Left Lung Replantation with Immediate Right Pulmonary Artery Ligation

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A CONTROVERSIAL issue related to physiologic problems in experimental lung transplantation concerns the functional competence of the replanted lung. Ligation of the opposite pulmonary artery immediately after replantation of one lung is a straightforward experimental preparation for testing the integrity of the replant. However, attempts to achieve long-term survival of dogs subjected to this procedure have been unsuccessful for many years. Consequently, extensive research efforts [2, 7, 14] have evaluated the role of factors which accompany replantation (interruption of bronchial arteries and lymphatics, denervation, and ischemic injury) in the subsequent function of this lung. Many investigators have observed that in dogs the denervated lung loses the ability to vary its vascular resistance.[1, 2, 7] It is believed that following ligation of the opposite pulmonary artery, vascular resistance to the replanted lung remains stabilized despite the increase in blood flow; [2] this elevates pulmonary arterial pressure and causes pulmonary edema and right heart failure. Some investigators have considered these problems to be related to the dog's anatomy and physiology. solutions and became convinced that the They resorted to a change of species for Kenya baboon was a better animal than the dog for studying lung transplantation.[5, 9]

Meanwhile, investigators of canine lung transplantation have become increasingly aware that results and conclusions of their studies will not be valid unless anastomotic imperfections are considered negligible in assessing the functional status of the replanted lung.[3, 4, 8, 13] Benfield and Coon [3] observed a duplication of various changes previously reported concerning total lung replantation in dogs which had undergone division and reanastomosis of the atrial cuff of the left lung as an isolated procedure. In some dogs temporary occlusion of the contralateral pulmonary artery caused severe acute increases in pulmonary artery pressure; if these dogs had undergone total lung replantation, the increased vascular resistance would have been attributed to the consequences of replantation. Waldhausen and associates [14] also reported that failure of venous anastomosis of the replanted lung caused pulmonary hypertension. On the other hand, Inoue and associates,[8] Veith and Richards,[11-13] and Daicoff and co-workers [4] pointed out that the site of pulmonary artery anastomosis was responsible for increased vascular resistance of the replanted lung.

It may be natural to consider the Kenya baboon, a subhuman primate, more repre-

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sentative of man than the dog for use in such studies. Nonetheless, the continued use of dogs is indispensable for several reasons perhaps least of which is their easy availability. A critical re-appraisal is needed of innumerable and to a large extent equivocal studies on non-immunologic aspects of canine lung transplantation performed during the last 20 years. Moreover, the knowledge that dogs commonly fail to survive on the function of the replanted lung alone makes further use of this species interesting.

In the present study a satisfactory surgical technic of lung replantation was used to minimize anastomotic imperfections. Our objective was to re-examine the ability of dogs to survive on the function of a replanted lung alone.

Methods

Mongrel dogs weighing 15–20 Kg. were used. Anesthesia was light and consisted of intermittent intravenous doses of Surital (thiamylal sodium). Respirations were controlled with intermittent positive pressure by means of a Bird respirator delivering a 40–60% oxygen-air mixture. In a first group of five dogs the left pulmonary artery was divided and re-anastomosed which was followed immediately by ligation of the right pulmonary artery. In a second group of 25 dogs the left lung was removed and replaced and this was followed immediately by ligation of the right pulmonary artery. These procedures were performed through a left fifth intercostal space thoracotomy so that both pulmonary arteries could be dissected free and encircled with tape.

Both groups involved division and reanastomosis of the left pulmonary artery which was performed in the following manner: A Potts' clamp was applied vertically to the left pulmonary artery so that the first upper lobe branch would be at the top and the artery was divided 2–3 mm. distal to the clamp, between it and the upper lobe branch. The level of this branch was used as a landmark to avoid torsion during the subsequent anastomosis. In anastomosing the divided artery any suturing from within the lumen was scrupulously avoided; first one side was sutured with over-and-over 5-0 vascular silk sutures and then the Potts' clamp was rotated and the other side was sutured in the same manner.

