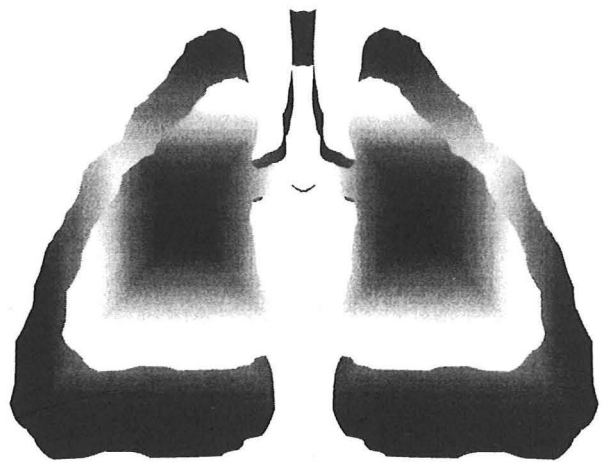
Induced Lung Growth: Physiology and Clinical Implications



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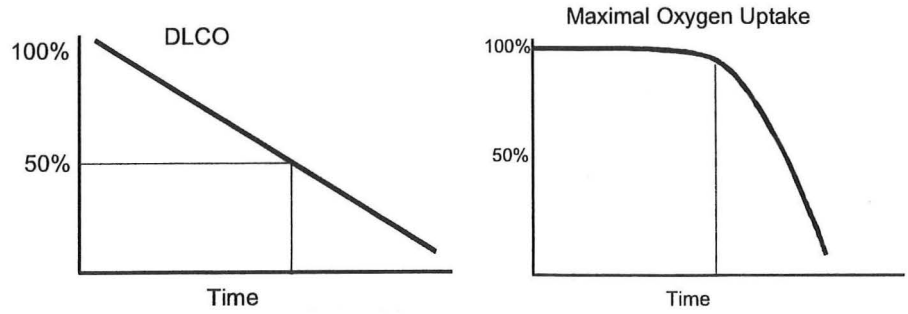
Academic Interests:

Mechanisms of normal and compensatory lung growth
Exercise pulmonary function and heart-lung interaction in health, disease and during adaptation to high altitude

Oxygen Transport Capacity of Lungs

In patients with chronic parenchymal lung disease (emphysema, pulmonary fibrosis), the rate of decline in pulmonary diffusing capacity (DL_{CO}) is progressive, but exercise capacity is not affected until late in the course, when more than 50% of lung units have been destroyed.



This pattern is distinct from that in heart or muscular disease, where less extensive disease involvement leads to impaired exercise performance and early development of symptoms. Why does functional impairment develop late in parenchymal lung disease, when lung destruction is already advanced? The answer is that there are large physiologic reserves of DL_{CO}, which can be utilized to compensate for the destruction of lung units.

The capacity of the lungs for O_2 transport (6 L/min) greatly exceeds that of the heart (3 L/min). Normally exercise is limited when transport capacity of the heart is reached. The average person exercising at sea level does not reach the limit of lung capacity, and will not experience any impairment in exercise performance until lung capacity is reduced below cardiac capacity. This discrepancy between cardiac and lung capacities reflects muscular deconditioning of the average person in our evolution towards a more and more sedentary life style.

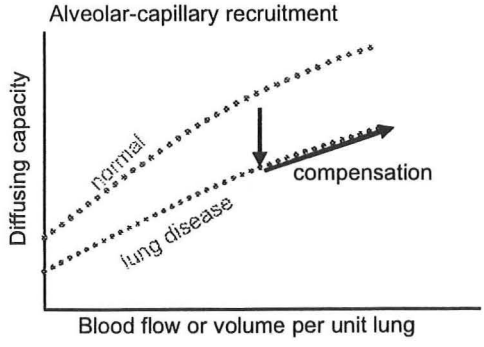
Sources of Physiologic Compensation

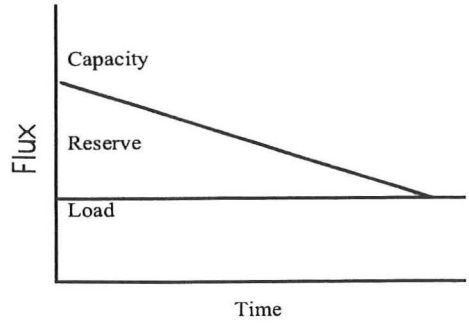
- Utilization of physiological reserves
- Remodeling of existing structure to enhance O_2 transport
- Compensatory growth of new lung tissue

The lung is the only organ receiving the entire cardiac output, which increases 5 fold from rest to exercise. The pulmonary vascular bed maintains a high capacitance and a low resistance through recruitment and distension of capillaries and alveoli.

At rest only 50% of capillaries, mostly at the base, are open sufficiently for red cells to pass through. At exercise, increased pressure opens capillaries at the apex, distends capillaries at the base, leading to **a)** increased capillary volume, which minimizes pulmonary arterial pressure, pulmonary vascular resistance and right ventricular afterload; **b)** increased capillary-red cell surface area, which increases DL_{CO}.

Similarly, at rest only 50% of alveoli are open and communicating with inspired air. At exercise, increase tidal volume opens and distends alveoli, leading to **a)** increased alveolar surface area, which increases DL_{CO}; and **b)** traction on small airways, which increases airway diameter and reduces airflow resistance.





