CHANGES IN PULMONARY VASCULATURE IN LUNG DISEASES WHICH LEAD TO PULMONARY HYPERTENSION

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ABSTRACT

The pulmonary vasculature was studied in lung biopsy/autopsy specimens of 20 cases, in conditions likely to lead to pulmonary hypertension. The changes were classified as per Edward and Heath classification and morphometric measurements to gauge medial and intimal hypertrophy were done. Medial hypertrophy was found to be the earliest and commonest change in all cases, irrespective of the pathogenic mechanism of pulmonary hypertension. Variable changes specific to various arteriopathies/vasculopathies were noted.

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KEYWORDS: Hypertension pulmonary; Pulmonary artery.

Introduction

The pulmonary vasculature is unique in the sense that it receives the venous return of the whole of the body except that from the heart. A vascular bed which receives such a huge amount of flow has to change and respond to various pathological changes in the lungs. This is reflected haemodynamically and clinically as pulmonary hypertension. The histopathological changes were initially studied in patients with congenital heart disease [1]. However, pulmonary hypertension can be brought about in a number of diseases which include rheumatic and congenital heart disease, restrictive and obstructive diseases of the lung, idiopathic primary pulmonary hypertension, certain drugs and collagen vascular diseases. Histological investigation of the lung often gives information about pulmonary hypertension, though it can by no means replace clinical evaluation or cardiac catheterization. The present study is an attempt to make clinicians and pathologists aware of the spectrum of changes in pulmonary hypertension. Some authors [2] recommend the use of the term arteriopathy/vasculopathy for these changes.

Material and Methods

A total of 20 cases were studied, which included both biopsy and autopsy cases. The biopsy cases were selected from those which reported to the cardiothoracic surgical centre at Army Hospital, Delhi Cantt during the period August 1989 to March 1991. Autopsy cases were selected from those done during the same period with diseases known to cause pulmonary hypertension. The cases were divided into 4 broad groups as shown in Table 1. The biopsy specimens were fixed immediately in the operation theatre in 10 per cent buffered formal saline. In autopsy cases, the lungs and heart were removed *en bloc* along with the trachea. After removal, 10 per cent formal saline was instilled through the trachea till the lungs were distended, the trachea was then tied with silk and the lung and heart block were put in formal saline for fixation. After fixation for at least a week 3 sections were taken from each lung, i.e., upper, middle/lingular and lower lobe of each lung.

All biopsy and autopsy slides were stained with routine H&E; elastic van Gieson stain and Perl's iron stain. Qualitatively the changes in the pulmonary vasculature were graded as per the Edward and Heath classification as shown below [1]. However, the sequence of these changes may not

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TABLE 1-

Age	Sex	Diagnosis	Biopsy/ Autopsy	Grade of changes	Intimal index	% media thickness	Remarks
Cases of plexogenic arteriopathy							
1 1/2 months	F	CHD	Autopsy	3	0.13	15.00	
4 months	M	CHD	Autopsy	3	0.22	38.33	Iron stain+
24 years	M	CVA	Autopsy	2	0.13	14.80	
8 1/2 years	M	PHT	Biopsy	1	0.07	15.90	
Cases of hypoxic arteriopathy							
32 years	F	Emph	Biopsy	2	0.30	8.18	Mus of art+
29 years	M	COLD	Biopsy	—	0.09	7.90	
49 years	M	Emph	Autopsy	1	0.04	9.60	Mus of art+
43 years	M	Emph	Autopsy	1	0.04	12.00	Mus of art+
Cases of congestive vasculopathy							
32 years	F	RHD-MS	Biopsy	1	0.12	20.00	Veins+
28 years	F	RHD-MS	Biopsy	1	0.18	14.14	Iron stain+
25 years	F	RHD-MS	Biopsy	1	0.05	11.70	Iron stain+
38 years	M	MS-PHT	Biopsy	2	0.39	17.30	Iron stain+
46 years	M	MI	Autopsy	—	0.08	7.80	Veins+
28 years	M	LVF	Autopsy	1	0.11	9.09	
27 years	M	CMpath	Autopsy	1	0.05	8.72	
Cases of diffuse lung disease							
33 years	M	Int-Fib	Biopsy	2	0.22	28.00	
31 years	F	Int-Fib	Biopsy	2	0.39	35.00	
65 years	F	Pne-Con	Biopsy	1	0.08	10.90	
27 years	M	Int-L.D	Biopsy	2	0.16	13.40	
29 years	M	SLE	Autopsy	—	0.05	6.60	

CHD- Congenital heart disease; Mus of art+ - Muscularization of arterioles present; Emph - Emphysema; Veins+ - Thickening of veins present; CMpath - Cardiomyopathy; Int-Fib - Interstitial fibrosis; Pne-Con - Pneumoconiosis; Int-L.D - Interstitial lung disease; PHT - Pulmonary hypertension

represent actual chronological progression [3].