Some other significant points of the replantation procedure are worth mentioning. The excised lung was cooled as rapidly as possible by perfusion (with 500 cc. of cold lactated Ringer's solution containing 50 mg. of heparin) through its artery at a pressure of 60 cm. The atrial cuff containing the ostia of the left pulmonary veins, the pulmonary artery and the bronchus were anastomosed in that order. The lung was ischemic about 45 minutes. In anastomosing the atrial cuff, suturing from within the lumen was avoided as in the case of the pulmonary artery. The posterior wall of the atrial cuff anastomosis was completed first as a continuous over-and-over suture (5-0 silk) and then the lung was retracted posteriorly and the anterior wall of the anastomosis was sutured. In this way intima-to-intima coaptation was obtained. For the bronchus, continuous 4-0 silk was used; the anterior wall was sutured from within the lumen everting all layers of both ends, then the posterior wall was readily sutured with an over-and-over continuous suture. The Satinsky clamp on the proximal bronchial end was then removed. Before the anastomosis, the distal bronchial end was trimmed to within 3–4 mm. of the lobar orifices. After the completion of the anastomosis a well-vascularized flap of surrounding tissue consisting of mediastinal pleura and bronchial lymph nodes was used to cover the posterior bronchial suture line. Postoperatively the endotracheal tube was usually removed

TABLE 1. *Pulmonary Arterial Pressures on Three Dogs Eight Months after Division and Re-Anastomosis of the Left Pulmonary Artery and Immediate Ligation of the Right Pulmonary Artery*

Dog No.	PAP Proximal to the Anastomosis	PAP Distal to the Anastomosis
1	35/15 ($\overline{25}$) mm. Hg	35/15 ($\overline{25}$) mm. Hg
2	30/15 ($\overline{20}$) mm. Hg	30/15 ($\overline{20}$) mm. Hg
3	28/16 ($\overline{20}$) mm. Hg	28/16 ($\overline{20}$) mm. Hg

within 2 or 3 hours and the drainage tube in the pleural cavity was removed on the evening of operation. The next day the dogs were permitted a regular diet. Antibiotic agents were administered for 1 week.

In three dogs of the replantation group pressures in the pulmonary artery proximal and distal to the site of the anastomosis were measured during operation, before and 15 minutes after ligation of the right pulmonary artery, with a pressure transducer connected to a silastic cardiac catheter. Pulmonary angiograms with pressure measurements on nine dogs and lung scans with macroaggragated radioactive serum albumin on seven dogs of this group were performed from 2 to 6 months after the procedure. Serial chest x-rays were taken during the postoperative period. Bronchograms using an oily contrast medium (Dionosil Oily) were obtained in five dogs from 5 to 8 months after operation. Arterial blood gases and pH were determined at frequent intervals during the postoperative period. Autopsies were performed on all dogs which died after the procedure.

The five dogs of the first group (left pulmonary artery anastomosis and right pulmonary artery ligation) were followed for long-term survival, in three of these dogs pulmonary artery pressures proximal and distal to the anastomosis were measured by opening the left chest 8 months after operation.

Results

Following operation the dogs usually regained consciousness within an hour. A significant observation was an increase in the respiratory rate at this time in all dogs of both groups. Generally the respiratory rate was 35–50 the day of operation and it further increased (45–70 at rest) the first postoperative day. This tachypnea was maintained for about 5 days and then the respiratory rate gradually became normal during the second postoperative week.

All five dogs of the first group are still alive and vigorously active more than 8 months after division and anastomosis of the left pulmonary artery and ligation of the right pulmonary artery. Their pulmonary arterial pressures are at the upper limit of normal and no pressure gradient exists across the anastomosis (Table 1).