Compensatory Lung Growth

Compensatory lung growth occurs only after physiological reserves are exhausted or prove insufficient to maintain gas exchange. This discussion summarizes some important issues:

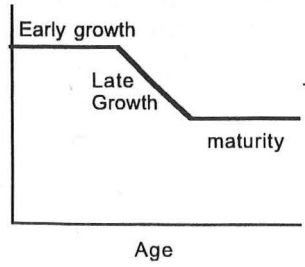
-Mechanisms of lung growth
-Models of induced lung growth
-Signals and mediators
-Relevance in lung disease

Postnatal Lung Growth and Development

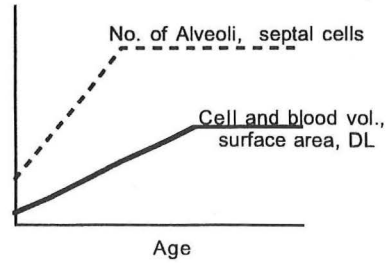
The lung progresses through two phases of development after birth:
a) Alveolar proliferation and hypertrophy, from 0 to about 8 years of age. Alveolar number increases from about 20 to 300 million; alveolar volume increases proportionally to somatic growth, i.e., volume density (volume ratio) of septal tissue to lung volume stays constant.

b) Alveolar hypertrophy continues from about 8 years of age to adulthood. Alveolar number stays constant, while alveolar size increases until the thorax stops growing, i.e., volume density of septal tissue to lung volume decreases.

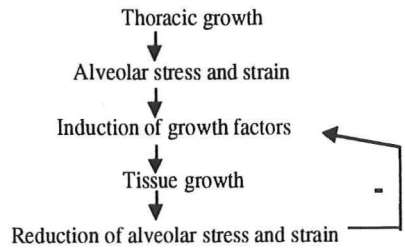
Volume Density of Septal Tissue



Alveolar & Cellular No. and Volumes



Mechanical interplay between the enlarging lungs and thorax is a major signal mediating postnatal alveolar development. During growth, the enlarging bony thorax exerts a negative intrapleural pressure and traction on the lung. The resultant **alveolar strain** activates a cascade of molecular events culminating in septal growth, which in turn reduces stress. As the thorax progressively enlarges, this interaction continues until somatic maturation is reached when epiphyses close and maximal thoracic size is achieved.



Attempts to Induce Lung Growth after Birth

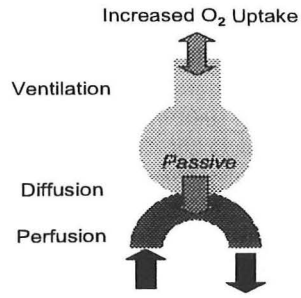
Strategy	**Examples**	**Lung Growth**
↑ O_2 demand	Exercise	+/-
	Cold exposure	+/-
	Hyperthyroidism	+/-
Gravitational gradient	3 g centrifugation	-
Hormones	Growth hormone	-
	Adrenalectomy	Synergistic
	Sex hormones	-
Hypoxia	High altitude exposure	++
Loss of alveoli	Lung resection (pneumonectomy)	++

Increased Metabolic Oxygen Demand

Because exercise training and other means of increasing metabolic O_2 demand is successful in stimulating hypertrophy of the myocardium and skeletal muscle, various investigators used a similar approach to stimulate lung growth. The rationale is that a chronically increased O_2 flux through the lung might stress the gas exchange unit and induce alveolar hypertrophy or hyperplasia. Unfortunately, this strategy is not universally effective; results from different laboratories are often conflicting. When metabolic O_2 demand increases the respiratory and cardiac pumps must work harder to increase convective O_2 delivery to the lungs and peripheral tissue; hence respiratory muscles and myocardium hypertrophy. At the alveolar blood-air interface, O_2 diffusion remains a passive process, i.e., diffusive gas exchange has not been stressed.

Determinants of
Rate of O_2 diffusion

-Surface area
-Alveolar-capillary ΔPO_2
-Septal thickness



Compensatory Lung Growth Induced by Chronic Hypoxia

Nearly 400 million people live at altitudes above 1,500m; hence growth and development of a significant fraction of the world's population is affected by hypoxia. While somatic growth is slowed and perhaps prolonged at high altitude regardless of ethnic origins [1, 2], most native highlanders show larger vital capacities and thoracic volumes than lowlanders. This is true of Tibetans resident in the Himalayas for more than 25,000 years [3], Quechua Indians resident in the Andes for 10,000 years [4-7], Ethiopians resident at altitudes of 1,500 to 3,700m for 2,500 years [8], and Caucasians resident in Leadville, CO for no longer than about 150 years [9]. Where measured, DL_{CO} is also increased in highlanders compared to lowlanders [9, 10]. Thus, the increased lung volume is independent of ethnic origin. It is unknown whether the increase volume and DL_{CO} is due to an increased alveolar number, or simply a more compliant thorax that allows the lung to expand to a higher volume. The higher DL_{CO} could be caused by non-structural adaptive changes such as reversible increases in microvascular pressures, blood volume or hematocrit. In order to dissect the mechanisms underlying the enhanced DL_{CO} in highlanders, these reversible changes must be allowed to subside after re-adaptation to sea level; these studies have not been done.

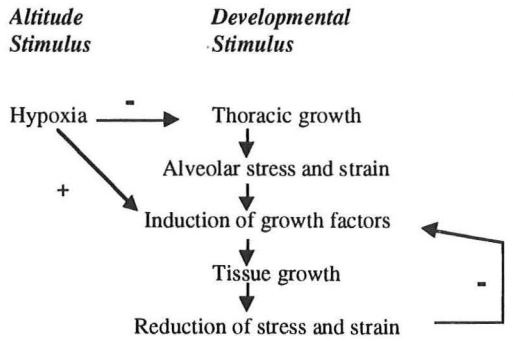
Most animal studies on high altitude lung growth have been in rats whose bony epiphyses never close and somatic growth continues throughout life; hence there is no final stable lung size. Chronic hypoxia equivalent to altitudes of 3,400-4,200m transiently accelerates lung growth and alveolarization in rats [11-15] while retarding somatic growth. Within about 3 weeks the lungs become 20% larger than in normoxic controls; then the rate of lung growth returns to normal although the relative increase in volume is retained [16]. Growth then continues throughout life. After rats exposed to high altitude are returned to sea level, their lungs stop growing while the lungs of their sea level controls continue to grow until lung size in the two groups are the same; hence, the increase in lung volume is not permanent [17]. Above 5,000m somatic growth is so retarded that it prevents an absolute increase in lung size relative to that in sea level controls although lung volume is large with respect to body weight [17]. Mice behave similarly. Exercise capacity and gas exchange has only been measured in rats after chronic exposure to altitudes above 5,500m [18]. Unlike in humans [19-21], efficiency of pulmonary gas exchange is not a significant limiting factor to oxygen transport in rats either at sea level or at high altitude [18].

