MUSCULARIZATION OF PULMONARY ARTERIES IN COAL WORKERS PNEUMOCONIOSIS

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INTRODUCTION

Smooth muscle hypertrophy occurs in the walls of small pulmonary arteries in coal workers pneumoconiosis (CWP), and has been suggested as a pathogenetic cause for cor pulmonale.[1] There are two types of muscular hypertrophy in the terminal pulmonary arterial tree in CWP, namely longitudinally oriented and circularly oriented smooth muscle hypertrophy. The purpose of this study is to examine the differences between their etiology and pathophysiology and to correlate the changes with right ventricular hypertrophy (RVH) in CWP. For this study, 72 autopsies without heart valvular or severe coronary lesions and without hypertensive left ventricular hypertrophy were drawn from a series of 120 unselected consecutive autopsies carried out in a southern West Virginia hospital serving mainly a coal mining community.

LONGITUDINALLY ORIENTED SMOOTH MUSCLE HYPERTROPHY

Etiology

In CWP, a longitudinally oriented smooth muscle layer or bundle may he seen in the walls of the terminal pulmonary arteries. This muscle layer is more prominent in the intimal wall, and sometimes in the adventitia, of terminal pulmonary arteries (diameter $> 120\mu$) than in those of small pulmonary arterioles (diameter $< 100\mu$) The development of such muscle fibers may be due to repeated elongation or stretch forces of the vessels as they pass around an abnormal air sac, as in emphysema, or around a fibrotic mass.[2,3] Pulmonary hypertension and alveolar hypoxia may help to stimulate its formation. The combination of high intravascular pressure and repeated stretch forces potentially exaggerates the development of longitudinal muscle hypertrophy in the pulmonary arteries.[4] Other factors such as smoking and chronic bronchitis may also induce some longitudinal muscle fibers in the intimal wall[5] but they are not as abundant as in emphysema or in CWP. It is believed that the longitudinal muscle fibers could make the vessel wall more stable and help to prevent its over distension when it is subjected to repeated stretching forces.[6]

Pathologic Features

At first, a small fasciculi of longitudinally oriented muscle fibers may develop in the intima of the vessels. Such small fascicular fibers may develop into a thicker continuous band of muscle (Figure 1) and then became separated from one another by collagen ana elastic fibrils. With the passage of time, fibrous tissue progressively replaces the muscle fibers leaving the appearances of a "nonspecific intimal fibrosis." These developments in the intima are the result of activity of myofibroblasts, which have the capacity to form smooth muscle cells and secrete collagen and elastin.[7] The ultimate outcome of the process is narrowing or occlusion of the lumen with fibroelastosis (Figure 2).

Correlation with Right Ventricular Hypertrophy

In emphysema, the development of longitudinal muscle in the pulmonary artery wall is not related to RVH and hence to pulmonary hypertension.[8] Measurements on the noncircularly oriented muscle in coal workers' vascular lesions in an earlier study of the Appalachian region also failed to demonstrate such a correlation.[9,10] In our recent study of 10 CWP cases with significant longitudinal muscle hypertrophy in the intimal walls of small pulmonary arteries, the thickness of such a muscle layer, expressed in percentage of longitudinal muscle area (PLA)*, did not show any correlation with RVH ($r = -0.205$) (Figure 3). This implies that the simple loss of vascular bed due to longitudinal muscle hypertrophy or intimal fibromuscular proliferation is not the main cause of cor pulmonale in CWP. The lungs may develop compensation mechanisms such as recanalization, collateral circulation or bronchopulmonary anastomosis which may ameliorate the pulmonary circulation.[3,11] The response of longitudinal muscle to stimuli is, therefore, unlikely to constrict the vessels and hence augment the pulmonary vascular resistance as circular muscle does.

CIRCULARLY ORIENTED SMOOTH MUSCLE HYPERTROPHY

Etiology

A newly formed or hypertrophied circularly oriented smooth muscle layer may exist in the medial wall of terminal pulmonary arteries in CWP, but is usually more prominent in the segment of pulmonary arterioles (diameter $< 100\mu$) sandwiched between an outer original and inner newly formed elastic lamina (Figure 4). In the normal, the medial circular muscle layer exists only in the pulmonary arteries (diameter $100–500\mu$), gradually turns to spiral fibers in the wall of arterioles (diameter $90–100\mu$), and vanishes in small arterioles (diameter $< 60\mu$) after birth.[12] Hypertrophy of medial circular muscle in these vessels appears to imply