Of the 25 dogs in the second group thrombosis at the vascular anastomoses was

TABLE 2. *Changes in Mean Pulmonary Artery Pressure during Left Lung Replantation with Immediate Right Pulmonary Artery Ligation*

	Before Replantation			After Replantation		
					Right PA Ligated	
	Control	RPA Clamped	RPA Unclamped	Left Lung	Proximal to LPA Anastomosis	Distal to LPA Anastomosis
No. 22	15	20	18	15	26	25
No. 23	12	25	15	14	25	25
No. 24	14	21	15	15	24	24

the cause of death in only three (dogs 3, 5, 13). Eighteen dogs lived more than 5 days, and 11 lived more than a month. Five dogs are still alive and active from 5 to 8 months after the procedure. Pulmonary arterial pressures measured proximal and distal to the anastomosis on three dogs are seen in Table 2; no pressure gradient was observed across the anastomosis. The causes of early death are seen in Table 3. Six dogs died during the first week with edema of the replanted lung. The results on dogs which survived more than a month after the procedure are summarized in Table 4.

Both arterial and venous phases of the pulmonary angiograms were normal on the left and were not visualized on the right (Figs. 1 and 2). No constriction was observed at the site of the anastomosis. Pulmonary arterial pressures were either at the upper limit of normal or moderately elevated (Table 4); there was no striking difference between the pulmonary arterial pressures of the two groups of dogs. All perfusion scans demonstrated normal and uniform perfusion of the replanted left lung with absent perfusion on the right (Figs. 3 and 4). Bronchograms were normal and the sites of the bronchial anastomoses were barely detectable (Fig. 5); however, disappearance of the contrast agent was not complete until the third or fourth day on the replanted lung, whereas the opposite lung was usually radiographically clear one day after bronchography.

TABLE 3. *Summary of the Results on Dogs Which Died within a Month Following Left Lung Replantation with Immediate Right Pulmonary Artery Ligation*

Dog No.	Survival (Days)	Anastomoses at Autopsy	Cause of Death
1	5	patent	Edema of the replanted lung
2	26	patent	Pneumonia in the replanted lung
3	7	Left atrial cuff thrombosis	Venous outflow obstruction in the replanted lung
4	7	patent	Edema of the replanted lung
5	5	Left atrial cuff thrombosis	Venous outflow obstruction in the replanted lung
6	4	patent	Atelectasis and pneumonia in the upper lobe of the replanted lung
9*	24	Left atrial cuff thrombosis	Venous outflow obstruction in the replanted lung
12	22	patent	Pneumonia in the replanted lung
13	4	patent	Edema of the replanted lung
14	9	patent	Several heartworms (*Dirofilaria immitis*) were present in the left pulmonary artery
18	4	patent	Edema in the replanted lung
20	7	patent	Empyema
23	1	patent	Edema of the replanted lung
24	4	patent	Edema of the replanted lung

* In this dog following replantation of the left lung the upper lobe could not be inflated and it was removed. The animal lived 24 days solely on the function of the replanted left lower lobe.

Discussion

Our results in this study show that dogs can survive solely on the function of the replanted lung. If operation is meticulously performed to eliminate the factor of unsatisfactory anastomoses, long-term survival of dogs with a raised but tolerable pulmonary arterial pressure can be achieved. As a matter of fact, the capacity of the dog's normal left lung to accept greater blood flow acutely without increasing the pulmonary artery pressure is significantly limited.[4] This implies that the modest increase in the pulmonary arterial pressure in our chronic survivors is not necessarily related

TABLE 4. *Summary of the Results on Dogs Which Lived More Than a Month Following Left Lung Replantation with Immediate Right Pulmonary Artery Ligation*