Edward and Heath Classification

Grade 1 : Medial hypertrophy and muscularization of arterioles.

Grade 2 : Medial hypertrophy. Cellular intimal proliferation.

Grade 3 : Medial hypertrophy. Intimal Fibrosis. Early generalized vascular dilatation.

Grade 4 : Progressive generalized dilatation. Plexiform lesions.

Grade 5 : Appearance of other dilated lesions. Vein-like branches of hypertrophied muscular lesions. Angiomatoid and cavernous lesions. Pulmonary haemosiderosis.

Grade 6 : Necrotising Arteritis.

Quantitatively, two indices were used to deter-

mine the changes in the muscular pulmonary arteries. The two indices were percentage medial thickness and intimal index. Both measurements were carried out on the sections stained with elastic Van Gieson stain. The percentage medial thickness were determined as follows :

Percentage medial thickness = Medial thickness/External diameter of the artery * 100. The external diameter of the artery was measured between the adventitial aspect of the media on either side of the artery. The medial thickness was measured by measuring the media on either side of the artery. The medial thickness was taken as an average of two measurements. If the artery was oval the measurements were taken along the shortest diameter, and in any plane if circular.

The intimal index was measured by first

measuring the area enclosed by the internal elastic lamina. The area enclosed by the internal elastic lamina was taken as the area it would occupy if it was in an unwrinkled state. Intimal index was then calculated as follows :

Intimal index = Area Occupied by Intima/Area enclosed by internal elastic lamina.

The value of this index varies from 0-1, indicating minimal to total occlusion of the arterial lumen by intimal changes due to fibrosis or proliferation [4].

The two indices were taken as an average of those measured in 5-10 muscular pulmonary arteries in cases of open lung biopsy. In the autopsy cases, 20 muscular arteries were measured in each lung, and the average of the 2 indices from the measurement of 40 arteries in each case was taken out. These measurement were made using a micrometer eyepiece and a stage micrometer.

Results

The mean age of patients was 29.3 years (range 1 and 1/2 months to 65 year). There were 7 females (35%) and 13 males (65%).

Changes in cases of Plexogenic Arteriopathy

These are as shown in Table 1. Case No 1 and 2 were both cases of congenital heart disease. Case 3 was a serving soldier in whom the cause of death was cerebral haemorrhage. The changes in the pulmonary arteries were an incidental finding. In case 4 open lung biopsy was done in a 8 and 1/2 year old boy, clinically diagnosed as a case of primary pulmonary hypertension.

Cases of Hypoxic Arteriopathy

The changes in the pulmonary vasculature in cases of hypoxic arteriopathy are as shown in Table. Muscularization of arterioles was seen in 3 out of the 4 cases.

Congestive Vasculopathy

There were 4 cases of lung biopsy and 3 of autopsy. All the four lung biopsies were carried out at the time of closed mitral valvotomy. Most of the cases showed increased medial thickness and were labelled as grade 1 changes. Only case 13 showed no changes. Grade 2 changes were seen in case 12, which showed intimal fibrosis and medial

hypertrophy. Iron stain was positive in 3 out of 7 cases.

Diffuse Lung Diseases

Changes in diffuse lung diseases are as shown in the table. In the lone case of SLE (case No 20), lungs showed neither vasculitis nor any changes suggestive of pulmonary hypertension as the medial thickness was 6.6 per cent and intimal index was 0.05.

Discussion

Plexogenic Arteriopathy

Both case 1 (Fig 1) and case 2 had congenital heart disease, with associated involvement of the pulmonary vasculature. Both cases showed grade 3 changes as per the Edward and Heath classification. Congenital heart disease as such is the most documented cause of plexogenic arteriopathy. In the arteriopathy, medial hypertrophy has been found to be the most common change, whereas others had medial hypertrophy in combination with intimal lesions [5]. Ultrastructurally, it has been found that intimal fibrosis may be initiated by migration of smooth muscle cells from the media and their conversion to myofibroblasts [6].

