THE EFFECT OF ALTERATIONS OF PULMONARY ARTERIAL AND ALVEOLAR GAS TENSIONS ON THE PRESSURE-VOLUME CURVE AND SURFACE TENSION OF DOG LUNGS.

Part I. A review of the literature.

Part II. An experimental study.

by

Edmund E. Faridy, M.D.

A Thesis

Presented to

The University of Manitoba

In Partial Fulfillment

of the Requirements for the Degree

of Master of Science

March 1968

THE EFFECT OF ALTERATIONS OF PULMONARY ARTERIAL AND ALVEOLAR GAS TENSIONS ON THE PRESSURE-VOLUME CURVE AND SURFACE TENSION OF DOG LUNGS.

By: Edmund E. Faridy, M.D.

Acute cessation of pulmonary blood flow in ventilated lobes and perfusion of lobes with hypoxic, hypercapnic blood increased the retractive forces of the lobes. These changes were reversed by perfusion with hypoxic, eucapnic blood.

Reduction in pulmonary blood flow, hypoxia-eucapnia, hypercapnia in the presence of high oxygen tension and non-respiratory acidosis did not alter the mechanical properties of the lobes.

TABLE OF CONTENTS

LIST OF FIGURES

PART II.

LIST OF TABLES

PART II.

Abstract

Part I

The current literature on the effects of alteration in pulmonary arterial blood flow and in alveolar gas tensions on the mechanical properties of the lung is reviewed. Pulmonary artery ligation, cardio-pulmonary bypass, oxygen at high pressures, and high concentrations of CO_2 in the inspired gas cause changes in the lung mechanics associated with a decrease in the activity of the lung lining material. Little is known regarding the mechanisms by which inactivation of surfactant takes place under these conditions. However, there is some evidence that on exposure of lung tissue to high pressures of oxygen, the inactivation of surfactant is secondary to inhibitors originating from plasma that has exuded onto the alveolar surface. Whether CO_2 exerts its effect directly or indirectly by altering the hydrogen ion concentrations of the cells is not yet clearly defined.

Part II

To further understand the roles of oxygen, CO_2, and pH on surface forces of the lung these studies were undertaken. The effects of acute alterations of pulmonary blood flow, pulmonary arterial blood gas tensions and alveolar gas tensions on the mechanical properties of the lungs were studied on the left lower lobes of open-chest dogs. The pressure-volume characteristics (expressed as percentage of the maximum lobe air volume) of ventilated lobes deprived of pulmonary

PART I. A REVIEW OF THE LITERATURE

A. Introduction

Over the past decade an appreciation of the role of the alveolar lining layer has provided new insight into the metabolism and function of the lung in health and disease. Many studies have been carried on in order to find evidence for the existence of a surface active substance in the lung, its source, its chemical identification, its relation to the lung metabolism, the effects of its alterations on lung function, and factors affecting the activity of the substance in the lung. One approach to understanding the conditions essential for the integrity of pulmonary surfactant is to examine the conditions in which it may be altered.

The present thesis is the study of the effects of alterations in the pulmonary circulation, the pulmonary blood gas tensions, and the alveolar gas tensions on the activity of the lung lining material (surfactant).

B. Pulmonary Artery Ligation

The effect of occlusion of the pulmonary artery on the lung has been studied by several workers. Schlaepfer (1) ligated one pulmonary artery in dogs and rabbits and noted atelectasis and some alveolar hemorrhage 10 hours after the ligation in rabbits and 8 days after the procedure in dogs. Several months after pulmonary artery occlusion, all of the lungs appeared normal. Lindskog and Gilman (2) ligated the pulmonary artery to the right lower lobe in 10 dogs and subsequently found no atelectasis. However, they sacrificed their animals from 15 - 256 days after ligation and had no information on the condition of the lungs during the first two post-operative weeks. Liebow and associates (3) ligated the left pulmonary artery in 11 dogs. They examined the lungs from these dogs 9 weeks to 25.6 months later and found no difference in the sizes of the left and right alveoli. Davis and co-workers (4) found hemorrhagic infarctions of the lungs in monkeys which were sacrificed 50 hours after pulmonary arterial occlusion. Catena and associates (5) noted that pulmonary edema and atelectasis had occurred in dogs sacrificed 7 days after pulmonary artery occlusion. However, the alveolar structure was normal in animals sacrificed several weeks after the surgical procedure.