The only two animal studies that addressed long-term effects of high altitude exposure on lung growth [22, 23] reached conflicting conclusions. In guinea pigs, bony epiphyses close at about 20 weeks of age and the rib cage stops growing [24]. Weanling guinea pigs raised from 2 to 16 weeks of age at a simulated altitude of 5,100m [22] show accelerated lung growth during the initial 3 weeks of hypoxic exposure, with 30% increase in lung volume and alveolar surface area compared to normoxic controls. After the first 3 weeks, lung growth rate slowed and the difference between groups progressively declined. The study was terminated before animals reached full maturity, but extrapolation of their data to 20 weeks suggested that at full growth lung volume and surface area would be similar between groups, and the ultimate lung size would be limited by the size of final size of the thorax. The authors conclude that hypoxia does not extend the upper limit of lung growth at maturity, but only accelerates the rate of its attainment.

Dogs raised at high altitude replicate the same stable increase in lung volume, DL_{CO} and resting pulmonary hemodynamic pattern as seen in human native highlanders [9, 23, 25]. At 3,100m, exercise capacity in normal dogs is limited primarily by pulmonary diffusive oxygen transport as in humans at high altitude. Beagles raised from age 2 to 14 months (beyond maturity) at Leadville, CO (3,100m) [23] show significantly larger lung volumes, septal tissue volumes and DL_{CO} than in matched controls raised to maturity in Dallas (160m). Differences were still present 9 months after returning to sea level. Results suggest that hypoxia enhances lung growth during maturation and ultimately leads to a greater gas exchange capacity at maturity. The rib cage was not larger in dogs raised at high altitude; rib length and curvature were not altered, but the dome of the diaphragm at a given transpulmonary pressure was lower to accommodate the larger lungs. Pulmonary vascular reactivity to hypoxia returned to normal but right ventricular hypertrophy persist 8 mo. after returning to sea level, suggesting permanent structural alterations in the pulmonary vasculature [25].

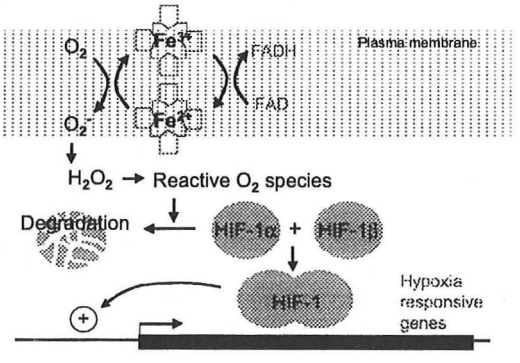
The above animal studies provide important clues as to how interplay among growth of the lungs, rib cage and diaphragm determine the final lung size. Dogs raised in moderate hypoxia (3,100m) had significantly larger lungs and higher DL_{CO} than dogs raised at sea level. Guinea pigs raised in severe hypoxia (5,100m) showed early acceleration of alveolar growth followed by a decline in growth rate below that in controls so that the projected size of the lungs at maturity was no larger. Results support the hypothesis that two independent but interacting growth stimuli are involved at high altitude. The primary stimulus is alveolar strain imposed by the growing thorax. The rate of lung growth is determined by the distending pressure generated by the outward recoil of the rib cage; if the thorax grows faster the lung keeps up by feed back control in order to minimize septal stress. The other independent additive stimulus is hypoxia, which stimulates lung growth but if severe enough may retard bony thoracic growth.

On initial ascent of an immature animal to high altitude, the combined stimuli (hypoxia + thoracic recoil) cause the alveolar growth rate to exceed that of the thorax temporarily. Space for the expanding lung is provided by passive expansion of the thorax along its normal pressure-volume curve until thoracic recoil pressure declines to a point where rates of lung and thoracic growth are equal, and by depression of the diaphragm.



Mediators of Response to Hypoxia

Whether cellular responses are due to hypoxia *per se*, or some associated signal (e.g. greater lung stretch) is not known. Lung stretch is discussed in a later section. The oxygen sensing and signaling process is probably shared among many types of cells. Although the identity of the cellular oxygen sensor is not known, a favin-heme protein residing in the plasma membrane has been proposed as a likely candidate [26]. This heme protein functions as an NADPH oxidase, transferring electrons through the favin and heme to molecular oxygen and generating superoxide which in the presence of iron is converted to reactive oxygen species, which then oxidatively modifies HIF-1α and induces rapid degradation of HIF-1α by the proteasome. At low oxygen tension, HIF-1α subunit is stable and can form a heterodimer with constitutively expressed HIF-1β subunit, thereby activating HIF-1, which translocates to the nucleus, binds to response elements in hypoxia inducible genes, and enhances transcription of these genes. Activation of HIF-1 is associated with induction of erythropoietin synthesis by the kidney, tyrosine hydroxylase in the carotid body, and vascular endothelial growth factor (VEGF) in a variety of cells.



