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Pulmonary Artery Occlusion and Lung Collapse Depletes Rabbit Lung Adenosine Triphosphate

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Background: **Although the bronchial circulation has traditionally been thought to provide adequate blood flow for the lung when the pulmonary artery is obstructed, recent studies have demonstrated that pulmonary artery occlusion results in lung injury. We hypothesized that after pulmonary artery occlusion, aerobic lung metabolic function is altered. We studied the changes in the concentration of adenine nucleotides as markers of injury in the intact rabbit lung after pulmonary artery occlusion in the presence and absence of pneumothorax.**

Methods: **A thoracotomy was performed on the rabbits, and an occlusive microvascular clamp was placed on the left pulmonary artery. The rabbit lungs were studied after 24 h of *in vivo* left pulmonary artery occlusion (n = 5), 24 h of left pulmonary artery occlusion with the lung collapsed by pneumothorax (n = 6), or 24 h of lung collapse alone (n = 5).**

Results: **Adenosine triphosphate concentrations of the occluded left lung decreased dramatically at 24 h in the group with pulmonary artery occlusion and collapse (adenosine triphosphate concentration 196 ± 32 ng/g for the left lung and 1,479 ± 197 ng/g for the right lung; $P < 0.001$). There were no differences between the lungs in the rabbits undergoing occlusion alone or collapse alone.**

Conclusions: **After pulmonary artery occlusion or lung collapse, adenine nucleotides are preserved if ventilation is continued. The increased permeability of rabbit lungs after 24 h of left pulmonary artery occlusion alone cannot be explained on the basis of depletion of high-energy phosphates. In the absence of ventilation due to lung collapse, pulmonary artery occlusion results in decreased adenosine triphosphate concentrations, demonstrating that the residual circulations (bronchial and pulmonary venous flow) are inadequate to support normal lung aerobic metabolism. (Key words: Lung(s): bronchi; circulation; reperfusion. Metabolism, lung: adenosine triphosphate.)**

PULMONARY embolism, thrombosis of pulmonary vessels due to the Adult Respiratory Distress Syndrome,[1,2] or continuous alveolar pressures in excess of pulmonary vascular pressure can temporarily interrupt pulmonary arterial flow to a lung region. However, lung injury due to pulmonary vascular occlusion has generally been found to be minimal or nonexistent in animal models, presumably because of flow from the systemic circulation *via* the bronchial circulation. Additional protection may result from the fact that oxygen supply is assured so long as regional ventilation is intact. A third possible source of oxygen as well as nutrients is reflux pulmonary venous blood flow. Gross morphologic examination of canine lung after regional pulmonary artery occlusion (PAO) supports the efficacy of these multiple oxygen and substrate delivery systems[3] because the lung remains viable with only minimal changes visible after prolonged unilateral PAO. However, despite the maintenance of relatively normal gross morphology after 24–48 h of PAO, the permeability of the subserved lung in rabbits has been shown to be increased.[4]

We felt it was important to study lung energy metabolism during PAO for two reasons. First, *in vitro,* even moderate decreases in high-energy phosphates lead to increased pulmonary endothelial cell permeability in cell culture.[5] Second, we have recently demonstrated that bronchial blood flow ($\dot{Q}_{br}$) declines markedly after PAO,[6] raising the question of whether the bronchial circulation might not provide adequate flow to meet lung metabolic needs.

In the experiments reported here, we hypothesized that after PAO rabbits would be unable to maintain nor-

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mal concentrations of high-energy phosphates. In order to study this, we occluded the pulmonary artery for 24 h and measured tissue high-energy phosphates. In one group of rabbits, we also produced an ipsilateral pneumothorax to study whether, in the absence of both ventilation and pulmonary arterial flow, the blood flow and oxygen delivery provided by the bronchial circulation were adequate to support the metabolic functions of the lung. Because of the presumed role of the bronchial circulation as a safety factor during PAO, we quantitated the effects of PAO and lung collapse on $\dot{Q}_{br}$.