Dog No.	Survival	Pulmonary Angiogram	PAP (mm. Hg)	Lung Scan	Bronchogram	Remarks
7	8 months	Normal on the left, not visualized on the right	—	Perfusion normal on the left and absent on the right lung	Satisfactory	Alive and well, chest x-ray normal
8	161 days	Normal on the left, not visualized on the right	—	Perfusion normal on the left and absent on the right lung	—	Died of left lower lobe pneumonia
10	68 days	—	—	—	—	Died of intussusception
11	7½ months	Normal on the left, not visualized on the right	35/12	Perfusion normal on the left and absent on the right lung	Satisfactory	Alive and well, chest x-ray normal
15	7½ months	Normal on the left, not visualized on the right	35/10	Perfusion normal on the left and absent on the right lung	Satisfactory	Alive and well, chest x-ray normal
16	66 days	Normal on the left, not visualized on the right	$\overline{25}$	—	—	Died. Left lung was necrotic. Several heart worms (*Dirofilaria immitis*) were present in the pulmonary artery. Anastomoses were patent
17	7 months	Normal on the left, not visualized on the right	45/20	Perfusion normal on the left and absent on the right lung	Satisfactory	Alive and well, chest x-ray normal
19	155 days	Normal on the left, not visualized on the right	45/15	Perfusion normal on the left and absent on the right lung	—	Died of pneumonia of the left lung. Anastomoses were patent
21	34 days	—	—	—	—	Died with empyema. Anastomoses were patent
22	73 days	Normal on the left, not visualized on the right	$\overline{26}$	Perfusion normal on the left and absent on the right lung	—	Died of left lower lobe pneumonia. Anastomoses were patent
25	5 months	Normal on the left, not visualized on the right	$\overline{24}$	—	Satisfactory	Alive and well, chest x-ray normal

to the replantation procedure itself. Another point that needs emphasis is the reversible nature of possible edema in the replanted lung. Pulmonary edema (unaccompanied by findings of thrombosis or narrowing at the atrial cuff suture line)

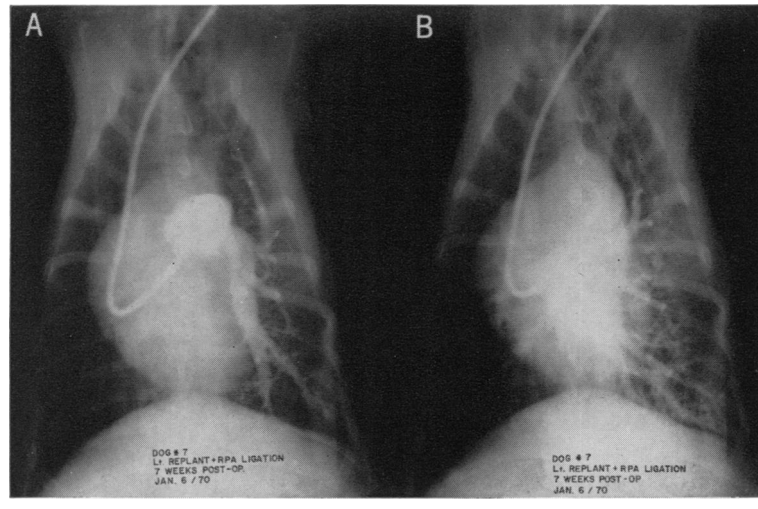

FIG. 1. Pulmonary angiogram of a dog 7 weeks after left lung replantation with immediate right pulmonary artery ligation: A—Arterial phase, B—Venous phase. The vascular tree of the left lung is normal and there is no constriction at the arterial anastomosis. Note that the vascular tree of the right lung is not visualized.

was a significant cause of early mortality. Varying degrees of edema were also observed during the first postoperative week, and disappeared completely by the end of the second week in dogs which later became chronic survivors. Subnormal arterial blood gas values frequently noted during this period became normal after the disappearance of the edema. We believe that potentially reversible ischemic and mechanical damage to the microvasculature of the graft during transfer is largely responsible for this edematous tendency which is augmented by any increase in the cardiac output (blood flow of the lung). During this period restricting the activity of the animal to a minimum is helpful. One should, therefore, be wary of attributing the aberrations in circulatory parameters related to the replanted lung during the first 2 or 3 postoperative weeks to denervation.