Parenchymal lung cells respond to oxygen tension differently from cells of other organs. Pulmonary parenchymal cells are exposed to a higher local O_2 concentration than cells of other organs, and respond to a much smaller decline in local O_2 concentration (below about 15%), whereas most *in vitro* studies of hypoxia are conducted at O_2 concentrations below 5%. Hypoxia also causes vasoconstriction in the pulmonary vessels, in contrast to vasodilation in systemic

vessels. Why the differential effect exists is not fully understood, but it is an important regulatory mechanism for matching ventilation-perfusion relationships and is a highly conserved response. In salamanders and frogs that are capable of gas exchange in both water and air, a hypoxic air environment causes vasoconstriction in the lungs, diverting blood flow to the gills as the animal submerges under water. Conversely, hypoxic water environment causes vasoconstriction in the gills, diverting blood flow to the lungs, which then become the major gas exchange organ as the animal surfaces to breathe air [27].

Effectiveness of enhanced alveolar growth at high altitude

A larger lung volume and DL_{CO} presumably enhance diffusive oxygen transport at high altitude. However, other structural and physiological adaptation to high altitude may counterbalance those benefits. In high altitude natives, peripheral chemoreceptor drive is impaired so that ventilatory response to hypoxia is depressed [28, 29]. Pulmonary vascular remodeling occurs in small arterioles in association with pulmonary hypertension [30-33]; maximal cardiac output is reduced. In high altitude populations airway dimensions are relatively small with respect to lung volume [4], suggesting that growth of alveoli and airways is dissociated, a condition termed "dysanaptic lung growth". These combined factors may adversely affect ventilation-perfusion matching, dead space ventilation and work of breathing; they can potentially impair exercise capacity at high altitude and sea level and offset much of the benefits afforded by a larger lung volume and DL_{CO}. The relative importance of these opposing adaptive responses in determining maximal oxygen transport at altitude or sea level is not known.

Compensatory Lung Growth in Response to Loss of Alveoli

-In animal models
-In human lung disease
-Pharmacological induction of lung growth

Pneumonectomy in Immature Dogs

Alveolar growth Immature dogs that undergo right pneumonectomy (55% resection) at 2 mo. of age show doubling of lung volume, DL_{CO} and lung tissue volume back to normal within 8 wk and remained normal up to maturity 1 year later [34]. Lung compliance and transpulmonary pressure-lung volume relationship remained abnormal throughout maturation. Alveolar septal tissue volume also returned to normal; however, volume of non-gas exchanging lung tissue (conducting airways and blood vessels) remained >50% below normal [35]. Pneumonectomy did not selectively affect growth of the thorax [35]. At maturity, maximal O_2 uptake and gas exchange during exercise were completely normal, despite persistent elevations in dynamic airway resistance and pulmonary vascular resistance. Maximal DL_{CO} and maximal cardiac output were completely normal [36, 37]. Post-mortem studies showed complete normalization of all alveolar-capillary cell volumes and surface areas [36]. Thus compensatory or regenerative alveolar growth is vigorous in the immature animal and returns long term gas exchange function to normal.

Airway Growth Compensatory growth of conducting airways and large pulmonary blood vessels after pneumonectomy is limited, leading to significant abnormalities in pulmonary mechanical and hemodynamic function that persist into adulthood. After pneumonectomy, conducting airways lengthened and tracheal diameter increased, exerting opposing influence on airway flow resistance. Overall, airway resistance is still increased in pneumonectomized

animals compared to normal animals. Thus, postpneumonectomy lung growth is also dysanaptic.

Pneumonectomy in Adult Dogs

Adult dogs that undergo resection of the smaller left lung (45% resection) show expansion of the remaining lung, returning lung volume to 90% of normal. Maximal exercise performance is well preserved. At a given work load, DL_{CO} of the remaining lung was 30% higher than in one lung of normal animals [38]; the increase was entirely due to the higher lung volume and capillary perfusion through the remaining lung since the entire cardiac output is now directed through one lung. Upon exercise, DL_{CO} does not rise as fast as cardiac output; hence arterial oxygen saturation declined [39]. Structural adaptation consists of enlarged alveolar air spaces and thinning of the alveolar-capillary tissue barrier, which significantly reduces the diffusive resistance and increases DL_{CO}. However, there was no increase in septal cell volume, i.e., no new tissue growth [40]. Thus in adult animals, compensation to the loss of <50% of alveoli is entirely from utilization of physiological reserves and remodeling of remaining alveolar-capillary structure that enhanced the transfer of O_2.

When the larger right lung was removed in adult dogs (55% of total), compensatory response is slow but progressive. At 2 mo. after resection, maximal O_2 uptake was only 50% of normal, associated with severe decline in arterial O_2 saturation and ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatch during exercise [41]. Severe pulmonary arterial hypertension developed upon exercise and maximal cardiac output was reduced by 50%. However, 6 to 12 mo. later, maximal O_2 uptake gradually improved to 85% of normal [42] and $\dot{V}/\dot{Q}$ relationships normalized [41]. At equivalent levels of pulmonary blood flow, DL_{CO} and arterial O_2 saturation was higher, while alveolar-arterial PO_2 gradient and mean pulmonary arterial pressure were lower in dogs after right than left pneumonectomy [41, 43]. Despite the removal of more lung tissue by right pneumonectomy, functional compensation was more vigorous than after left pneumonectomy, because an additional compensatory mechanism, alveolar tissue growth, was elicited. After right pneumonectomy, volumes of all septal cellular components (epithelium, endothelium, interstitium) increased by 60 to 200% above control values, the increase being more pronounced at 5 than 16 mo. after pneumonectomy. Capillary blood volume and surface areas of alveoli and capillaries increased by 20-50%. At 5 mo. after pneumonectomy, the tissue-plasma diffusion barrier was significantly thicker than normal, but by 16 mo. had returned to normal associated with an increased DL_{CO}. Since alveolar dimension and septal thickness were normal, alveolar number increased proportional to the increase in lung volume. Thus, if the stimulus is sufficiently strong (>50% lung resected), compensatory alveolar growth can be elicited even in fully mature animals.