Materials and Methods

Adenosine Triphosphate Studies

Three groups of rabbits were studied: left pulmonary artery occlusion alone (LPAO), left lung collapse (C), and left pulmonary artery occlusion with lung collapse (LPAO + C). The study protocols were approved by the Animal Care Committee of the University of Washington and the Animal Studies Subcommittee of the Seattle Veterans Affairs Medical Center. All rabbits initially underwent a sterile left thoracotomy under halothane anesthesia and the left pulmonary artery was occluded with an atraumatic microvascular clamp. In C rabbits, the clamp was placed but then immediately removed. This brief occlusion was performed to control for effects of the surgery. In the other two groups, the clamp was left in place for 24 h. In LPAO rabbits, the lung was reexpanded and the chest evacuated before closure. In LPAO + C and C rabbits, the chest was closed without reexpanding the left lung. A cannula was left in the chest after closure and air injected to raise the intrapleural pressure to between 0 and 2 cmH_2O. The cannula was then removed. The rabbits were then awakened and analgesia provided with buprenorphine 0.02–0.05 mg/kg subcutaneously.

At 24 h, rabbits underwent a second thoracotomy under barbiturate anesthesia. In C and LPAO + C rabbits, the lung was inspected to ensure persistent collapse. (In the first five such rabbits, we performed chest roentgenograms before the second thoracotomy to confirm persistent total left lung collapse. After we found this to be effective, we discontinued this practice and merely inspected the lung at the time of the second thoracotomy). The lower lobe of each lung was then quick frozen using tongs with 85-g aluminum blocks on each side precooled in liquid nitrogen. The sample was immediately placed in liquid nitrogen in a precooled ceramic mortar and ground into a fine powder. The adenine nucleotides of the sample were then extracted with 3.3 ml chilled 6.66% trichloroacetic acid. The mixture was vigorously agitated and centrifuged. The supernatant was neutralized by mixture with 3.9 ml high-performance liquid chromatography–grade 1,1,2-trichlorotrifluoroethane (Aldrich Chemical) and 1.1 ml 0.5 M Alamine-336 (Henkel, LaGrange, IL). After vigorous agitation, the mixture was centrifuged at 1,000 *g*, 4°C, for 5 min, and the aqueous layer then removed and analyzed for adenine nucleotides using anion-exchange high-performance liquid chromatography.[5]

We studied an additional eight LPAO + C rabbits in which the second thoracotomy and lung sampling were at either 2 (n = 4) or 4 h (n = 4).

Blood samples were processed by drawing the blood from an arterial cannula and snap freezing it by immediately injecting it into liquid nitrogen. All further steps for adenine nucleotide analysis were identical to those used in processing the lungs.

Energy charge, a traditional measure of the energetic status of the cell was calculated using the formula[7]

$$\text{Energy charge} = \frac{[\text{ATP}] + 0.5[\text{ADP}]}{[\text{ATP}] + [\text{ADP}] + [\text{AMP}]},$$

where [ATP] = concentration of adenosine triphosphate; [ADP] = concentration of adenosine diphosphate; and [AMP] = concentration of adenosine monophosphate.

Morphology

For two LPAO + C rabbits, tissue specimens were fixed in 4% buffered formalin immediately after animals were euthanized (24 h after surgery) and kept at 4°C for at least 12 h. The tissues were then dehydrated through a graded alcohol series, infiltrated with xylene, and embedded in paraffin at 56°C as previously described.[8] Sections were then cut, deparaffinized, and stained with hematoxylin and eosin. For localization of bacteria, additional sections were stained by the Brenn and Brown techniques. The specimens were examined by light microscopy.

Data Analysis

Data were analyzed using Student's paired *t* test to identify differences between the right and left lungs.

