Physiologic Changes Associated with Autotransplantation of the Lung

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THE MAJOR obstacle to successful lung transplantation remains lack of control of the immune response of the recipient. Nevertheless, with autotransplantation of the lung, without problems of rejection, function by the grafted lung has been disputed. Several investigators have shown that the dog can survive both acute and chronic bilateral reimplantation of the lung.[7, 10] In general these lungs have shown some functional abnormalities. Faber and co-workers successfully studied five dogs with bilateral grafts, most of which had some elevation in pulmonary vascular resistance as late as ten months following operation.[3]

In the present study components of autotransplantation, sectioning of nerves, ligation and division of bronchial arteries or reanastomosis of veins, were analyzed to elucidate physiologic changes in autotransplanted lungs. It is evident that mere survival with a transplanted lung should not be the goal of such a major undertaking, but rather that function should be essentially normal.

Method

Mongrel dogs weighing between 12 and 18 Kg. were anesthetized with thiopental sodium (30 mg./Kg.) and ventilated with a piston respirator. A left thoracotomy was performed under sterile conditions through the fifth intercostal space, and one of the following procedures carried out:

Group I. In six control dogs the chest was merely opened and closed in the standard manner.

Group II. In four dogs vagosympathetic denervation was performed. The resected sympathetic chain included the sixth dorsal sympathetic ganglion at its lower end and the caudal cervical ganglion at its upper end. The vagosympathetic trunk was exposed in the midcervical region, and an inch-long segment was excised.

Group III. In five dogs the bronchial arteries to the left main stem bronchus were identified coming from either the aorta or the intercostal arteries and were ligated and divided.

Group IV. In eight dogs the pulmonary arteries were exposed and divided. The distal ends were then perfused with 60–80 ml. 6% dextran (avg. mol. wt. 110) in saline with 3,000 U aqueous heparin/300 ml. The pulmonary arteries were reanastomosed with 6-0 Dacron suture, using a posterior everting Blalock suture and a continuous anterior suture. After one hour clamps were released, and the circulation through the lungs re-established.

Group V. In six dogs the pulmonary veins and the left atria were exposed, and after the lungs were flushed with 60–80 ml.

Submitted for publication September 14, 1966.

Supported by USPHS Grants HE09243 and HE02035, Heart Program Project H-6308 from the USPHS (NHI), and by the Riley Memorial Association.

* Recipient USPHS (NHI) Career Development Award.

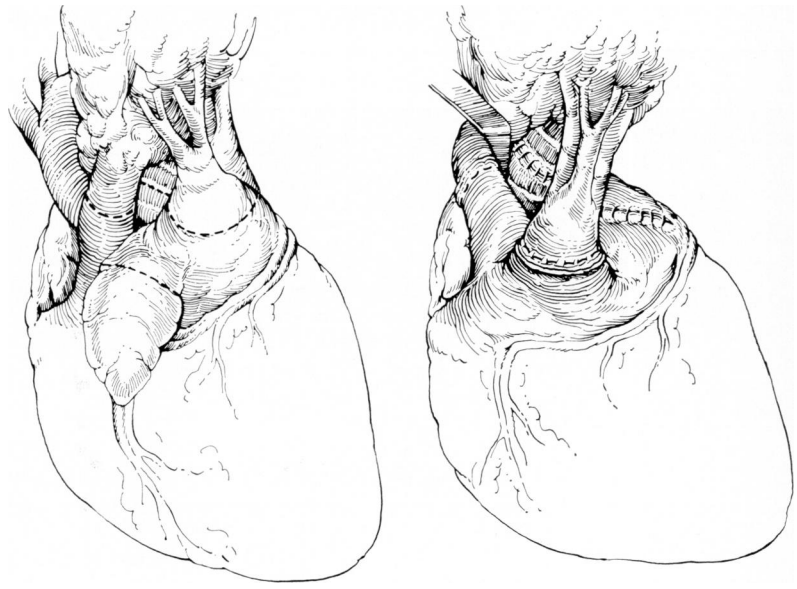

FIG. 1. Surgical technic of left lung autograft.

dextran-heparin solution, the veins and an attached cuff of corresponding atrium were excised after pulmonary arteries, bronchi, and other hilar structures such as bronchial arteries were occluded with a vascular clamp. Atrial defects were closed with fine Dacron sutures. The cuffs of left atria and veins were reimplanted into the atrial appendages. Blood flow to the lungs was reestablished after approximately one hour.