The anatomical changes of unilateral pulmonary artery ligation consists of focal atelectasis, bronchial degeneration, and hemorrhage several days after ligation with an estimated reduction

of the resting lung volume by 1/3 to 1/2. As bronchial collateral circulation increases, these changes regress; within several months the lungs are grossly normal. Bloomer and colleagues (6) measured the collateral blood flow following ligation of the left pulmonary artery in dogs. In their studies the collateral blood flow averaged 300 ml./minute/sq. meter body surface area one month after pulmonary artery ligation and 450 ml. after six months.

Van Allan et al (7) suggested that atelectasis was secondary to obstruction of bronchioles due to degeneration and desquamation of the lining epithelium. Clements et al (8) demonstrated that stability of alveoli is dependent upon a highly surface-active alveolar lining layer, the pulmonary surfactant. This substance is produced by the lung tissue and its integrity is presumably dependent upon an adequate pulmonary capillary blood flow (9, 10). Therefore a reduction or cessation in pulmonary artery blood flow could cause an alteration in lung cellular function affecting production of surfactant which could lead to atelectasis. Thus it could be postulated that atelectasis observed following pulmonary artery ligation has been the result of a deficiency of surfactant as well as secondary to obstruction of airways.

In recent years a number of investigators have carried out studies in order to find a relationship between atelectasis following unilateral pulmonary artery ligation and a deficiency in surface activity of the lung lining material. Finley et al (11) measured minimal surface tension of dog lung extracts in chronic pulmonary

artery ligation and found elevated values 15 hours after ligation which returned to normal after six months. Giammona et al (12) showed that 4 hours after ligation of one pulmonary artery, the surface tension measured on the lung extracts and the deflation pressure-volume curves were unaltered. However, two weeks after ligation the lung had a smaller air volume at each pressure during deflation and its extracts had a higher minimal surface tension. Their data suggests a close relationship between altered surface forces and the pressure-volume characteristics of the lung after pulmonary artery ligation. Chernick et al (13) carried out similar studies on 17 dogs for a period of 2 - 98 days. They showed that the total lung volume was reduced by 40 - 50% of control lungs for the first 35 days following ligation. Lobes ligated from 2 - 14 days had a significant decrease in proportional volume deflation, indicating increased retractive forces of inflatable alveoli. Minimal surface tension was significantly elevated for this group. By 25 - 35 days, both minimum surface tension and increased retractive forces had returned to normal values. The decrease in total lung volume was converted to normal after 50 days of pulmonary artery ligation. Edmunds et al (14) in their extensive studies, have demonstrated that unilateral pulmonary artery occlusion reduces inflatable lung volume, causes an increase in lung weight and produces focal areas of hemorrhagic atelectasis which cannot be inflated by either gas or saline. In the hemorrhagic areas alveoli are filled with red cells and alveolar septa are thickened and infiltrated with macrophages, lymphocytes, plasma cells, and a few

polymorphonuclear cells. Other areas of lung remain entirely normal and show no ultrastructural alterations. These areas contain surface-active alveolar lining material and show no change in pulmonary mechanical relationships. These areas are unchanged biochemically from opposite non-ligated lung but the hemorrhagic atelectatic areas of the ligated lung show a decrease in phospholipid content, dipalmitoyl phosphatidyl choline, and alterations in esterified fatty acid composition and enzyme activity. Their data indicates that pulmonary arterial occlusion does not cause a generalized increase in alveolar surface forces, but that focal rather than general changes occur in lung following pulmonary artery ligation.

Alteration in surface activity of lung lining material in conjunction with the changes following pulmonary arterial occlusion has been demonstrated. It is not yet shown whether the deficiency in the activity of surfactant is primary or secondary to the structural changes in the lung such as hemorrhage or edema.

Howatt et al (15) have shown that occlusion of the left pulmonary artery, for 2 - 7 hours, in the fetal lambs affected the surface properties of the upper part of the lung at 124 - 128 days gestation (when the alveolar surface properties are undergoing active development), but had no effect on more developed lung at 135 days gestation. They have suggested that the actively developing lung is particularly susceptible to the effects of diminished blood flow. This difference could have been a result of different experimental conditions designed

for the two groups of lambs under study. The smaller lambs were not ventilated but the larger lambs were ventilated with room air. However, in a similar study, Adams et al (16) demonstrated that unilateral pulmonary arterial occlusion had no effect on surface activity and phospholipid content in the non-ventilated fetal lambs at gestational age of 128 - 140 days.