Bronchial Blood Flow Studies

We studied $\dot{Q}_{br}$ in seven rabbits, including two that followed the PAO protocol, two that followed the C

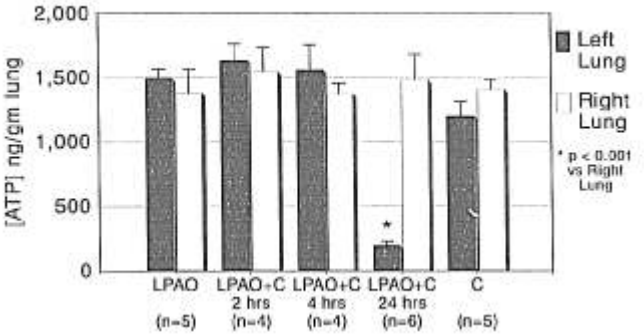

Fig. 1. Concentrations of adenosine triphosphate (ATP) in the right and left lungs of rabbits. C = collapse alone for 24 h; LPAO = left pulmonary artery occlusion alone for 24 h; LPAO + C = collapse and left pulmonary artery occlusion for 24 h. The duration (2, 4, or 24 h) is noted for the three groups of LPAO + C rabbits.

protocol, and one that followed the LPAO + C protocol. In addition, we studied two control rabbits that had no surgery before the measurement of $\dot{Q}_{br}$. Thus, $\dot{Q}_{br}$ was studied after either 24 h of PAO, 24 h of collapse, or 24 h of PAO and collapse.

On the day of measurement of $\dot{Q}_{br}$, rabbits were anesthetized with sodium pentobarbital. A left ventricular catheter was placed for injection of 15-μm spheres impregnated with fluorescent dye (FluoSpheres(R), Molecular Probes) and an aortic catheter placed *via* the femoral artery for withdrawal of a reference flow sample. Because of the possibility that some spheres might pass through peripheral arteriovenous shunts and lodge in the pulmonary arterial circulation and falsely elevate $\dot{Q}_{br}$ values, we clamped the left PAO in the control and C rabbits just before microsphere injection. Three million spheres were then injected into the left ventricle and a simultaneous reference sample withdrawn from the aorta at 2 ml/min. A cardiac output was measured simultaneously. Duplicate measurements of $\dot{Q}_{br}$ were performed and the two values averaged. The rabbits were then euthanized and the lungs processed.

Processing of the samples followed the techniques of Glenny *et al.*[9] The lungs were prepared for analysis by air drying for 48 h, then divided into cubes of approximately 1 cm^3. Individual cubes were then placed in 2 ml 2-ethoxyethylacetate for an additional 48 h to dissolve the spheres and extract the dye. Samples were then filtered and the filtrate assayed using fluorescence spectrophotometry. The blood reference sample was processed by dissolution of the blood in 12 N KOH followed by extraction of the dye with 2-ethoxyethylacetate. Flow was then calculated by comparing fluorescence in the lung to the fluorescence from the reference sample, which had a known flow of 2 ml/min.

Flows among the four groups were compared using one way analysis of variance, and least-significant-difference testing was used to identify differences between specific groups.

Results

At 24 h, PAO combined with lung collapse had dramatically reduced adenosine triphosphate (ATP) and adenosine diphosphate contents in the left lung when compared with the contralateral lung (fig. 1 and table 1). Energy charge was also reduced. Neither LPAO alone nor collapse alone resulted in a difference between the two lungs.

The changes observed after 24 h of LPAO + C were not observed at either 2 or 4 h (fig. 1 and table 1).

Table 1. Adenine Nucleotide Concentrations

		Adenosine Triphosphate		Adenosine Diphosphate		Adenosine Monophosphate		Energy Charge	
	N	L	R	L	R	L	R	L	R
LPAO	5	1494 ± 69	1380 ± 185	297 ± 63	259 ± 68	95 ± 41	70 ± 27	0.88 ± 0.02	0.89 ± 0.02
LPAO-C2	4	1637 ± 120	1546 ± 186	385 ± 29	361 ± 71	150 ± 27	141 ± 60	0.84 ± 0.03	0.84 ± 0.05
LPAO-C4	4	1559 ± 194	1369 ± 80	413 ± 69	412 ± 87	164 ± 54	170 ± 64	0.83 ± 0.04	0.81 ± 0.04
LPAO-C24	6	196 ± 32*	1479 ± 197	59 ± 10*	252 ± 49	39 ± 11	63 ± 23	0.77 ± 0.03†	0.89 ± 0.03
C	5	1197 ± 111	1407 ± 71	411 ± 87	389 ± 89	84 ± 23	35 ± 4	0.83 ± 0.04	0.88 ± 0.02

Data are ng/g of lung wet weight (uncorrected for blood content). Data are mean ± SEM. LPAO = 24 h of left pulmonary artery occlusion; C = 24 h of left lung collapse; LPAO-C = both occlusion and collapse, with the number following (2, 4, or 24) indicating the duration (h).