Group VI. In eight dogs the entire left hilia were stripped leaving only bare pulmonary arteries and veins. The bronchi, pulmonary lymphatics, autonomic nerves, and bronchial arteries were transected. The bronchi were reanastomosed with fine Dacron sutures.

Group VII. In eight dogs hilar stripping, as described in Group VI, and division of the pulmonary arteries, as described in Group IV, were carried out.

Group VIII. In nine dogs the pulmonary arteries, bronchi, and pulmonary veins with a cuff of atrium were exposed, clamped, and divided. Lungs were removed from the chest and perfused through pulmonary arteries with 60–80 ml. dextran-heparin solution. Cuffs of atrium were sutured to the incised left atrial appendages with continuous everting Dacron sutures (Fig. 1). The pulmonary arteries were reanastomosed with continuous everting mattress sutures. The bronchi were repaired last using Dacron. No attempts were made to reanastomose nerves, bronchial arteries, or lymphatics.

Left lungs were reimplanted in three Macaca rhesus monkeys, weighing between 8 and 10 Kg. in a manner similar to that used in dogs.

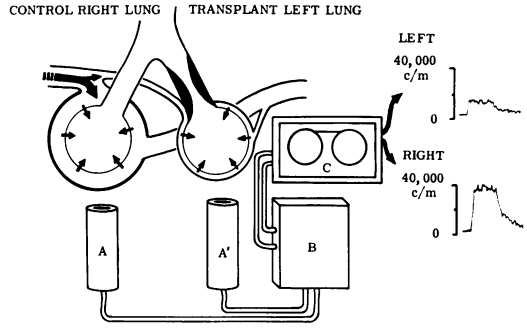

FIG. 2. Diagram of the method for pulmonary function studies with Xenon[133]. A and A') right and left cylindrical lead collimators. B) count rate meter. C) tape recorder. Representative curves from a control right lung and autografted left lung are shown on the right.

TABLE 1. *Hemodynamic Data After Canine Lung Autotransplantation*

	Both Lungs Perfused	Transplanted Lung Perfused
Mean Pulmonary Artery Pressure	15 ± 4 mm Hg	42 ± 9 mm Hg*
Mean Femoral Artery Pressure	120 ± 15 mm Hg	
Cardiac Output	2.69 ± 1.2 L/min	2.81 ± 1.L/min
Arterial O_2 Saturation	Control Lung Perfused	Transplanted Lung Perfused
Air Breathing	88 ± 9%	76 ± 5%*
O_2 Breathing	98.2 ± 1%	92 ± 1%*

* $p < 0.05$

TABLE 2. *Ventilation Data After Canine Lung Autotransplantation*

Study	Control Lung	Transplanted Lung
O_2 Consumption/min	102 ± 50 ml	21 ± 10 ml*
Minute Ventilation	2.92 ± 0.9 L/min	1.46 ± 0.7 L/min*
Ventilation/O_2 Consumption Ratio	3.4 ± 0.3	9.0 ± 3.1*
Carbon Monoxide Absorption	Transplanted Lung/Control Lung Ratio 0.38 ± 0.2	

* $p < 0.05$

TABLE 3. *Normal Control Dogs*

	Xenon Study		Autopsy	
Dog No.	Days Postop	Count Ratio	Days After Xenon	Findings
N-1		1.28		
N-2		1.05		
N-3		1.18		
N-3		1.18		
N-4		0.99		
N-5		1.07		
	Control Thoracotomy			
60	7	1.03	128	normal
61	7	1.13	128	normal
68	8	1.03	2	normal
103	0	0.98		
	2	1.2		
	4	0.84	20	normal
104	0	1.1		
	2	0.96		
	4	1.01		
	25	0.95	9	normal
106	1	1.1		
	3	1.2		
	14	1.1	9	normal

The animals in all groups were then studied for from one day to 1.5 years, sacrificed, and autopsied. Sections of lungs from both hilum and periphery were taken for microscopic study.