Mediators of Compensatory Lung Growth

The regenerated alveoli after pneumonectomy show normal size and cellular composition, i.e., a balanced growth pattern. One can expect the biochemical mediators of compensatory alveolar growth to be similar to those involved in normal developmental lung growth. Differential display analysis in a rat model has demonstrated the up-regulation of at least 200 genes in the remaining lung after pneumonectomy; few have been systematically studied. Preliminary data from our laboratory show an increase in the *in vivo* expression of epidermal growth factor (EGF)

and its receptor in dog lung after pneumonectomy, similar to that observed during postnatal maturation [44].

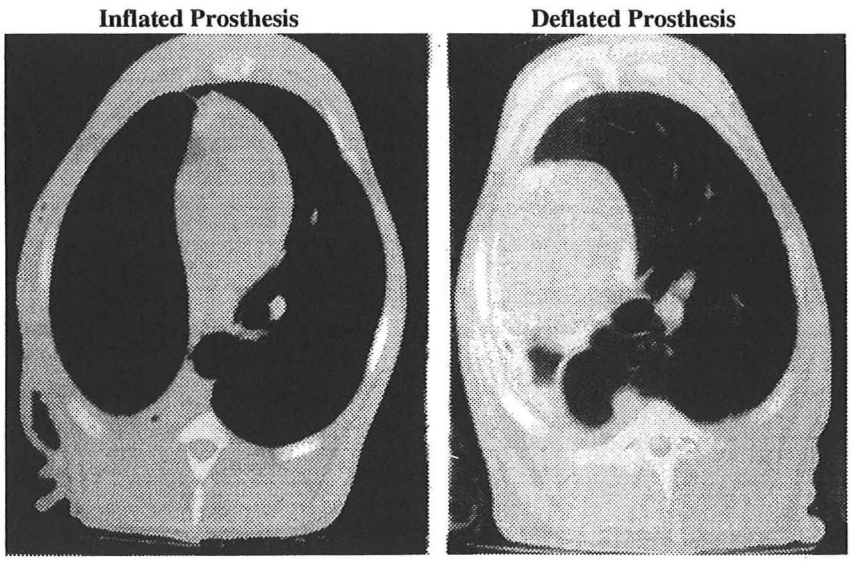
There are two phases of compensatory alveolar growth, similar to that seen during normal lung growth. Initially there is cellular proliferation associated with thickening of alveolar septa, followed by remodeling and structural maturation, which is associated with thinning of the septa. Programmed cell death is implicated in the second maturational phase, shown by a reduction in the number of fibroblasts and type II epithelial cells which are cleared by alveolar macrophages [45].

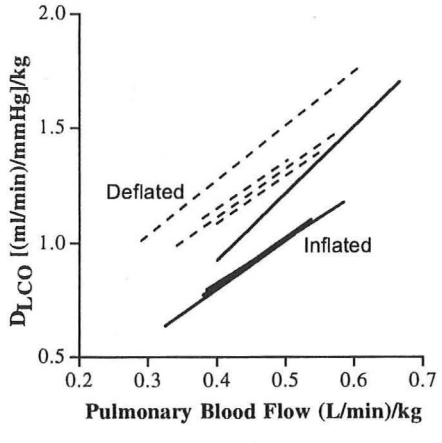
Mechanical Signals Initiating Compensatory Lung Growth

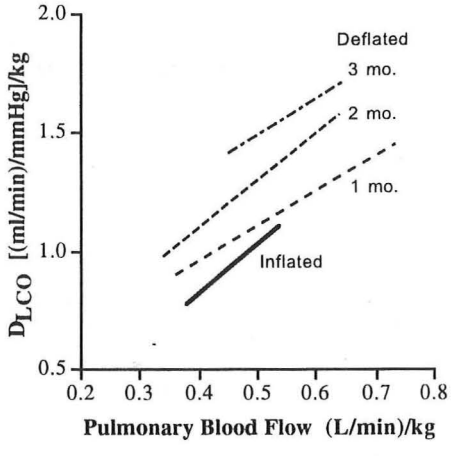
Signals initiating compensatory lung growth are believed to related to local mechanical forces; the search for circulating factors has thus far been negative. The lung is subject to complex physical forces including ventilation, perfusion and surface tension. Cyclic breathing movements can be observed in the human fetus beginning at 10 wk. of gestation, and play an important role in regulating fetal and postnatal lung development. Mechanical strain on fetal rat lung cells increases DNA synthesis [46, 47] as well as gene and protein expression of endogenous growth factors, such as platelet-derived growth factor (PDGF)-β receptor [48]. Abolishing fetal breathing movements by spinal cord transection reduces lung DNA synthesis and gene expression of insulin-like growth factor (IGF)-II. Increasing or decreasing lung volume in fetal sheep by tracheal obstruction or lung liquid drainage also causes corresponding changes in IGF-II expression. Ligation of one pulmonary artery increases perfusion to the remaining pulmonary vasculature and enhances alveolar growth in the contralateral lung of newborn pigs [49]. However, in ferrets after pneumonectomy, restricting pulmonary blood flow by banding one lobar pulmonary artery had no effect on the compensatory increase in DNA and protein content [50].

Since alveolar-capillary strain and shear forces are greatly exaggerated after pneumonectomy due to expansion of the remaining lung, preventing these mechanical forces might prevent compensatory alveolar growth. We tested this hypothesis in adult dogs after right pneumonectomy by inserting inflatable custom-shaped silicone prosthesis in place of the resected right lung. The inflated prosthesis returned the mediastinum to the midline and prevented lateral expansion of the remaining lung. Control animals underwent the same procedures, but the prosthesis was left deflated, allowing mediastinal shift and expansion of the remaining lung.

