Re-Initiation of Compensatory Lung Growth after Subsequent Lung Resection

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Background

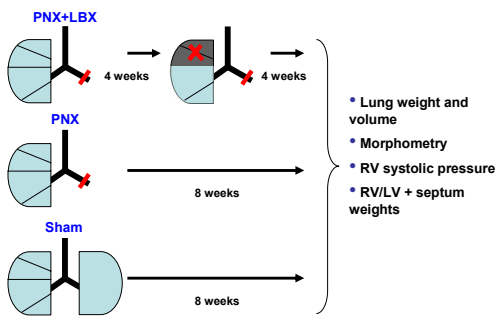
Pneumonectomy (PNX) or lobectomy (LBX) are often the last option for treatment in patients that otherwise cannot be cured such as patients with lung cancer or congenital lobar emphysema. In the management of lung pathologies such as cancer, the chance of local recurrences after an initial lung resection have an incidence from 1 to 5% per year; and repeat resection comes with significant risk of death and complications compared with the initial surgery.

In experimental animals PNX induces rapid compensatory lung growth (CLG) of the remaining lung where lung weight, volume, DNA, and protein are restored to control levels by 3 weeks. This CLG occurs to maintain the lung's vital function of providing O_2/CO_2 exchange. Although CLG has been documented in children, it has not been reported in adult patients. Our ultimate goal is to be able to manipulate those mechanisms that regulate and induce CLG (alveolarization) to benefit patients with end-stage lung disease or injury, or to induce healthy lung maturation in severely premature infants.

To our knowledge, there have been no animal studies into sequential lung resection to explore the potential of the lung to undergo more than one episode of CLG. In the present study, our objectives were to: 1) utilize a model of sequential lung resection in the adult rat, 2) describe the CLG process in this model, and 3) explore the cardiopulmonary effects of sequential lung resection.

Materials and Methods

Outline of the groups and measurements:



Materials and Methods

Surgery. Adult, male Sprague-Dawley rats were anesthetized with inhaled halothane followed by endotracheal intubation and ventilation with room air. Left pneumonectomy (**PNX**, n=9) was performed through a left thoracotomy. The left hilum was isolated and ligated with a titanium clip and the left lung excised. Sham surgery (**Sham**, n=8) consisted of left thoracotomy only. Animals in the **PNX+LBX** group (n= 6) underwent a left PNX followed by 4 weeks of recovery, after which a right bi-lobectomy was performed followed by another 4 weeks of recovery. For the right bi-lobectomy, animals underwent a right posterolateral thoracotomy and the upper and middle lobes were ligated with a titanium clip and excised. The chest was closed in layers.

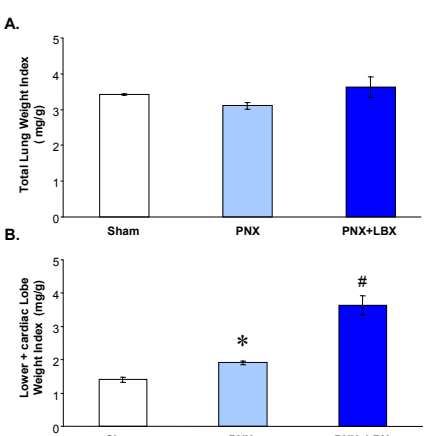
Lung Harvest and Weight/Volume Indices. Four weeks after bi-lobectomy in PNX+LBX group (8 weeks after PNX or Sham surgery), rats were anesthetized and lungs were blotted dry, and weighed. The upper and middle lobes were then ligated and carefully dissected out, and the lower + cardiac lobe weight was obtained. To obtain lower + cardiac lobe volumes, lower + cardiac lobes received intratracheal instillation of 4% paraformaldehyde to a pressure of 25 cmH_2O. The total lung volume was obtained by volume displacement.

Lung Morphometry. Lung morphometry was performed on hematoxylin and eosin stained slides (5 random fields per animal) using a three-level sampling technique and point counting technique as previously described (*J. Thorac. Cardiovasc. Surg.* 120:916-22, 2000).