Cardiac catheterizations were performed in the usual manner, using a Dotter triple lumen balloon catheter passed through the right external jugular vein. By inflation of the balloon in the right or left pulmonary artery, the contralateral artery pressure could be measured when total cardiac output was diverted through that lung. Cardiac output was measured by the Fick principle. Ventilation and oxygen consumption for each lung were measured separately with a Lattegola tracheal divider.[6]

Regional perfusion of each lung was measured by injection of $Xenon^{133}$ as described by Ball *et al.*[1] (Fig. 2). Animals were anesthetized with thiopental sodium, and, after endotracheal intubation, placed

TABLE 4. *Denervation*

Dog No.	Xenon Study: Days Postop	Xenon Study: Count Ratio	Autopsy: Days After Xenon	Autopsy: Findings
17	17	1.76	370	normal
19	17	1.01	370	normal
20	17	1.2	387	normal
21	17	1.1	381	normal
		Division of Bronchial Arteries		
984	374	1.17	358	normal
12	20	1.25	387	normal
13	17	1.0	399	normal
14	20	1.25	384	normal
15	17	1.01	384	normal
		Division of Left Pulmonary Artery		
1	20	1.28	67	normal
18	16	0.95	84	normal
25	16	1.25	67	normal
31	14	1.25	121	normal
66	16	1.14	187	normal
67	17	0.94	196	normal
78	21	3.49	88	LPA occluded
99	29	1.3	120	normal
		Division of Left Pulmonary Veins		
41	58	2.08	117	LMPV stenosed; LUPV occluded
43	98	1.42	168	LPV stenosed
45	81	1.4	128	LUPV occluded
86	21	1.26		lost
90	21	2.19	64	LMPV occluded; LUPV
93	21	1.69	58	LPV occluded

on their abdomens. Two 1.25-inch scintillation counters, fitted with 4-inch cylindrical lead collimators, were placed over the chest posteriorly at the apex of the diaphragm, a point determined by previous fluoroscopy.

The lungs of five dogs with left lung autotransplants and three Macaca rhesus monkeys with lung grafts were radioscanned after intravenous injection of macro-aggregated radio-iodinated albumin, as described by Sabiston and Wagner.[8] These studies were performed from three to six months after transplantation.

Results

Results of cardiac catheterization in five dogs with left lung autotransplants are shown in Table 1. There was marked elevation of pulmonary artery pressure when cardiac output was forced through the reimplanted lung by balloon occlusion of the appropriate pulmonary artery. Occlusion of the previously divided and anastomosed pulmonary artery, however, did not raise the pressure. Since cardiac output remained essentially unchanged, the rise in pressure with occlusion of the normal pulmonary artery was due to an abnormally high vascular resistance across the transplant.

When breathing air, the systemic arterial oxygen saturation fell to $76 \pm 5\%$ when the transplanted lung alone was perfused. A slightly reduced arterial oxygen saturation was also present when only the control lung was perfused. This was com-

TABLE 5. *Hilar Stripping and Division of Bronchus*

Dog No.	Xenon Study: Days Postop	Xenon Study: Count Ratio	Autopsy: Days After Xenon	Autopsy: Findings
2	38	0.98	453	normal
10	16	1.22	455	normal
32	15	2.12	7	bilateral pneumonia
110	3	1.24	8	normal
111	2	1.17	6	expired, unknown cause
115	8	0.94		
	57	1.3	8	normal
117	7	1.61	57	normal
123	6	1.96	8	Lt. empyema, lung consolidation, necrosis of bronchus
	Hilar Stripping, Division of Bronchus and Left Pulmonary Artery			
34	150	1.94	97	normal
35	150	1.6	97	LPA occluded
36	150	1.22		lost
37	10	1.26	14	normal
48	21	1.76	210	bronchus & LPA obstructed
49	37	1.22	246	normal
52	21	2.45	272	normal
53	22	1.22	217	normal

patible with the abnormal ventilation perfusion relationship commonly observed in anesthetized dogs. Breathing 100% oxygen raised the arterial saturation, but some hypoxia was still present when only the transplanted lung was perfused. These changes were statistically significant.

