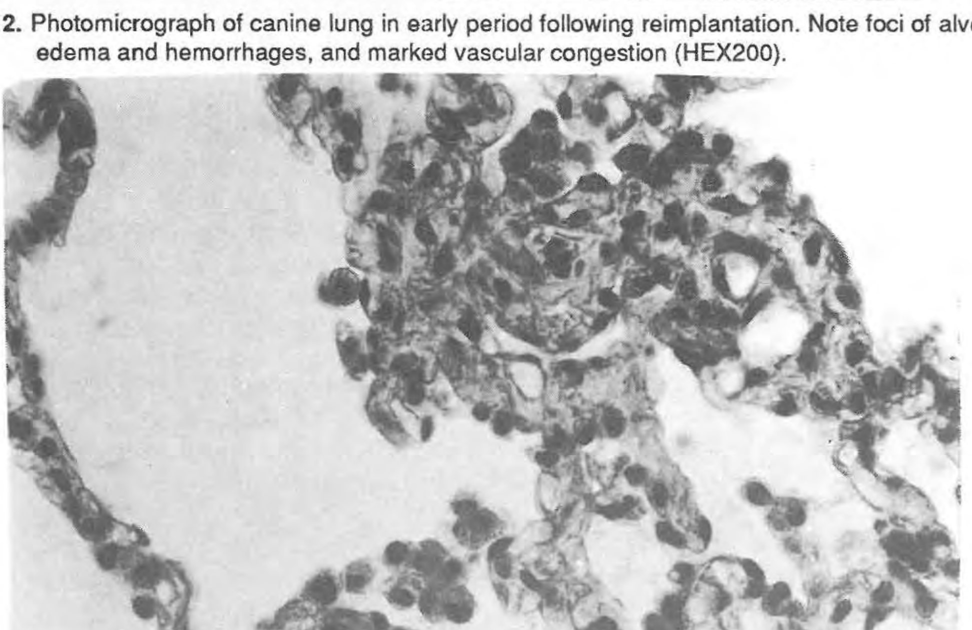

Figure 13. Histologic appearance of reimplanted lung in late period, showing alveolar septal thickening, macrophage and epithelial cell in alveolar spaces, and mild vascular congestion (HEX250).