* $P < 0.001$.

† $P < 0.05$.

In the two rabbits that underwent light microscopy after LPAO + C, we noted areas of hemorrhage, edema, and inflammation (fig. 2). However, the lung did not appear irreparably damaged, and the basic alveolar structure remained intact. Bacterial stains did not demonstrate any visible organisms after 24 h of LPAO + C.

$\dot{Q}_{br}$ to the left lung was 0.1% of cardiac output in the control rabbits (fig. 3) but was less than one fifth of that value after 24 h of either PAO or left lung collapse, and less than one-twentieth of that value after PAO and collapse ($P < 0.01$ for differences among the different conditions, LPAO, LPAO + C, and C groups were all different from control at the $P < 0.05$ level).

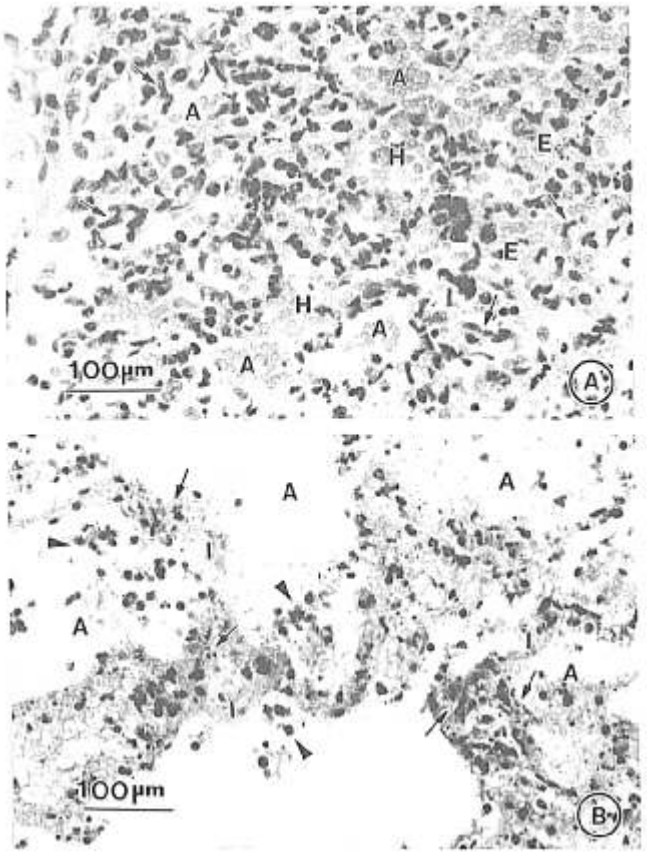

Fig. 2. Left lung section from an LPAO + C rabbit (*A*) demonstrates alveolar hemorrhage (H) and edema (E). Cells remain apparently viable, with typical nuclei of variable shapes in the interstitium and alveoli. Compare this with a section of a control rabbit lung 24 h after euthanasia with the lung left *in situ* (*B*). This micrograph demonstrates coagulative necrosis with cells that are detached from the basement membrane, and changes in both the cytoplasm and nuclei are evident (arrows). The cytoplasm is more eosinophilic than usual, and the nuclei are smaller, spherical, and strongly basophilic and pyknotic. Many pyknotic nuclei have broken into smaller fragments and scattered into the cytoplasm (arrows). (Hematoxylin and eosin.)