Differential bronchospirometry in five dogs showed significant reduction in minute ventilation and a greater decrease in oxygen consumption with a consequent rise in the ventilation oxygen consumption ratio of the lung transplant (Table 2). Carbon monoxide absorption of the transplanted lung was greatly reduced, as shown by a low ratio when compared to the control lung.

Xenon studies were carried out in 59 dogs and in three Rhesus monkeys. Perfusion ratios, comparing experimental to opposite control lung, were considered abnormal if greater than 1.3. Results are shown in Tables 3, 4, 5, 6. In five control animals, without an operative procedure, count ratios were close to 1.0 ranging from 0.99 to 1.28.

Group I, Control Thoracotomy. In six dogs the left chest was opened for one hour and then closed. The dogs were studied on the day of operation and at intervals of up to 25 days. All animals had normal ratios, and no abnormalities were found at autopsy.

Group II, Left Lung Denervation. The ratios in three of four dogs were normal, ranging from 1.0 to 1.2. A fourth animal had a ratio of 1.76, although all animals in this group were normal at autopsy.

Group III, Left Bronchial Artery Ligation. Five animals in this series had normal ratios ranging from 1.00 to 1.25 and at autopsy, no abnormalities were found.

Group IV, Division of Pulmonary Artery. In eight dogs with left pulmonary arteries transected and reanastomosed all but one had normal Xenon ratios ranging from 0.94 to 1.3. At autopsy pulmonary arteries were patent in those dogs with normal

TABLE 6. *Left Lung Autograft*

Dog No.	Xenon Study: Days Postop	Xenon Study: Count Ratio	Autopsy: Days After Xenon	Autopsy: Findings
191	468	1.17	351	normal except for granulation tissue in bronchus
325	443	1.8	351	bronchus occluded
5	31	1.33	402	abcess LUL bronchus and LPV stenosed
22	11	1.32	400	normal
24	28	1.51	370	bronchus, LPA and LPV stenosed
109	0	2.89		
	5	2.55		
	7	1.23		
	12	1.64		
	27	1.34		
	47	1.68		
	73	2.06	8	bronchial cartilage absent
112	1	3.56		
	16	1.41		
	36	2.15		
	65	1.71	8	abcess LUL; bronchial cartilage absent; LUPV and LMPV occluded
126	5	4.1		
	25	1.55		
	54	1.01	8	thick tracheobronchial secretions; bronchial cartilage absent
16	16	1.6		
	102	1.36	8	LUPV occluded
Monkey No.				
1	65	1.89	372	normal
2	40	2.25		
	459	1.75	8	abcess LUL; LPA, LPV and bronchus obstructed
3	27	2.73		
	448	2.26	9	abcess LUL; LPA, LPV and bronchus obstructed

ratios, although a circular scar at the site of anastomoses did not have the usual elasticity of adjacent vessel. In one dog with an abnormal perfusion ratio (3:49), the pulmonary artery was stenosed at the site of anastomosis.

Group V, Division of Pulmonary Veins. Five dogs had abnormal Xenon count ratios over the chest, and, at autopsy, had either one or more pulmonary veins completely blocked by scar or severe stenosis at the site of the anastomosis. One dog had a normal perfusion ratio, but was unfortunately lost to follow up.

Group VI, Left Hilar Stripping and Division of the Bronchus. In five dogs with left hila stripped of nerves, lymphatics, and bronchial arteries and transection and reanastomoses of the bronchi, normal perfusion ratios were found, ranging from 0.94 to 1.24. Three dogs had abnormal ratios (1.61, 2.12, 1.96); two of these animals had pneumonia, one also had empyema. The third dog had no abnormalities at autopsy performed 57 days after a perfusion ratio of 1.61 was measured.