Naturally some temporary impairment of function and a reasonable mortality rate

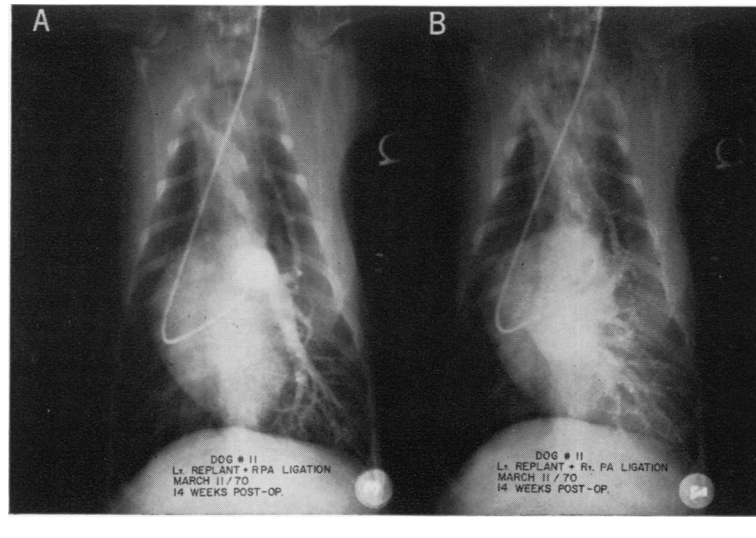

FIG. 2. Pulmonary angiogram of another dog 3½ months after left lung replantation with immediate right pulmonary artery ligation: A—Arterial phase, B—Venous phase. The vascular tree of the left lung is normal and there is no constriction at the arterial anastomosis. The vascular tree of the right lung is not visualized.

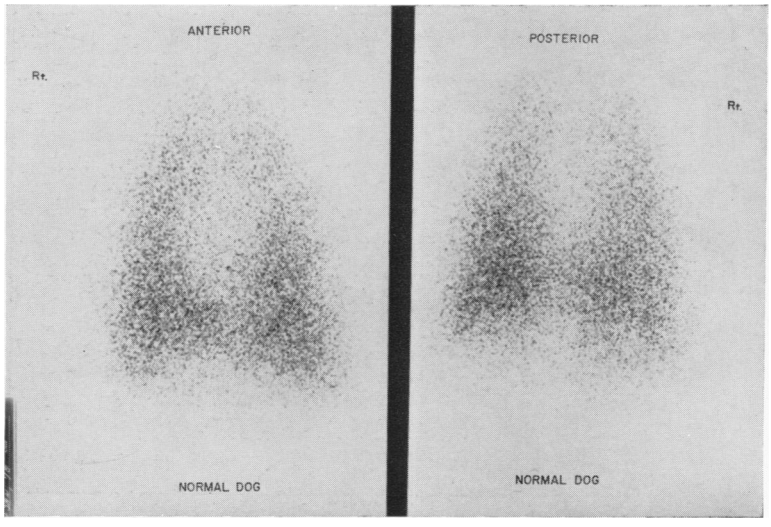

FIG. 3. Lung scan of a normal dog with macroaggragated radioactive serum albumin. This figure is to be compared and contrasted with the next figure.

are acceptable after removal and replacement of a lung especially when this is combined with contralateral procedures. Haglin and Arnar [5] who carried out some informative studies of lung replantation on baboons had a 30-day mortality of 42% following left lung replantation. Nevertheless, 12 of the survivors were subjected to contralateral pneumonectomy several months later with only two deaths. Four of the remaining ten baboons died within the subsequent 2½ months. Obviously, most of the deaths in their series as well as those in our own series were iatrogenic, rather than caused by failure of the replanted lung to serve the respiratory needs of the animal. The work of these investigators is appropriate in that a subhuman primate was used for a comparative experimental lung transplantation study because of its closer similarity to man. Joseph and Morton [9] have also had good results with baboons