Case 4 was a case of primary pulmonary hypertension. The incidence of primary pulmonary hypertension is reportedly higher in the Indian subcontinent [7,8]. More recent studies have found increase in progesterone receptors in the nuclei of migratory myofibroblasts [9]. However, another recent study indicates that severity of clinical disease was not necessarily associated with advanced histopathological changes. It has also been surmised in the same study that gastrin-releasing peptide from pulmonary endocrine cells may be involved in the process [10].

Hypoxic Arteriopathy

Our results in cases of hypoxic arteriopathy match with those of other authors [11]. Muscularization of arterioles is common in emphysema (Fig 2). This has been also found on ultrastructural studies [12]. Hypoxia is a potent vasoconstricting influence in pulmonary hypertension in these cases. When persistent it produces intimal thickening, inflammatory changes and medial hypertrophy [13]. We did find medial hypertrophy in 3

Fig. 1: Medial and cellular intimal proliferation in an infant of congenital heart disease (H&E, 600X) (Case 1)

Fig. 2: Showing muscularization of an arteriole in a case of emphysema (H&E, 600X) (Case 7)

cases. Intimal thickening was found in only one case in our series, which doesn't compare too well with that of other authors [14]. The number of cases studied [4] is too small to comment on the significance of this finding.

Congestive Vasculopathy

Most authors feel that there is a poor correlation between medial thickness and severity of mitral valve disease and/or associated hypertension [15]. Again medial hypertrophy was found to be the commonest change in this vasculopathy. Muscularization of veins was seen in 2 of the cases, emphasising the reason why it is known as a vasculopathy and not arteriopathy. Iron stain was positive in 3 of the cases (Fig 3). Though haemosiderosis is of limited value in the diagnosis of pulmonary hypertension, it may be helpful in the diagnosis of the cause of pulmonary hypertension. Pulmonary hypertension in patients with

Fig. 3: Showing positive prussian blue reaction (Perl's iron stain, 150X)

Fig. 4: Muscular pulmonary artery showing marked medial hypertrophy and intimal fibrosis causing virtual obliteration of the lumen (EVG, 150 X) (Case 16).

Mitral Stenosis results from passive backward transmission of the elevated left atrial pressure, pulmonary arteriolar constriction [16] and organic obliterative changes in the pulmonary vascular bed [17]. There is an element of reversible pulmonary vasoconstriction as well [18].

Changes in Diffuse Lung Disease

The arterics in these cases showed moderate to severe medial hypertrophy. Intimal fibrosis was found in 3 of the 4 cases (Fig 4) as evidenced by the increase in the intimal index. It has been pointed out that the changes in diffuse lung diseases resemble those of congestive vasculopathy [19]. However, we did not find any thickening of the media of the veins.

In the lone case of SLE, there was no involvement of the lung, nor was there any evidence of pulmonary vasculitis [20]. Hence, no change

suggestive of pulmonary hypertension is present in this case.

We conclude that the commonest histopathological change in cases of pulmonary hypertension is medial hypertrophy of the muscular pulmonary arteries. This is irrespective of the pathogenetic mechanism leading to pulmonary hypertension and therefore we recommend that the measurement of percentage medial thickness of the muscular pulmonary arteries be done in all cases where it is necessary to diagnose/exclude pulmonary hypertension. We feel that the measurement of intimal index is not useful as it does not differentiate between intimal cellular proliferation or fibrosis. However, the authors who proposed its use had used sophisticated software to calculate the intimal index, whereas we measured it by the micrometer, and subsequent mathematical calculation. Our measurement of this index may therefore have inherent inaccuracies. Another method which has been recently used to quantify intimal thickening is the assessment of intimal area as a function of the artery diameter [11]. It may be noted that unlike percentage medial thickness there is no standard method to quantify the intimal thickening. We found that grading as per the Edward and Heath Classification alongwith measurement of the percentage medial thickness gives a fairly comprehensive picture of the changes.

The major limitation of this study is that the pulmonary artery pressures were not measured by cardiac catheterization. The number of cases were also small. A study involving a larger number of cases in a cardiothoracic centre correlating it with measurement of pulmonary artery pressures will elucidate matters. However, this was a retrospective study involving autopsy cases also, it was observed that the histopathological changes seen were definitely suggestive of pulmonary hypertension as described in the literature.

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