Group VII, Hilar Stripping and Division of the Bronchus and Division of the Left Pulmonary Artery. Four of eight dogs had normal perfusion ratios (range 1.22 to 1.26), and three had no abnormalities at autopsy. The fourth animal was lost. Four

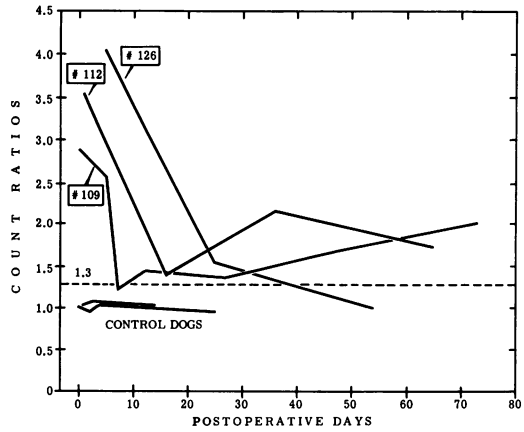

FIG. 3. Postoperative serial Xenon[133] studies of three dogs with left lung autografts. The count ratios over the control right and operated left lungs are shown on the ordinate. The findings in two control dogs with a thoracotomy are also shown remaining below a ratio of 1.3.

dogs had high perfusion ratios (1.6, 1.94, 1.76, 2.45), but at autopsy only two had some narrowing of the pulmonary anastomoses. The other two had no abnormalities.

Group VIII, Left Lung Autografts. Five dogs had standard autografts of the left lung. They were studied with Xenon[133] from 11 to 468 days after operation. All but one (No. 191) had abnormal perfusion ratios, although two dogs had ratios near normal (Nos. 5 and 22). Autopsies were performed approximately one year after the Xenon tests. Two dogs (Nos. 191 and 22) were essentially normal anatomically, although one had some granulation tissue at the bronchial anastomosis. Both animals had normal or near normal perfusion ratios. Four dogs had partial or complete occlusion of bronchi, pulmonary arteries, or pulmonary veins. In some more than one anastomosis was involved. One dog had an abscess cavity in the left upper lobe.

Four additional dogs, with standard autografts, had serial Xenon tests from the day of operation to 102 days. All four animals had considerable initial improvement of perfusion ratios, two actually reaching normal (Fig. 3). However, two dogs again had rises in perfusion ratios. At autopsy, two dogs with ratios of 1.01 and 2.06 had

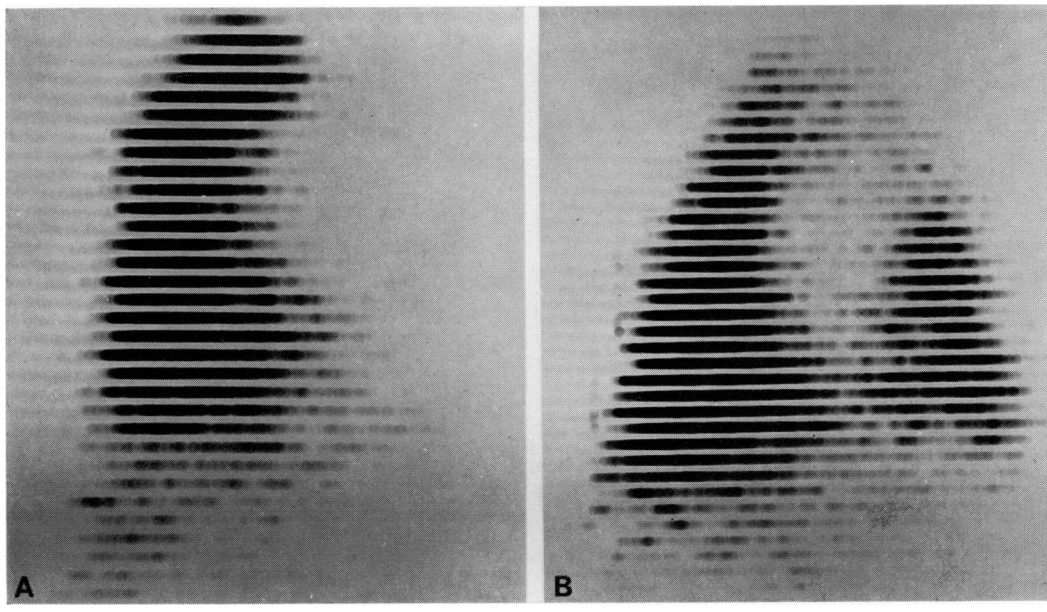

FIG. 4. Lung scans with macro-aggregated radioactive serum albumin in a monkey and a dog. A) little radioactivity can be detected over the autografted left lung of a monkey, while the scan from the normal right lung is readily seen, suggesting a marked discrepancy of lung perfusion between right and left. B) a scan in a dog with left lung autograft shows some decrease in perfusion of the left upper lobe while the lower lobe appears more normal.