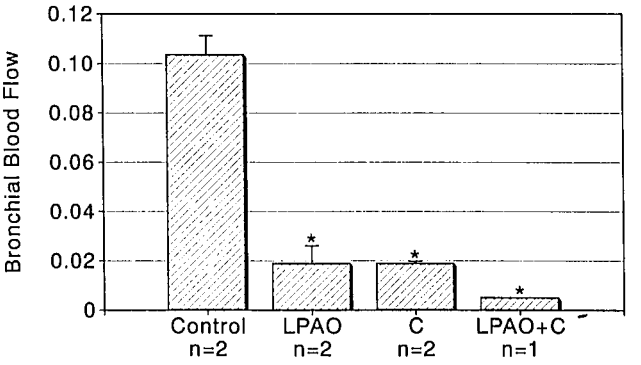

Fig. 3. The y axis represents bronchial blood flow to the left lung parenchyma as a percentage of cardiac output in control rabbits and tested rabbits. LPAO = left pulmonary artery occlusion alone for 24 h; C = collapse alone for 24 h; LPAO + C = collapse and left pulmonary artery occlusion for 24 h. Values are means ± SEM. *$P < 0.05$ *versus* control using one-way analysis of variance followed by least-significant-difference testing.

Discussion

The important findings of this paper are that in rabbits (1) the lung cannot maintain a normal bioenergetic state for more than 24 h if pulmonary artery blood flow is absent and the lung collapsed and (2) the increased permeability after 24 h of PAO, described in previous studies, is not attributable to decreased ATP. This paper is also the first demonstration that lung collapse decreases $\dot{Q}_{br}$ and reconfirms that PAO decreases $\dot{Q}_{br}$.

This study was prompted by the finding that PAO for 24 h increased permeability.[4] Because the bronchial circulation decreases initially after PAO,[6,10] we considered whether the lung distal to an occlusion might be suffering from an inadequate supply of oxygen or substrate. The lung is a highly metabolically active organ[11] but is generally protected from suffering ischemia given its dual circulation and alveolar oxygen. However, a combination of insults such as PAO with subsequent decreased $\dot{Q}_{br}$ could theoretically result in ischemia. In fact, we found that ATP depletion did not occur unless ventilation was also absent.

The study design used pneumothoraxes to eliminate ventilation to the left lung. Because the positive pressure in the pleural space was limited to 2 cmH_2O, capillary blood flow in the bronchial circulation should not have been significantly affected. However, pneu-

mothorax does exert two other possible adverse effects on the lung; oxygen does not reach the alveoli, and due to the absence of ventilation, reflux pulmonary venous flow is absent.[12]

The preservation of high-energy phosphates by continued ventilation may be the result of continued oxygen delivery to the lung tissue *via* direct alveolar diffusion. However, a second possibility is that the changes seen in the LPAO + C rabbits resulted from substrate deprivation from the lack of blood flow. Ventilation could prevent such substrate depletion by continuing to produce retrograde flow *via* the pulmonary venous system. Obermiller *et al.*[12] have shown that tidal ventilation results in reverse pulmonary blood flow after pulmonary arterial obstruction.

Loss of ATP in the lung has been used as a marker of injury in a variety of clinical and experimental situations including oxidant injury,[5,13,14] severe injury, burns and critical illness,[15–17] endotoxemia,[18] and hypoperfusion–hypotension.[19,20] Although ATP is widely used as a marker of injury, its significance for cell function remains unclear. Using inhibitors of ATP synthesis, it has been shown that decreases of ATP to concentrations similar to those seen in endothelial cells after injury do not necessarily correlate with cell dysfunction.[21,22] In an isolated endothelial cell preparation, however, loss of ATP was highly correlated with increased permeability.[5]

In our studies, ATP concentrations remained normal at a time when permeability is known to be increased.[4] Thus, observations of the correlation in some systems of low ATP and increased permeability may not represent cause and effect.[5,21,23]

The very low concentrations of whole-lung ATP seen in the LPAO + C rabbits did not represent total necrosis of the lung tissue based on histologic examination. This is consistent with findings in lung fibroblasts in cell culture that the cell membrane may remain intact at ATP values as low as 10% of baseline.[24] This is also consistent with the observation that alveolar structure and function recover after even severe lung infarction. We have also previously shown that despite reductions of ATP to 10% of baseline in endothelial cells in culture, the majority of cells remain viable and monolayer integrity returns within 24 h.[5]

The persistence of normal concentrations of ATP for 4 h after occlusion and collapse demonstrates that the anastomotic $\dot{Q}_{br}$ does provide some support to the lung after PAO, because complete hilar occlusion for 15 min (with presumed interruption of $\dot{Q}_{br}$) results in alveolar septal necrosis.[25] After complete hilar occlusion and resection of the lung from the rabbit, ATP concentrations decrease rapidly, reaching less than one third of baseline within 30 min.[26,27] This contrasts with normal concentrations of ATP for at least 4 h in our preparation with the bronchial circulation intact.