About 1 year later, DL_{CO} was lower at rest and exercise [51] and structural alveolar growth was impaired [52] in dogs with an inflated prosthesis. However, reducing alveolar strain did not completely abolish either physiologic compensation or regenerative alveolar growth. Instead of enlarging across the midline, the remaining lung grew caudally about 20% by depressing the diaphragm, suggesting that alveolar growth did not occur simply to fill an empty space, but occurs even when strain is minimized and space is not readily available. Thus, alveolar strain is an important but not the only signal for compensatory lung growth. Other signals such as endothelial shear due to increased perfusion to the remaining lung must also play a role.





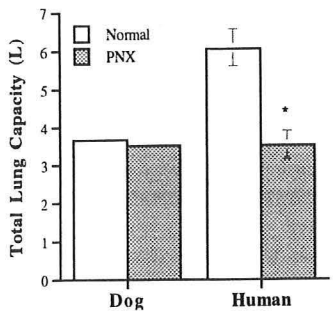


Above right: Delayed prosthesis deflation after 10 mo. of inflation led to a progressive increase in DL_{CO} and a vigorous tissue response over the subsequent 3 months, indicating that the effect of preventing alveolar strain is fully reversible.

Pneumonectomy in Patients

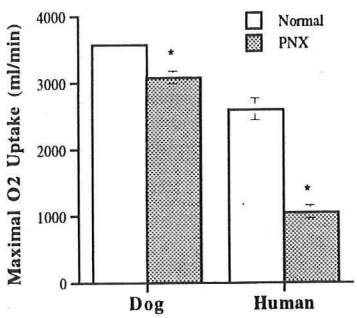
Pneumonectomy is performed with a curative intent in patients with localized lung cancer, trauma or infection resistant to antibiotics. In postpneumonectomy patients who have relatively normal remaining lungs (FVC, FEV_1 and FEF_{25-75} >80% of normal predicted for one lung) and

no evidence of residual disease, expansion of the remaining lung is limited and lung compliance remains abnormally reduced compared to age-matched controls [53, 54]. Pulmonary arterial hypertension develops during exercise but not at rest. Impairment of gas exchange is generally mild and does not cause arterial O_2 saturation to drop during exercise until > 67% of lung tissue has been removed. The increase in DL_{CO} with respect to cardiac output is normal [53].



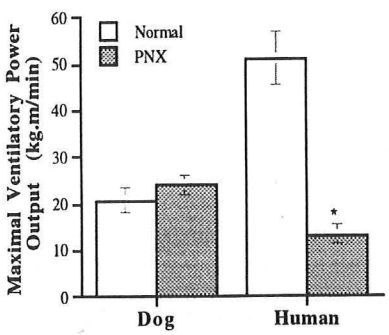
Lung Volume

Lung expansion is limited in patients after pneumonectomy (PNX). Total lung capacity (TLC) is 40% below normal. In dogs after pneumonectomy, TLC returns to within 90% of that for two lungs of controls.
Mean±SEM. *p<0.01 vs. respective controls.



Aerobic Capacity

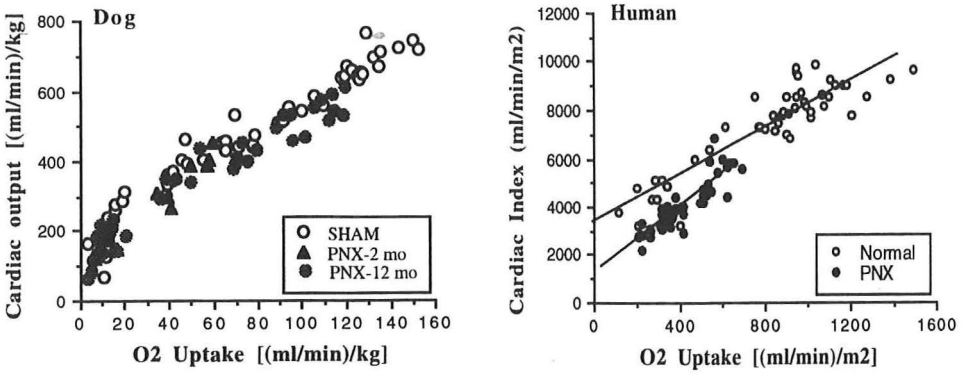
Maximal oxygen uptake is severely impaired by 60% in patients after left or right pneumonectomy compared to age-matched control subjects (vs. 14% reduction in dogs after right pneumonectomy).
Mean±SEM. *=p<0.05 vs. respective control group.



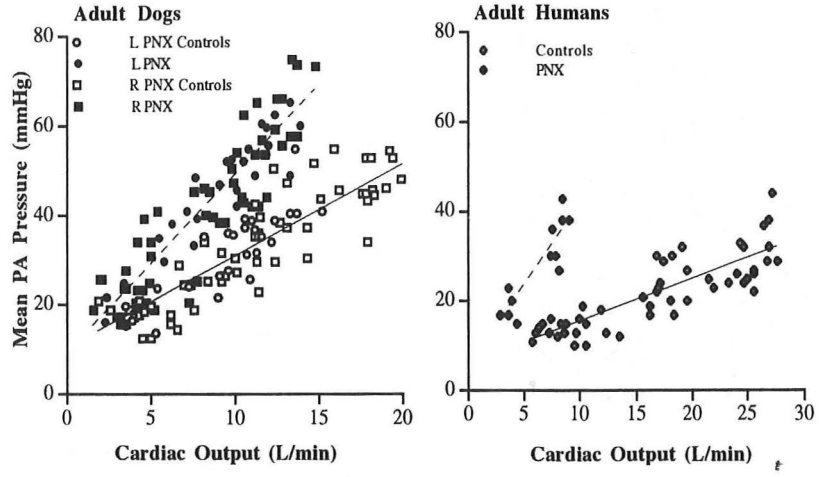
Respiratory Muscle Function

Maximal ventilatory power output is severely reduced in patients but not dogs after pneumonectomy, i.e., respiratory muscles are not effective in power generation in patients after pneumonectomy. An intensive respiratory muscle endurance training program did not improve maximal ventilation or maximal O_2 uptake in pneumonectomized patients [54]. Thus respiratory muscle dysfunction after pneumonectomy is not due to muscle deconditioning.
Mean±SEM. *=p<0.0001 vs. respective controls.