patent anastomoses. The third dog, with an abnormal ratio (1.7), had an abscess cavity in the left upper lobe, with consolidation of the remaining lobe. The upper and middle lobe veins were occluded and the lower lobe and its vein were normal. The fourth dog, with a ratio of 1.36 eight days prior to autopsy, had an occlusion of the upper lobe pulmonary vein. All four dogs had no bronchial cartilage distal to the anastomosis of the bronchus. The mucosa was atrophic, and the bronchus was pliable. Microscopic sections showed necrosis of the bronchus for approximately 1 to 2 cm. distal to the anastomosis.

The three rhesus monkeys all had abnormal Xenon tests, with ratios ranging from 1.89 to 2.73 approximately four weeks after operation, while preoperative control values ranged between 1.03 and 1.15. At autopsy one year after implant, one animal with a ratio of 1.89 had normal anatomical findings, save for some old granulomatous nodules. Unfortunately, no recent Xenon study was done. The other animals had large abscess cavities of the left upper lobes with obstruction of all three anastomoses.

Lung scans in both dogs and monkeys after injection of macro-aggregated radioiodinated albumin confirmed results of the Xenon studies, and, in addition, suggested that the most frequent site of inadequate perfusion after left lung transplant was the left upper lobe. Representative scans are shown in Figures 4A and B.

Discussion

The use of $Xenon^{133}$ for assessing regional ventilation and perfusion and external counting was first described by Knipping and co-workers,[5] and it was amplified more recently by Ball, Steward, Newsham, and Bates.[1] Quantitative data can be obtained by the use of a combined single-breath and rebreathing technic together with intravenous administration of dissolved $Xenon^{133}$. Only one counter over each side of the chest was used in these experiments, as the dog has such a narrow upper thorax, making counts in this region unreliable. Control studies in normal dogs showed a slightly higher count over the right chest when compared to the left, and a count ratio range of from 0.9 to 1.3 was accepted as normal. Washout ratios did not add significantly to this study.

The $Xenon^{133}$ test, as performed, does not discriminate between differences in regional perfusion of one lung as precisely as do injections of macro-aggregated radioiodinated albumin and lung scanning. It does, however, permit rapid and reasonably accurate screening of a large number of animals and the results correspond well to those obtained with lung scanning.

The method of pulmonary denervation used was similar to that described by Shumacker and associates.[9] This method avoided transection of mediastinal lymphatics and bronchial arteries, although complete denervation is far less assured when compared to autografting. Xenon perfusions in this group of animals were abnormal in one dog. At autopsy this animal had normal anatomical findings, and the discrepancy between test results and autopsy one year later, cannot be explained. Left-sided pneumonia or atelectasis which subsequently resolved may have been the cause.

Bronchial artery ligation and division was performed without gross injury to mediastinal lymphatics or nerves. The completeness of the vessel transections was studied by injection of a Barium sulfate-gelatin-formalin mixture into the descending thoracic aorta. No barium entered the hilus of the lung after bronchial artery transection. All animals had normal perfusion ratios, and at autopsy all had essentially normal lungs.

Stripping of hilar structures, leaving pulmonary arteries and veins bare, and tran-

secting and reanastomosing the bronchi should simulate physiologically autografted lungs. However, studies with Xenon^{133} suggested no elevation of vascular resistance in either the immediate postoperative period or as late as six months following operation. All but one dog with high ratios had pneumonia and this dog had an elevated ratio one week after operation, but when autopsied two months later was normal.

It is difficult to conceive of nerves or lymphatics remaining intact following hilar stripping and division of bronchi. Other authors found similar normal vascular resistance in stripped lungs, although one group of investigators showed some increase in pulmonary vascular resistance. It is our impression that these dogs have difficulty with pulmonary secretions. Dogs with bilateral stripping of the hilum, done for another study, or unilateral stripping and contralateral pneumonectomy had a high mortality due to atelectasis and pneumonitis. Bilateral absence of pulmonary and bronchial reflexes inhibits or depresses the cough reflex and influences respiratory rhythm. Further studies on pulmonary denervation to clarify these points are needed.