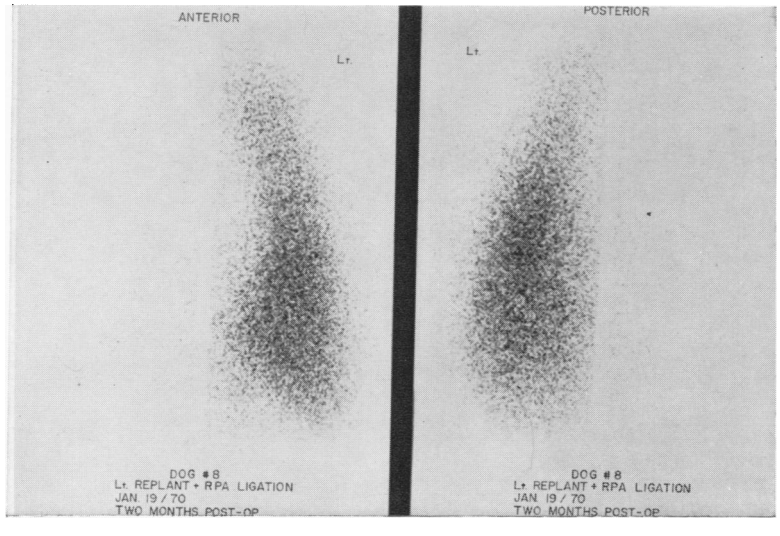

FIG. 4. Lung scan of a dog 2 months after being subjected to left lung replantation with immediate right pulmonary artery ligation. Normal and uniform perfusion of the left lung and absent perfusion on the right lung. All other lung scans were like this.

undergoing left lung replantation and immediate contralateral pulmonary artery ligation. In comparing our present data with the results of replantation studies on the baboon, however, there appear to be no major differences between the two species. The replanted dog lung also returned to normal frequently as demonstrated by survival despite the simultaneous ablation of the function of the opposite lung. It has been suggested that the dog lung (especially the upper lobes) is prone to atelectasis, and that breakdown of the bronchial anastomosis or later abnormal bronchograms of the replanted dog lung are to be expected.[5, 6] The experience of our group does not concur with this view. Observation of certain technical principles uniformly ensures a very satisfactory bronchial anastomosis with elimination of any early or late complications. Attempts to restore the continuity of the systemic arterial blood supply of the replanted lung to improve healing of the bronchus would not be worth the effort. It would seem that familiarity of the investigators with a given species is a more important element in predicting the results.

The cause of the increased vascular resistance of the replanted canine lung noted by a number of investigators is at the present time a matter of dispute. Allgood and associates,[2] as a result of their studies concerned with immediate alterations in dynamics after lung replantation and hilar stripping, have attributed the inability of the replant to vary its vascular resistance to denervation. Wildevuur's group [15] observed later development of pulmonary hypertension in replanted lungs. Recently, however, there has been a tendency to attribute most of the abnormal characteristics observed in lung replants (assuming a satisfactory atrial cuff anastomosis) to the indistensible pulmonary arterial anastomosis rather than to altered innervation.[4, 8, 12, 13] Veith and Richards,[10, 11, 12, 13]