Cardiac and Hemodynamic Response after Pneumonectomy



Above: In dogs 1 yr. after pneumonectomy submaixmal cardiac output was well preserved; maximal cardiac output was 20% below that in controls. In patients studied months to years after pneumonectomy, cardiac output at a given O_2 uptake is reduced and maximal cardiac output is 60% below that in controls.

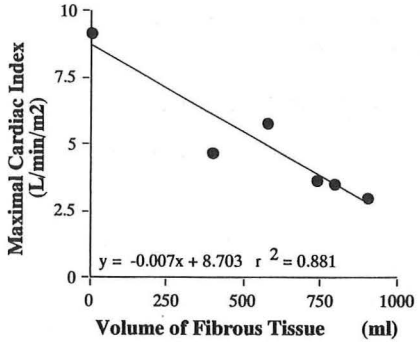


Above: After pneumonectomy (PNX), resting mean pulmonary arterial pressure (PAP) is normal or mildly elevated, but rises steeply with respect to cardiac output upon exercise; the slope of increase is similar between species indicating that the increase in right ventricular afterload is similar. In dogs peak PAP increases above 70 mmHg, compared to about 45 mmHg in control animals. In patients, peak mean PAP does not exceed that in control subjects (about 40 mmHg). In contrast, normal individuals acclimatized to high altitude can easily reach mean PAP of 60 mmHg and still maintain normal cardiac outputs during exercise. Longtime residents at high altitude can reach mean PAP of 72 to 109 mmHg during exercise.

These comparisons show that pulmonary arterial hypertension *per se* cannot explain the reduction of submaximal and maximal cardiac index in patients after PNX. Rather, there is an additional impairment in the right ventricular response to an elevated afterload. Normally the right ventricle is able to overcome an elevation in pulmonary vascular resistance by dilatation and/or enhanced contractility in order to preserve maximal cardiac output. Right or left ventricular hypertrophy has not been observed at post-mortem in dogs after right lung resection; hence ventricular dilatation utilizing the Starling mechanism is the more likely explanation for the preservation of maximal cardiac output in dogs. On the other hand, patients are unable to utilize these mechanisms to maintain their maximal cardiac output.

To determine if impairment in stroke index is due to physical deconditioning, we studied postpneumonectomy patients and age-matched normal subjects before and after an intensive exercise training program over 8 weeks [55]. In control subjects, maximal O_2 uptake increased by 23% after training, due to improvements in both maximal stroke index and peripheral O_2 extraction. In patients, maximal O_2 uptake increased less (by 16%), due entirely to enhanced peripheral O_2 extraction; maximal stroke index did not improve. Thus, cardiac dysfunction in patients cannot be explained by physical deconditioning, suggesting anatomical factors that irreversibly restrict stroke index.

Anatomic Restriction after Pneumonectomy



Right: Magnetic resonance image of a patient after left pneumonectomy. The left hemithorax is highly distorted and partially collapsed and mostly occupied by the heart. There is significant intrathoracic fibrous adhesions. Excursion of the chest wall and hemidiaphragm during respiration is impaired. The ventricular wall is almost entirely surrounded by rigid structures (fibrous tissue, immobile rib cage and hemidiaphragm), i.e, a non-compliant cardiac fossa.

Left: The average volume of intrathoracic fibrous tissue is 624 ml in patients and negligible in dogs after pneumonectomy. There is a strong inverse correlation between maximal cardiac index and fibrous tissue volume, suggesting that fibrous adhesion impair ventricular output.

Functional Significance of a Compliant Cardiac Fossa

The cardiac fossa is a potential space within which the heart resides, normally bounded by the lungs and the diaphragm. The cardiac fossa imposes significant physiologic constraints on ventricular expansion even at normal heart volumes; it restricts ventricular expansion before there is pericardial restriction, thereby promoting interventricular interdependence [56]. Compliance of the structures forming the cardiac fossa is therefore a major determinant of ventricular output. The respiratory system imposes a compliance load on diastolic cardiac filling; lung distension increases the tension on the walls of the cardiac fossa [57], raises local epicardial pressure above ambient pleural pressure [58], and causes stroke volume and cardiac output to fall [58-60]. For example, during positive end-expiratory pressure (PEEP), lung distention greatly increases lateral pressure on the heart even in the open-chest condition, and reduces stroke volume by reducing ventricular filling [60]. Thus compliance of the cardiac fossa is significantly less than predicted from pleural pressures.

Lung expansion after pneumonectomy has both beneficial and detrimental consequences. Expansion increases alveolar-capillary surface for gas exchange leading to augmentation of DL_{CO}. Mechanical stretch is a potent signal that enhances regenerative lung growth. On the other hand, lung expansion imposes a greater constraint on diastolic ventricular filling. In the dog, the beneficial effects of lung expansion are fully exploited after pneumonectomy, while the detrimental effect on diastolic ventricular filling is minimized by the fact that elastic recoil of the remaining lung returns to normal through remodeling of septal connective tissue and/or regenerative alveolar growth. In the patient after pneumonectomy, fibrous adhesion restricts lung expansion; hence DL_{CO} is limited. Ventricular function is impaired because compliance of the cardiac fossa is reduced by fibrous adhesions and fixation of the chest wall and hemidiaphragm.