To further elucidate why autografts which uniformly showed elevation in pulmonary vascular resistance differed from stripped lungs, a number of dogs had transection and reanastomosis of pulmonary arteries added to stripping. Three of these animals had normal perfusion ratios and at autopsy no abnormalities, while four had significant decreases in counts over the left chest. Two animals had marked stenosis or obliteration of the pulmonary arteries. Studies in other dogs with division and reanastomosis of the pulmonary veins showed that six had abnormal perfusion ratios. At autopsy these animals had severe stenosis of the anastomosis. One animal had normal Xenon^{133} tests but was lost to follow up.

Catheterization data showed marked pulmonary hypertension in all animals with autotransplants and in addition, there was a marked decrease in oxygen consumption. The findings, suggestive of an abnormal ventilation perfusion ratio, were borne out by Xenon^{133} studies. These severe abnormalities in the immediate postoperative period persisted up to 1.5 years after the operation. The late findings are consistent with anatomical obstruction of bronchial, pulmonary arterial, or venous anastomoses. As pulmonary vascular resistance was elevated immediately after implant, anatomical changes could not have been a factor. Retained secretions and atelectasis elevate pulmonary vascular resistance, but not sufficiently in animals with hilar stripping. Pulmonary veins are said to have a sphincteric mechanism,[4] and venous spasm could play a role in early vascular changes. In this light four dogs followed through the postoperative period, are of interest in that they showed progressive improvement (Fig. 3).

Previous studies from this laboratory showed no abnormality of pulmonary surfactant content and static compliance of the reimplanted lung.[11] This might have been predicted as the pulmonary artery supplies the alveolus, which is responsible for elaboration of the lipoprotein. Bronchi and bronchioles are damaged by grafting because branchial arteries are permanently interrupted. That bronchial artery ligation did not affect the lung is explained by the fact that blood supply to bronchial submucosa was intact in animals in which bronchial arteries alone are divided. Necrosis and associated edema of the bronchi at the anastomosis early in the postoperative period (seven to ten days), may be a factor in the abnormal ventilation of these animals. It is not established whether distal bronchi can react to stimuli by constricting or dilating, or whether ciliary epithelium functions.

These studies suggest that elevation in pulmonary vascular resistance is due initially to venous spasm and is accentuated by atelectasis. With time, usually about three to four weeks, these factors subside and pulmonary vascular resistance returns to normal. This improvement may be interrupted by gradual stenosis and obstruction at one of the anastomotic sites, particularly in veins.

As animals with one denervated lung and normal vascular resistance tolerate contralateral pneumonectomy or lung denervation poorly, denervation must have some influence other than on pulmonary vascular resistance, probably changes in breathing or cough reflexes.

Whether interruption of bronchial arteries permanently damages distal bronchi and ciliated epithelium is not known but may be a significant adverse effect of lung reimplantation.

Summary

Following pulmonary autotransplantation in five dogs, cardiac catheterization and ventilation studies showed both high pulmonary vascular resistance and decreased diffusion in the autotransplanted lung. Fifty-nine dogs were given intravenous injections of radioactive Xenon^{133}, and perfusion ratios of the control right lung and the manipulated left lung were obtained by comparing counts over both chest walls. The following necessary steps in autotransplantation of the lung, were evaluated: 1) thoracotomy, 2) denervation, 3) bronchial artery ligation, 4) division of the pulmonary artery, 5) division of the pulmonary veins, 6) hilar stripping and division of the bronchus, 7) hilar stripping, division of the bronchus and pulmonary artery, and 8) left lung reimplantation.

At autopsy animals having abnormal Xenon tests had some obstruction of one or more of the anastomoses, while the other animals were essentially normal. Necrosis of bronchi at suture lines was common. These studies suggest that pulmonary hypertension of the autotransplanted lung is due to failure of vascular anastomoses, especially of veins. Transection of nerves, lymphatics, and bronchial arteries alone had little effect. Studies in three monkeys confirmed these findings.

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