PULMONARY VASCULAR CHANGES IN DIFFUSE LUNG DISEASES.

Thesis
submitted f or partial fulfillment of
M.D. degree of chest diseases

By

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ABBREVIATIONS

A--aD02	Alveolar arterial oxygen tension gradient
ARDS	Adult respiratory distress syndrome.
BAL	Broncho-alveolar lavage
BOP	Bronchiolitis obliterans and interstitial pneumonitis.
Cdyn	Dynamic compliance.
CFA	Cryptogenic fibrosing alveolitis.
COPD	Chronic obstructive pulmonary disease.
CT	Computerized tomography.
DIP	Desquamative interstitial pneumonitis.
EAA	Extrinsic allergic alveolitis.
e.g.	For examplie.
FEV1	Forced expiratory volume first second.
FPF	Familial idiopathic pulmonary fibrosis.
FRC	Functional residual capacity.
FVC	Forced vital capacity
GVHR	Graft versus host reactaion.
H & E	Haematoxylin and eosin.
HLT	Heart lung transplantation.
HRCT	High resolution computerized tomography.
i.e.	That is to say
Ig	Immunoglobulin.
ILD	Interstitial lung disorder (or disease)
IPF	Idiopathic pulmonary fibrosis.

MEFV	Maximum Expiratory Flow
no	Number
O2	Oxygen
PaCO2	Partial pressure of arterial CO2
PaO2	Partial pressure of arterial O2
PAS	Para amino salicylic acid.
PGE2	Prostaglandin E2
RV	Residual volume.
SLE	Systemic lupus erythematosus.
SLT	Single lung transplantation.
TLC	Total lung transplantation.
UIP	Usual interstitial pneumonitis.
VC	Vital capacity.
CREST	Variant of scleroderma
R.V.H.	Right Ventricular Hypertrophy.
^{99}Tc DTPA	Technesium labelled diethylenetriaminopento-acetate.
V/Q	Ventilation perfusion ratio.
I^{131}	Radioisotope iodin.
MAA	Microaggregates albumin.
^{99m}Tc	Radioisotope technisium ^{99m}
In^{111}	Radioisotope indium.
Kev	Kiloelectron volt.
CO	Carbon monoxide
Sa O2%	Arterial oxygen saturation
REM	Rapid eye movement

[illegible]	[illegible]
A.F.B	Acid fast bacilli.
L.E.	Lupus erythematosus.
Anti DNA	Anti-Deoxyribonucleic Acid.
Rh. A	Rheumatoid arthritis.
H.P.	Hypersensitivity pneumonitis.
CPR	Clincial, Radiological and physiological score.
FVC/P	Forced vital capacity/predicted.
U/L	Upper/Lower zone ratio.

Introduction

The regional distribution of blood flow depends on the relationships between alveolar pressure, pulmonary arterial pressure, pulmonary venous pressure, and interstitial pressure. It is influenced by the structural support of the lung within the chest and to a greater degree than ventilation, by gravity or acceleration. Local pulmonary blood flow is influenced by the intravascular and perivascular pressure and vascular resistance. Any condition which cause localized changes in vascular resistance such as hypoxic vasoconstriction, perivascular oedema such as hypoxic vasoconstriction, perivascular oedema or pulmonary emboli, will reduce local blood flow and cause more blood to flow to the other parts of the lung (9).

Radionuclic studies, such as ventilation-perfusion imaging or Gallium 67 scanning, play a relatively small but important role in the diagnosis of pulmonary diseases. Ventilation-perfusion studies are important in the diagnosis of pulmonary embolism and also in the management of patients with carcinoma of the bronchus or other condition that may require pulmonary resection (74).

Ventilation perfusion scans are rarely performed in the routine clinical management of interstitial lung diseases but are being increasingly used to assess the V/Q relations of such patients undergoing single lung transplantation (35).

AIM OF THE WORK

Detection of pulmonary vascular changes in diffuse "interstitial" lung disease using radioisotopic perfusion scanning.

THE STRUCTURE AND FUNCTION OF THE ALVEOLAR INTERSTITIUM AND ITS REACTION TO INJURY

It is mandatory to know the normal structure and function of the alveolar interstitium and its reaction to injury in order to understand how the interstitial pulmonary fibrosis develops.

The Structure of the Alveolar Interstitium:

The Alveolar interstitium is a thin sheet of tissue in the alveolar wall bounded by the basal surfaces of alveolar epithelial cells and capillary endothelial cells. It continues with that around the vascular tree and connects to the perilobular and subpleural tissues (8). It is formed of : (a) epithelial and endothelial basement membranes that forms the boundaries of the interstitium, (b) connective tissue matrix, (c) mesenchymal cells, (d) inflammatory effector cells, and (e) other molecules (9).

The basement membrane is composed of at least 50 different proteins secreted by the epithelial cells. The major proteins are (a) collagen type IV which forms the structural backbone of the basement membrane, (b) laminin which binds the cells to the basement membrane, (c) heparan sulfate proteoglycan which forms an anionic barrier retarding movement of the protein, and (d) nidogen which aggregates basement membrane components into a nest like structure (8,10). The basement membrane is formed of 2 layers; (a) lamina lucida which lies directly under the cells and is formed mainly of laminin and (b) lamina densa which lies to the inside and is formed mainly of collagen IV (8)

The connective tissue matrix comprises fibrous, elastic, and amorphous structures. The fibrous one is the collagen, mainly type I and III in a ratio of 2:1 (11). Fibrils composed mostly of type I collagen are thick and have a high tensile strength while fibrils rich in type III collagen are thinner and more compliant (12). The elastic component is the elastic fiber which is formed of central amorphous elastin and peripheral supporting microfibrilis (8). The amorphous component of the connective tissue matrix i.e. the "ground substance" includes different porteoglycans and fibronectin (12). The latter is a glycoprotein which plays a central role in cell matrix interaction through its ability to interact with cells, collagen type I, and proteoglycans. It also acts as a chemotactic factor, as a component factor for mesenchymal cell growth and proliferation, and as a link between intra-alveolar fibrin and interstitial fibroblasts. The latter action enhances intra-

alveolar fibrosis which an injury causes damage to the endothelial cells with intra-alveolar leak of plasma contents including fibrin (8).