The ability of the bronchial circulation to maintain normal ATP concentrations at two and four but not 24 h was unexpected. We considered whether the persistence of small amounts of trapped oxygen in the alveoli at the time of collapse could account for this: Fisher and Dodia[28] have demonstrated that decreases in lung tissue ATP content occur only after the alveolar oxygen tension is reduced to 0.7 mmHg. However, given a lung oxygen consumption of approximately 3 $ml \cdot h^{-1} \cdot g^{-1}$ dry lung,[29] approximately 10–15 ml oxygen would need to remain trapped at the time of collapse to support the lung for 4 h. This far exceeds the volume of the collapsed lung.

The decline in ATP in the LPAO + C rabbits is sufficient based on *in vitro* studies to produce a significant change in endothelial cell microstructure and an increase in permeability.[5,30] However, the maintenance of baseline concentrations of high-energy phosphates in the animals subjected to LPAO alone disproved our hypothesis that the increased permeability after prolonged *in vivo* LPAO in ventilated lungs would correlate with decreased ATP. While this was certainly true using whole-lung measurements, it is conceivable that we are missing highly localized changes. One possibility is that declines in ATP in metabolically active endothelial cells might be masked by the gross nature of our sampling.

A second possible explanation for increased permeability in spite of normal ATP concentrations in LPAO rabbits is that regions of the lung with poor ventilation may result in patchy areas of energy depletion. PAO results in surfactant depletion and progressive loss of lung volume[3,31] and consequent regions of hypoventilation. Such a theory would be consistent with the patchy nature of reperfusion injury on histologic examination.

Our studies were prompted in part by our prior observation that $\dot{Q}_{br}$ decreased after 24 h of PAO.[6] We hypothesized that the decreased $\dot{Q}_{br}$ plus the absent pulmonary flow might result in decreased ATP. The studies of $\dot{Q}_{br}$ presented in this report demonstrate that it decreases markedly after either LPAO or left lung collapse, and yet ATP concentrations are preserved, suggesting that $\dot{Q}_{br}$ may not be the critical

factor resulting in maintenance of lung energy state.

Our findings run counter to the traditional thinking that $\dot{Q}_{br}$ preserves lung tissue in the face of PAO. The decline in $\dot{Q}_{br}$ to very low levels in rabbits in which ATP concentrations remained normal would argue against its playing a key role in preservation of energy state. Rather, it raises the possibility that alveolar oxygen or reflux pulmonary venous flow may be more important mechanisms of supporting lung metabolism. An alternative explanation that cannot be excluded is that some very low level of $\dot{Q}_{br}$—less than 0.02% of cardiac output—is all that is needed to support normal aerobic metabolism.

Our findings that residual circulation after PAO and lung collapse is adequate to support the lung for a period of hours but not days would have important clinical implications if the same were true of humans. Some caution must be used in applying the results to humans as the bronchial circulation demonstrates substantial interspecies and intraspecies variability.[32,33] In our control rabbits, about 0.1% of cardiac output went to the left lung parenchyma. We found no other reports quantifying $\dot{Q}_{br}$ in rabbits other than the prior one from our own laboratory with virtually the same result.[6] Our data are comparable to those found in several dog studies, although data have been highly variable even within species.[32] $\dot{Q}_{br}$ has been difficult to quantitate in humans because of the invasive techniques required, and measurements have been made only during cardiopulmonary bypass and include a significant component of noncoronary cardiac blood flow.[34] It is thus conceivable that if $\dot{Q}_{br}$ were much higher in humans, LPAO + C might have a greater margin of safety than in rabbits.

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