C. Cardio-pulmonary Bypass

One of the most frequent pulmonary complications following open-heart surgery and circulatory bypass procedures is pulmonary congestion and edema, which could be a potentially lethal event in the post-operative period (17, 18, 19, 20). In the most severe form of "pulmonary congestion syndrome" the patient usually leaves the operating room, following intracardiac surgery in reasonably good condition, but, within the first few hours he develops fever, increasing cyanosis, dyspnea and hypotension. Physical examination may reveal increasing signs of pulmonary edema, and radiologic examination may reveal diffuse clouding of the pulmonary fields.

Extra-corporeal circulation produces changes in lung function. Studies on human subjects and experimental dogs have shown that carbon monoxide and oxygen diffusion are diminished, alveolar-arterial gradients for oxygen is increased and an average right to left shunt of 24% of the cardiac output is noted when breathing air (21, 22). Gas volumes in all functional compartments except residual volume are reduced and lung compliance is decreased (23, 24). If death occurs it is with the symptoms of acute pulmonary failure and this usually occurs within the first two days. Post-mortem studies show that the lungs are dark red and congested, with focal zones of collapse and parenchymal hemorrhages. Microscopically there are usually many small zones of hemorrhage with blood cells and clear proteinacious

edema fluid filling the alveoli and bronchi, in association with focal collapse, pulmonary edema and engorgement of small blood vessels.

There are so many events during and after the operation which could predispose to pulmonary hemorrhage that it is difficult to assign primary significance to any one. Littlefield et al (25) have concluded from their experiments on dogs that the pulmonary hemorrhages and congestion seem to be caused by a positive surge of pulmonary capillary pressure during or at the end of perfusion. This damaging transient or prolonged increase in pulmonary capillary pressure was the result of overfilling of the left atrium. Baer et al (20) and Kottmeier et al (26) have shown that "pulmonary congestion syndrome" does develop in experiments where the left auricle is drained, concluding that the left auricular distension and pulmonary back flow could not be considered to be responsible for the pulmonary changes. No correlation between perfusion volume, blood flow, arterial blood pressure, oxygen saturation, and pathologic changes was found. However, they (26) were able to find embolic material grossly and microscopically in the lungs of several animals sacrificed within the first 24 hours. Material found in the oxygenator resembled that which was found in the lung. Hepps et al (27) showed that the addition of low molecular weight dextran to the blood and hemodilution perfusion where the hematocrit was reduced to less than 15% lessened the adverse effects of cardio-pulmonary bypass upon the lung, as evidenced by lowered minimal surface tension and improved microscopic

appearance. Many advantages have been ascribed to low molecular weight dextran, including the prevention of intravascular aggregation and sludging. It has been suggested by Bernstein and associates (28) that the reduction in red blood cell aggregation by the addition of low molecular weight dextran is due to an increase in red blood cell electronegativity which produces repulsion between red blood cells and therefore prevents aggregation. It is possible then that micro-embolization of the pulmonary vascular bed occurs during cardio-pulmonary bypass and leads to an ischemic injury, resulting in the release of circulating inhibitors of the surfactant. Gardener et al (29) measured the surface tension of lung extracts prepared from lungs of patients or experimental dogs undergoing cardio-pulmonary bypass for a period of between 36 - 96 minutes. The minimum surface tension of these extracts were much higher than the control values. They also demonstrated that lung extracts mixed with blood, which had been re-circulated in the bubble oxygenator from 4 - 12 hours, had a high minimum surface tension. When the same extracts were mixed with un-perfused blood, minimal surface tensions were within normal limits. They have suggested that the denaturation of the plasma proteins in the oxygenators, where the blood was in direct contact with air or oxygen (30), could be a factor in the alteration of surface-active material. However, Mandelbaum et al (31) have failed to show an inhibitory substance of pulmonary surfactant in the pump oxygenator blood. In their study blood inhibited pulmonary surface activity of normal lung extracts before and after circulation through the disc oxygenator.

Although the etiology of lung pathology following cardiopulmonary bypass is not clear, the changes have been shown to be associated with alterations in the surface forces of the lung. To what extent alterations in the surfactant are primary or secondary to edema and hemorrhage is not clear.