The connective tissue matrix is produced by mesenchymal cells: mainly fibroblasts and myofibroblasts: and to a lesser extent by epithelial cells. Fibroblasts and myofibroblasts produce collagen type I and collagen type III at a ratio of 5:1. However, the actual ratio is 2:1 due to production of collagen type III by the epithelial cells also(8).

The members of mesenchymal cells include fibroblasts, myofibrolasts, smooth muscle cells, pericytes, myofibroblasts-like cells and undifferentiated mesenchymal cells. The latter one is probably the precursor of the other cells (8). Fibroblasts are the main member, comprise 37% of all parenchymal cells, and occupy approximately two-thirds of the volume of the interstitium (9). The major functions of mesenchymal cells are to produce the connective tissue matrix and to modulate the mechanical properties of the interstitium. Myofibroblasts may have an important influence on both blood and air flows (8).

In the normal lung there are approximately 80 effector cells per alveolus (13). These cells are both within the alveolar interstitium and on the alveolar epithelial surface. Greater than 90% are alveolar macrophages (13), effector cell with a life span of months to years (14). They are mostly derived from blood monocytes that migrate through the alveolar walls but also they can replicate in the normal lung (14). One normal role of the alveolar macrophage is to defend the lower respiratory tract from inhaled organisms

and particulates. Macrophages normally accomplish this using surface receptors such as those for C 3b component of complement and the Fc region of IgG (15). In addition, alveolar macrophages can phagocytose particulates that are not opsonized (16). Although quiescent in healthy individuals, when activated, the human alveolar macrophage releases a variety of mediators relevant to inflammatory and immune processes (16).

Most of the remaining 10% is made up by both B- and T-lymphocytes, the proportion of them is the same as in blood. They are quiescent in the healthy lung (16). Less than 1% is made up by neutrophils, eosinophils, basophils, and mast cells (18). The effector cells play a vital role in defending the lungs on the one hand and in injuring the interstitium on the other (8).

Lipids, carbohydrates, proteins and small solutes are filtered from plasma into the interstitium. Few of these are of critical role e.g.α-1-antitrypsin; the most potent antielastase. Other molecules may be secreted by various cells e.g. PGE2 which has inhibitory effect on inflammatory and mesenchymal cell proliferation, and catalase which has an antioxidant property (8)

The alveolar interstitium runs a process of continuous turnover by continuos degradation of its components at a certain rate and balance. The disturbance in this balance is of a vital role in the pathogenesis of interstitial pulmonary fibrosis e.g. disturbed balance between degradation and production of collagens with over production results in thickening of the alveolar interstitium and fibrosis (8).

Function of the Alveolar Interstitium:

The four basic functions of the alveolar interstitium are (a) defining the alveolar architecture, mainly by intact basement membrane, (b) contribution to the mechanical behaviour of lung tissue, mainly by fibroblast and connective tissue matrix, (c) modulation of alveolar-capillary exchange of plasma constituents, and (d) lower respiratory tract defense (8).

Other Parenchymal Cells:

The alveolar epithelial cells line the air spaces while the capillary endothelial cells lines the blood capillaries.

The alveolar epithelial cells are two types:

1. ***Type I Pneumocytes:*** They form 30% of the alveolar epithelium and cover 90% of the surface area of the alveoli (13). They are large cells with flattened cytoplasm; hence called membranous; and few organelles and probably metabolically dependent upon the central perinuclear portion; an observation which may explain why these cells are vulnerable to a variety of injuries (17).

2.Type II Pneumocytes: They are cuboidal cells interposed between membraneous pneumocytes. They contain prominent lamellar bodies, hence called granular; thought to be the source of pulmonary surfactant. Granular pneumocytes have a much greater capacity for division and a shorter turnover time than membranous pneumocytes and probably represent the reserve cells of the alveolar epithelium. They proliferate and replace membranous

pneumocytes when the latter are destroyed. This proliferation of alveolar pneumocytes can occur in a wide variety of circumstances and appear to be a non-specific reaction to injury (17). It is a feature present in the fibrosis-type injury of the alveolar interstitium (8).

N.B. The Alveolar interstitium is not an isolated structure: the distortion, fibrosis, and destruction types of injury almost invariably involves the whole of the alveolar wall to some extent.

Reaction of the Alveolar Interstitium to Injury:

Different injuries to the alveolar interstitium results in one or more of the following three reactions:

1- Distortion; a process in which the interstitium is widened by the accumulation of cells and/or extra cellular materials; as in sarcoidosis.

2- Fibrosis; a process in which the normal alveolar interstitium is damaged and replaced by an increased number of mesenchymal cells and their connective tissue products namely collagen; as in cryptogenic fibrosing alveolitis (CFA).

3- Destruction; a process in which there is a loss of the integrity of the interstitium; as in emphysema (8).