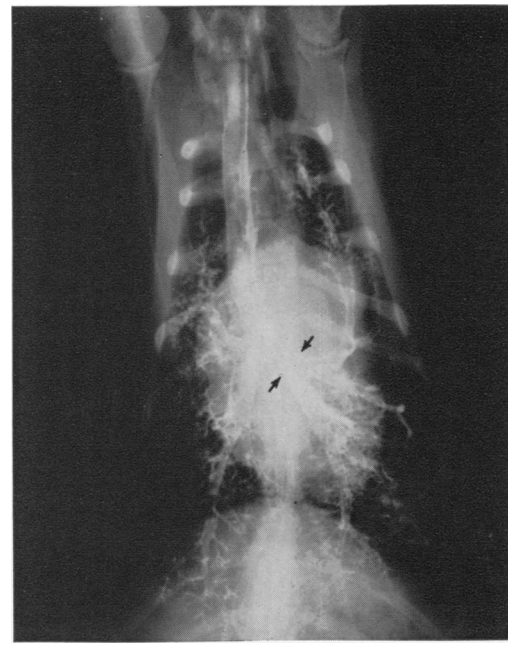

FIG. 5. Bronchogram of a dog 5 months after left lung replantation with immediate right pulmonary artery ligation. Bronchial anastomosis is not detectable (it is presumably at the site shown between the arrows). Bronchial tree of both lungs are comparable and normal.

have recently published data which they interpreted to show that the high fixed vascular resistance observed with right pulmonary artery ligation following left lung replantation was located at the arterial anastomosis. They believed they had avoided this fixed resistance by angioplastic widening of the pulmonary artery anastomosis. In their opinion, with distensible arterial anastomoses, replanted or allografted lungs normally vasodilate with increased flow and can unilaterally sustain dogs in which they are implanted with simultaneous contralateral pulmonary artery ligation. Briefly, they placed a snug-fitting, non-constricting cloth band around the left pulmonary artery and then immediately ligated the right pulmonary artery. Nine of ten such dogs died within 48 hours. In another ten dogs the right pulmonary artery was ligated immediately

following left lung replantation using a standard pulmonary artery anastomosis. All died within 48 hours also. In both these groups ligation of the other pulmonary artery caused a significant pressure gradient across the pulmonary artery anastomosis or band. In contrast, eight of ten dogs receiving either a replant or allograft with a distensible (with patch angioplasty) anastomosis survived more than 5 days after operation without any pressure gradient across the anastomosis.

In the light of our own data, however, a clear definition of so-called standard anastomosis is urgent. In this study we have performed the pulmonary artery anastomosis without angioplasty and also even oblique sectioning of the artery was deliberately avoided so as to produce an experimental model which could be used as a baseline for evaluating the need for angioplastic widening of the pulmonary artery. The perpendicularly divided artery was anastomosed carefully so as not to compromise its lumen. All dogs of the first group are alive now 8 months after the procedure and the results of the second group are satisfactory in terms of survival (Tables 3 and 4); pulmonary arterial pressures are not much higher than one would expect with the left lung accommodating the entire cardiac output.[4] No significant pressure gradient was observed across the anastomosis (Tables 1 and 2). We are thus convinced that enlarging the arterial anastomosis by patching is not a requisite and unnecessarily compromises the simplicity of the procedure. Nevertheless, an important consequence of these meticulous studies by Veith and Richards [10, 11, 12, 13] has been the demonstration that a lung replanted or transplanted with a suitable technic can have a near normal decrease in vascular resistance with increasing flows, and that the recipients of such grafts can tolerate simultaneous ligation of the contralateral pulmonary artery. Similarly, a study by Daicoff and associates [4] which demonstrated that even minimal constriction of the pulmonary arterial anastomosis produces a significant obstruction when the entire cardiac output passes through it is an admonition for accurate anastomosis.

Summary

In 25 dogs left lung replantation and right pulmonary artery ligation was performed. Eleven lived more than a month, the longest survivor is alive 8 months after the operation. Pulmonary arterial pressures were moderately elevated. In five dogs the left pulmonary artery was divided and simply re-anastomosed, then the right pulmonary artery was ligated; no significant pressure gradient developed across the anastomosis. All five dogs are alive 8 months after operation.

These studies demonstrated that when operation is meticulously performed to eliminate unsatisfactory anastomoses, long-term survival of dogs solely on the function of the replanted left lung with a modest and tolerable increase in pulmonary arterial pressure can readily be achieved. Although constriction of the vascular anastomoses should be conscientiously avoided, an angioplastic widening has not been necessary. It appears that the various previously reported changes in the function of the replanted lung are to a large extent a reflection of technical imperfections.

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