D. Experimental Atelectasis

Avery and Mead in their study of lungs of infants with hyaline membrane disease, have considered the possibility that atelectasis alone could be deleterious to the surfactant (32). Since then a number of investigators have studied the effect of induced atelectasis in experimental animals and pathologic atelectasis in human subjects on the surface forces of the lungs. Avery and Chernick (33) found that after 24 hours atelectasis induced by a large pneumothorax in rabbits, some diminution in surfactant was present. They postulated that the occasional recollapse of lungs following re-expansion after prolonged atelectasis (34) could be on the basis of the loss of surfactant. Finley et al (11) studied the effect of absorption atelectasis (following bronchial ligation) in dogs on surface forces of the lungs. They found an increase in minimum surface tension after 48 hours of bronchial ligation which returned to normal by 50 days. They postulated that airlessness per se was not detrimental since surface tension was normal in extracts prepared from lungs that were still collapsed 8 and 10 weeks after ligation of the bronchus; and that the increase in surface tension following bronchial ligation was most probably secondary to a loss of pulmonary blood flow. Their conclusion is based on the alterations of surface forces observed following pulmonary artery ligation and the fact that following bronchial ligation blood flow to the lung is reduced proportionately to the degree

of pulmonary collapse (35, 36, 37, 38). The blood flow through an atelectatic area is continuously decreasing during the first month, until practically no blood is passing through the non-ventilated part of the lung. According to Peters and associates (37), 10 - 15% of the cardiac output returns to the lung 1 - 2 months after ligation of the bronchus. On the basis of this observation, Finley et al (11) have suggested that the return to normal surface tension 8 - 10 weeks after bronchial ligation in their experiments may be related to the return of blood flow through alveolar capillaries. Sutnick and Soloff (39) demonstrated a decrease in surface activity of the lungs as evidenced by an increase in minimum surface tension as early as 45 - 90 minutes following ligation of the bronchus in dogs. They further demonstrated that the inflated portions of the atelectatic lungs had normal surface activity as compared to that of the controls.

Up to this time studies dealing with the effect of atelectasis upon the surface active properties of saline lung extracts were not in agreement. Using different extraction techniques, the investigators had reported early (39), time related (33, 11), or no (40) alteration in extract activity in experimental atelectasis. Levine and Johnson (41) studied the effect of the extraction method on apparent activity of lung extract using three extraction techniques - chopping, mincing, and pestle homogenization. They noted that all extraction methods gave highly active extracts when aerated lungs were used; but extracts from airless lungs prepared by chopping or mincing, invariably showed higher minimum surface tensions, lower stability indices and took

more time to reach minimum tension than did extracts of the same lungs when aerated. However, lung extracts made by homogenization from airless lungs showed normal surface activity. The authors indicated that the differences could be due to a decreased area of saline-alveolar contact during the extraction and suggested that the lungs should be inflated prior to saline extraction for measurements of surface activity. Yeh et al (42) confirmed the findings of Levine and Johnson. They showed that the collapsed lungs from 1 - 194 days did show higher surface tensions when studied in the collapsed state, but if they were re-inflated immediately before extraction of the surfactant, no abnormalities were found. This indicates that atelectasis per se is not deleterious to the surfactant.

Levine and Johnson (43) extended their experiments on atelectatic lungs to include a study of the pressure-volume characteristics of the lungs. They produced left lung collapse by pneumothorax in rabbits for a period of 90 minutes to 8 days. The atelectatic lungs showed a progressive decrease in "inflatability" with duration of collapse. An increase in airway pressure at any inflation volume as well as a decrease in total volume at maximum inflation pressure were seen. The alteration in opening pressure with duration of atelectasis was also seen during saline inflation of atelectatic lungs as compared to the controls. However, the deflation portion of the air pressure-volume diagram when compared on the basis of percent were not different from those of the controls. Since a highly surface active material was

demonstrated in the collapsed lung from the tracheal foam, the alterations in the saline and air inflation pressure-volume curves were considered to be due to altered tissue characteristics as demonstrated previously (38, 44) by histologic studies of the lung after collapse. These changes begin in the elastic fibers 30 minutes after bronchial ligation, and consist of alteration in position and form of the fibers, and, to a lesser degree, in disturbance of their structure (thickening, swelling). The changes are progressive and by the 5th. to 9th. months thin, tightly stretched elastic fibers arranged in bundles are found in the bronchi, the visceral pleura and the intra-alveolar septa. These changes could be secondary to the reduced pulmonary arterial blood flow which accompanies atelectasis. In spite of these structural changes, the experimental observations reveal that the lung easily and completely re-expands when bronchial ligation is released and the endobronchial mucus is aspirated (45). Furthermore, the lung does not seem to be functionally handicapped, since the blood that flows through gets normally oxygenated after re-expansion of the lung.