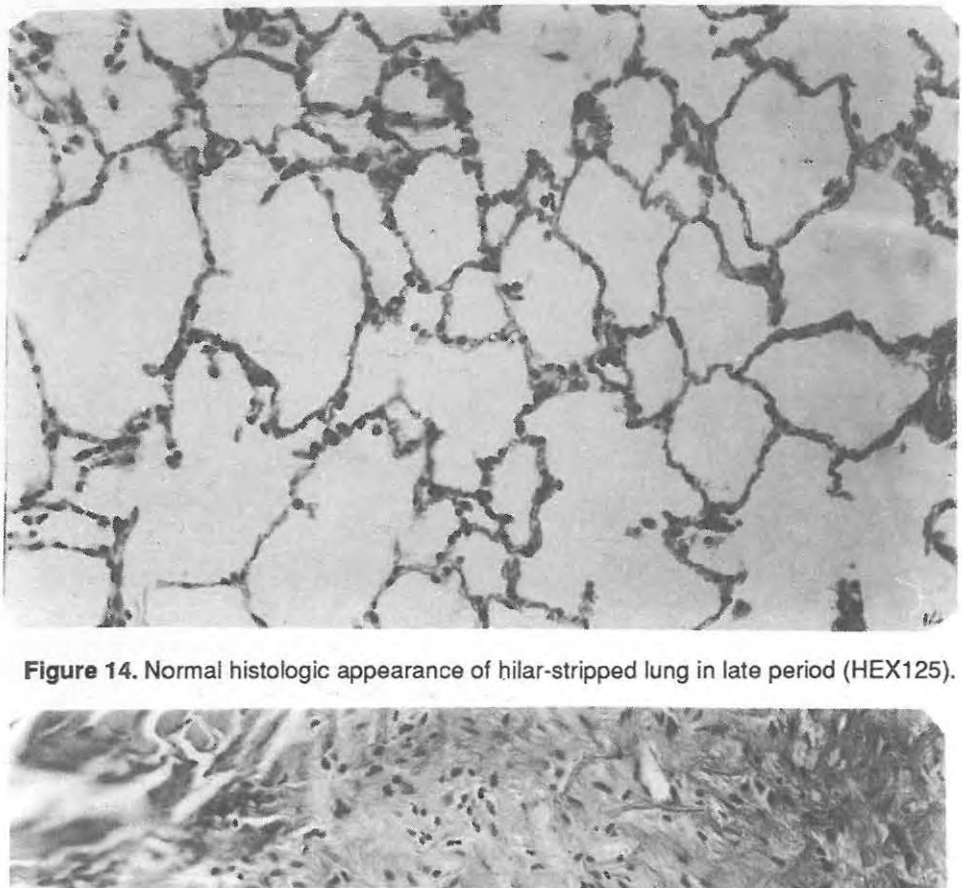

Figure 14. Normal histologic appearance of hilar-stripped lung in late period (HEX125).

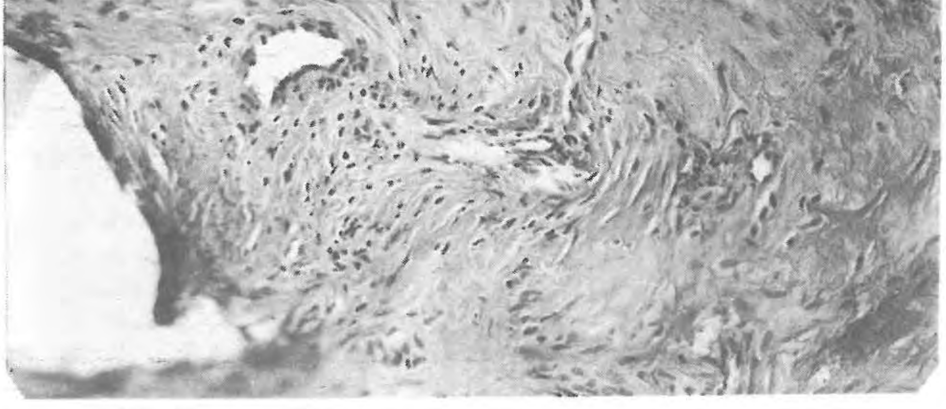

Figure 15. Histologic appearance of pulmonary artery anastomosis at 30th day, showing chronic inflamatory cells and fibrosis. (HEX200)

A reliable transplantation technique is the first prerequisite for transplantation research. We used the technique of the Toronto Lung Transplant Group (9) in our study, overall survival rate for the operation and follow-up period of 30 days was 60 %. This survival rate was % 70 in hilar-stripped group. The few dogs that died did so as a result of imperfect anastomoses. Essential to achieve these results were the refinements of conditions during anesthesia: prevention of dehydration by intravenous saline infusion, maintenance of body temperature, and careful control of the artificial ventilation to avoid high airway pressures.

In the series of Trummer and Christiansen (10), they reported that 25 dogs who died within 1 month lived from 1 hours to 19 days (The survivors rate was % 41.8). The major cause of death within the first three days was pulmonary infarction secondary to thrombosis of the pulmonary veins (% 36), between 3 and 7 days the major cause of death was bronchial necrosis and its complications (% 12). In this series, the rate of technical errors was 16 percent compared with 15 per cent in our study.

Scintiscans and chest roetgenograms are frequently used to assess the function of the transplanted lungs (7, 8, 10). In experiments on dogs it appeared that lung perfision scintiscan (1, 4) and chest roetgenograms (7, 8, 10) give a good indication of the perfusion and ventilation of the transplanted lung. Also, pulmonary function after the lung reimplantation can be evaluated by bronchospirometric (3,16), pneumoangiographic, bronchographic (16), pulmonary flowmetric (1, 4) studies.

Perfusion and ventilation of the transplanted lungs are affected independently by the reimplantation response. Perfusion is influenced by the patency of the vascular anastomoses and by hilar stripping of the lung. The patency of the pulmonary artery appeared to be most important. Stenosis of its anastomosis resulted in a very low perfusion of the lung immediately after transplantation (1, 3, 7, 16). The increased vascular resistance of the transplanted lung is caused by stenosis of vascular anastomoses (16). Even indistensibility of the pulmonary artery anastomosis has been shown to obstruct the perfusion of the lung.Indeed, the two dogs in our study died from respiratory insufficiency because of pulmonary artery (PA) stenosis. A widely patent PA immediately after transplantation results in initially normal perfusion of the lung, which is even better than after hilar stripping. The gradual decrease of the perfusion in this group is probably due to fibrosis of the anastomosis, as seen at death (7).