Right Ventricular Hypertrophy and Systolic Pressure. Right ventricular systolic pressure (RVSP) was measured by direct intracardiac puncture. At death, hearts were removed and dissected to isolate the free wall of the RV from the left ventricle and septum (LV+S). The ratio of RV and LV+S weight (RV/LV+S) was used as an index of RV hypertrophy, which develops as a result of pulmonary hypertension.

Results

Figure 1. Total lung weight index was similar in all groups (**A**), however lower+cardiac lobe weight index was increased following PNX and further increased following PNX+LBX (**B**). *p=0.0001 vs. Sham, #p=0.0001 vs. PNX



Results

Figure 2. Lower+cardiac lobe volume index was significantly increased following PNX and further enhanced following PNX+LBX (*p<0.05 vs. Sham, #p=0.0001 vs. PNX)

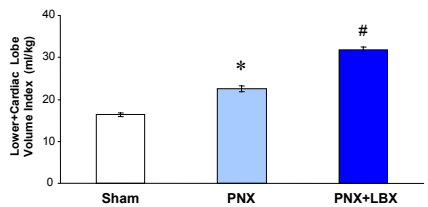


Figure 3. Right ventricular systolic pressure (RVSP) was significantly elevated only following PNX+LBX (*p=0.01 vs. Sham and PNX).

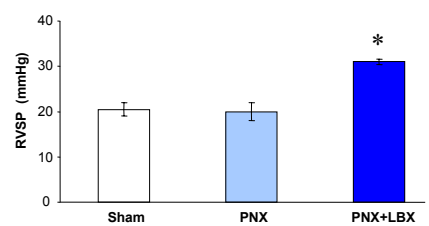
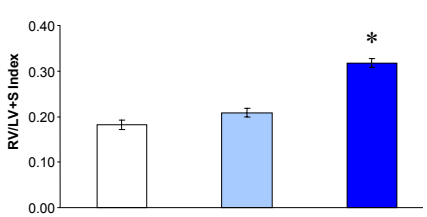


Figure 4. Right ventricular hypertrophy was significantly increased only following PNX+LBX (*p=0.0001 vs. Sham and PNX).



Results

Figure 5. Lung histology. Lung sections were stained with hematoxylin and eosin (200X). Gross lung histology appears normal among all groups with no signs of edema, cellular infiltration or thickening of septa.

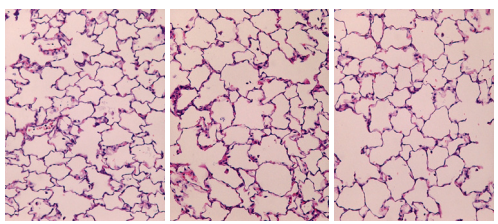


Table 1. Morphometric analysis:

	Sv	TVvr	Tvra	TVrt
Sham	173.2 ± 9.9	7.4 ± 0.4	5.3 ± 0.3	1.8 ± 0.1
PNX	139.1 ± 6.9§	10.7 ± 0.2§	8.2 ± 0.3§	2.3 ± 0.2
PNX+LBX	119.1 ± 7.7*	15.1 ± 0.8#	12.2 ± 0.7#	2.5 ± 0.2*

Values are means ± SEM. Sv = alveolar surface density (cm^2/cm^3); TVvr = total volume of respiratory region (mL); Tvra = total volume of respiratory airspace (mL); TVrt = total volume of respiratory tissue (mL). *p<0.05 vs. Sham; §p<0.001 vs. Sham; #p<0.0001 vs. PNX and Sham.

Conclusions

- To our knowledge, this is the first experimental model of sequential lung resection utilized to study the modulation of post-pneumonectomy CLG.
- Bi-lobectomy after PNX re-initiated a CLG response in the remaining lung of adult rats.
- In contrast to PNX alone, growth after PNX + bi-lobectomy involved a greater hypertrophic response (reduced alveolar surface density) and also resulted in pulmonary hypertension.
- This study provides novel information regarding the potential for CLG after repeated lung resections.
- A better understanding of lung growth has enormous clinical applications, since fields such as reduced size lung transplantation and pulmonary insufficiency can benefit from the modulation and induction of lung growth.

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