Functional Significance of Thoracic and Diaphragmatic Mobility

Wait et al [61] studied regional mechanical function of the diaphragm in adult dogs by following the motion of radiopaque markers implanted along the ventral surface of the hemidiaphragm. Regional motion of the muscle during breathing were recorded before and 8 weeks after right pneumonectomy. After pneumonectomy the right costal hemidiaphragm is distorted, with a greater curvature at end-expiration and less curvature at peak inspiration. Fiber shortening during contraction is greater. Subsequently we showed that hyperplasia of the right hemidiaphragm occurs in dogs after right pneumonectomy, i.e., muscle mass increases without a change in fiber size [62]. By increasing its mass, the dog diaphragm can effectively overcome the mechanical disadvantage imposed by anatomical distortion and maintain normal power generation after pneumonectomy.

In the patients after pneumonectomy, immobilization of the hemithorax on the side of lung resection by fibrous adhesion essentially reduces functioning respiratory muscle mass by half, resulting in grossly impaired ventilatory power generation. In addition, the restricted expansion of the lung accentuates the anatomical distortion and consequent mechanical disadvantage of the respiratory muscles, resulting in a lower efficiency of the entire respiratory pump. Because of these anatomical abnormalities, compensatory lung growth is unlikely to be significant in the adult patient after pneumonectomy. If fibrous adhesions could be ameliorated to optimize lung

expansion and restore normal heart-lung interactions after pneumonectomy, regenerative lung growth can be expected to occur as in the dog.

Compensatory Lung Growth in Congenital Diaphragmatic Hernia

Another model of alveolar insufficiency where compensatory lung growth could be systematically studied is congenital diaphragmatic hernia (CDH). This is a disorder of embryonic development with failure of the pleuoperitoneal canals to close at about 8 weeks of gestation, leading to a defect in the diaphragm. Liver and gut grow into the chest cavity, causing compression and hypoplasia of the lung. The hypoplastic lung is small and has fewer airway generations. Lung hypoplasia is associated with delayed or absent expressions of several growth-promoting substances, including calcitonin gene-related peptide (CGRP) [63] and vascular endothelial cell growth factor (VEGF) before birth [64]. Gene expressions of endothelin-1 and endothelin-A receptor, which cause vasoconstriction, are upregulated before birth and probably mediate the pulmonary hypertension and pulmonary vascular muscularization in CDH.

CDH is associated with a high neonatal mortality from respiratory failure and persistent pulmonary hypertension. After birth, infants with CDH show increased expressions of growth-promoting substances such as VEGF [65] and bombesin-like peptides [66] in lung tissue. The postnatal response probably reflects a secondary attempt to increase the pulmonary vascular bed and accelerate lung growth in order to alleviate pulmonary hypertension. With the advent of extracorporeal membrane oxygenation and early surgical repair, many patients now survive long term, despite a high incidence of bronchopulmonary dysplasia. Ijsselstijn et al [67] measured resting lung function in 40 long-term survivors of CDH (age 7 to 18 years) and reported persistent airway obstruction and sensitivity to methacholine challenge. However, total lung capacity and DL_{CO} are normal compared to age-matched subjects without CDH. These data provide indirect evidence that "catch-up" lung growth occurred in these patients after birth. Exercise studies have not been done to define the nature and extent of such growth.

Pharmacological Induction of Lung Growth

It is safe to say that no single substance can reproduce the entire complex phenomenon of lung growth. Administration of any single compound has usually led to promising but limited effects. This area is still in its infancy, but recent focus has been the use the retinoid derivatives to stimulate alveolar growth.

Retinoic acid

Retinoic acid and other vitamin A compounds are important molecules for epithelial cell growth and maturation in may organs. In the lung, retinoic acid stimulates cell proliferation of serum-deprived type II cells, with an increase in cell number in a dose-dependent manner [68]. Retinoic acid also stimulates biosynthesis of extracellular matrix proteins [69, 70]. Potential mechanism of action include induction of EGF receptor synthesis [71], and blocking of inhibitory effects of insulin-like growth factor (IGF) and transforming growth factor β-1 (TGF β-1) on type II cell proliferation [68, 72]. However, the actions of retinoic acid are complex, with its various receptors often having opposing actions.

Retinoic acid administration to neonatal rats during the critical period of alveolar formation results in an increase in alveolar number and opposes the growth suppressing effects of glucocorticoids, although alveolar surface area is unchanged [73]. In a rat model of elastase-induced emphysema, retinoic acid treatment ameliorates the destruction of alveoli [74]. Prenatal retinoic acid treatment reduces the severity of lung hypoplasia in a rat model of nitrofen-induced congenital diaphragmatic hernia [75]. These effects appear to be independent of mechanical forces acting on the alveolar septa. The National Heart, Lung and Blood Institute is currently sponsoring a national initiative to study mechanisms of retinoic acid on alveolar formation in animal models, and a pre-clinical multi-center trial exploring the possible use of retinoids in the treatment of emphysema.

Potential caveats in this approach: a) Retinoic acid selectively stimulates epithelial and perhaps interstitial cell growth. Without a balanced stimulation of endothelial cell growth, the functional benefit of retinoic acid may be limited. b) Retinoic acid stimulates alveolar septal formation without increasing total surface area, suggesting other mechanisms that independently regulate the lengthening of alveolar septa. Without an associated increase in alveolar-capillary surface area, the functional benefit in gas exchange may be limited.

Potential Clinical Applications

Induction of lung growth in patients with chronic parenchymal lung disease could potentially retard the development of exercise impairment. It could be used in combination with surgical therapy such as lung volume reduction surgery in the treatment of advanced emphysema. It could also promote lobar lung transplantation and the use living-related lobar allograft, where a lobe is transplanted and subsequently stimulated to grow in the recipient's chest.

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