Hilar stripping of the lung causes permanently abnormal values of pulmonary vascular resistance, and mildly impaires perfusion (1, 3, 7, 8, 10, 14, 16). Our results support the conclusions of other authors that a constant decrease of perfusion in the transplanted lung is not caused by hilar stripping but rather by imperfect vascular anastomoses (13, 16). It is unclear how hilar stripping induces the transient decrease of perfusion. Blood vessels might be compressed by perivascular edema, which was present for some days after hilar stripping. However, this does not appear to be a satisfactory explanation for the decrease in perfusion,because the edema resolves rapidly, whereas perfusion remaines decreased for two weeks (7).

Wagner et al (13, 14) showed that blood flow to reimplanted lungs was lowest during the first postoperative week but returned to % 89 of preoperative measurement six weeks after operation, and upper lobar was more profoundly reduced by lung reimplantation than was lower lobar flow; six weeks after reimplantation, mean blood flow to lower lobes equalled that measured preoperatively. They concluded that vascular resistance of the reimplanted canine lung increased temporarily after canine lung increased temporarily after operation but returned to normal within 6 weeks, and the absence of anastomotic imperfections, this temporary increase in vascular resistance at resting blood flows was probably due to increased extravascular water and postoperative atelectasis, and the change was greatest in the upper-middle lobe and was not related to denervation or to obstruction of pulmonary veins. The findings related to the changes of PA pressures ini our study groupps were resembling to the outcomes of above studies.

One of the major complications after reimplantation of lungs in dogs is pulmonary hypertension and its causes are probably structural defects of the anastomosis of brochus, pulmonary artery or pulmonary veins. However, pulmonary hypertension has also been reported in dogs without structural defects, and in these cases the cause of the high pulmonary arterial pressure is usually attributed to the denervation of the reimplanted lung (5). Wildevuur et al (16) conclude that structural defects of the vascular anastomosis after reimplantation of lungs in dogs were always caused by technical failures associated with this type of surgery in dogs. Briefly, pulmonary hypertension after reimplantation may be caused either by anastomotic defects or by an intrinsic process involving an increase in vascular resistance.

Ventilation of the lung graft is decreased for some days after transplantation because of interstitiel and alveolar edema, which is abserved in the bronchus during transplantation, in histologic sections, and on chest roentgenograms (7). The increased densitiy of lung grafts on chest roetgenograms is the most common phenomenon of the reimplantation response described in dogs (2, 8, 10). We could histologically demonstrate that the edema formation increased proportionally to the duration of graft ischemia, confirming previous studies in dogs (2). The injurious effect of ischemia might be reduced by improved preservation of the lung graft, but this was not the aim of our study.

Pulmonary edema also develope with no ischemia of the lung after hilar stripping. Although the extent of the edema is mostly less than after transplantation, its histologic pattern is the same (7). It seems likely that pulmonary edema is caused by hilar stripping injury of the lung and is aggravated by ischemia. This explanation is in accordance with the findings of Wildevuur et al (16).

They showed that bilateral hilar stripping, when combined with ischemia of the lungs for at least one hour, diminished arterial oxygen tension. This injury of the lung by hilar stripping has been attributed to disruption of various structures: bronchial arteries, lymphatics, and nerves (8, 12). Our studies do not show which of these structures is most siguificant hilar stripping injury.

A noticeabale aspect of histology of transplanted and hilar-stripped lungs in the first week after the operation is the distribution of edema, extending from the hilus along vessels and brnochi toward the periphery. This edema may be overlooked if only peripheral biopsy specimen of the lungs are investigated (7, 8). These histologic findings in isogeneically transplanted lungs are charecteristic of the reimplantation response and in further studies could be distinguished easily from rejection phenomena in allografted lungs, where infiltration by mononuclear cells predominates (7).

Finally, this study on the reimplantation response in canine lungs shows that both perfusion and ventilation are mildly decreased by hilar stripping, and this decrease of perfusion is only transient, whereas a permanent decrease is caused by stenosis of vascular anastomoses resulting from imperfect suturing. The decrease of ventilation by hilar stripping in the case of transplantation is markedly aggravated by graft ischemia. This alliance of hilar stripping and ischemia provokes interstitial and alveolar edema, which disappears in toto within one week.

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