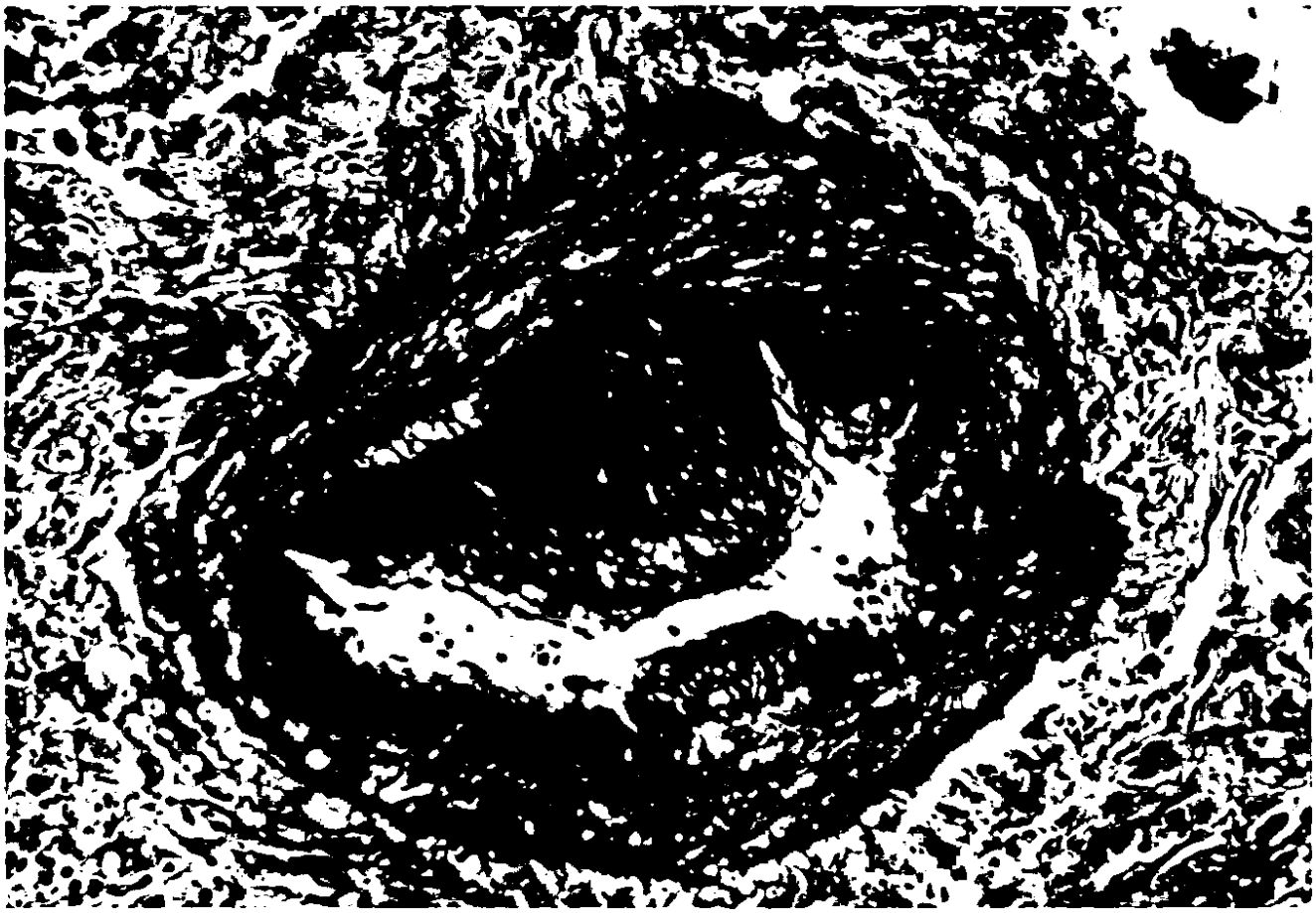

Figure 1. A 67-year-old coal worker with 25 years of underground mining exposure. He had PMF, CALD and severe emphysema with complications of cor pulmonale and right ventricular failure. Note the band of longitudinal smooth muscle in the intimal wall of a small pulmonary artery located in fibrotic tissue. (Van-Gieson elastin stain) (380X).

active vasoconstriction and increased muscular work intermittently or continuously for a prolonged time.[13] The most potent stimulant is chronic alveolar hypoxia which causes the terminal pulmonary arteries to constrict and gives rise to an increased quantity of smooth muscle in the medial layer.[5,9,14] Another stimulant is pulmonary hypertension, that is, the small arteries will also constrict in response to a sudden increase in pressure.[15] There are genetic differences in the responsiveness of the pulmonary circulation to hypoxia, pulmonary hypertension and other various physiological and pathological stimuli.[16,17] The pulmonary vascular resistance of individual CWP may be modified by many factors.

Pathophysiology

In CWP, especially in progressive massive fibrosis (PMF) or complicated with other chronic airway lung diseases (CALD), such as chronic bronchitis, brochiolitis, bronchiectasis and pulmonary tuberculosis, disorders of ventilation and perfusion and decreases of diffusing capacity may be severe enough to cause chronic alveolar hypoxia and hypoxemia.[18,19] Chronic hypoxemia and pulmonary hypertension may exert their functional effects throughout the entire pulmonary arterial tree, but the most reactive part is at the arterioles both in affected and normal areas (Figure 5).[20] Although the presence of a hypertrophied medial muscle layer does not cause constriction, once it is stimulated, a thicker circular muscle layer has a stronger contraction. Thus, a vicious cycle between constriction, medial hypertrophy and pulmonary hypertension will be formed leading to RVH.[4]

Correlation with Right Ventricular Hypertrophy

There are close correlations between the development of arteriolar muscularization and RVH in emphysema as well as in CWP.[7,21,22] This suggests the possibility that such muscularization represents the organic basis for the increased pulmonary resistance in these diseases. The percentage of medial wall thickness (PMT) in pulmonary arterioles (diameter $< 100\mu$) of 57 coal miners and 15 controls in

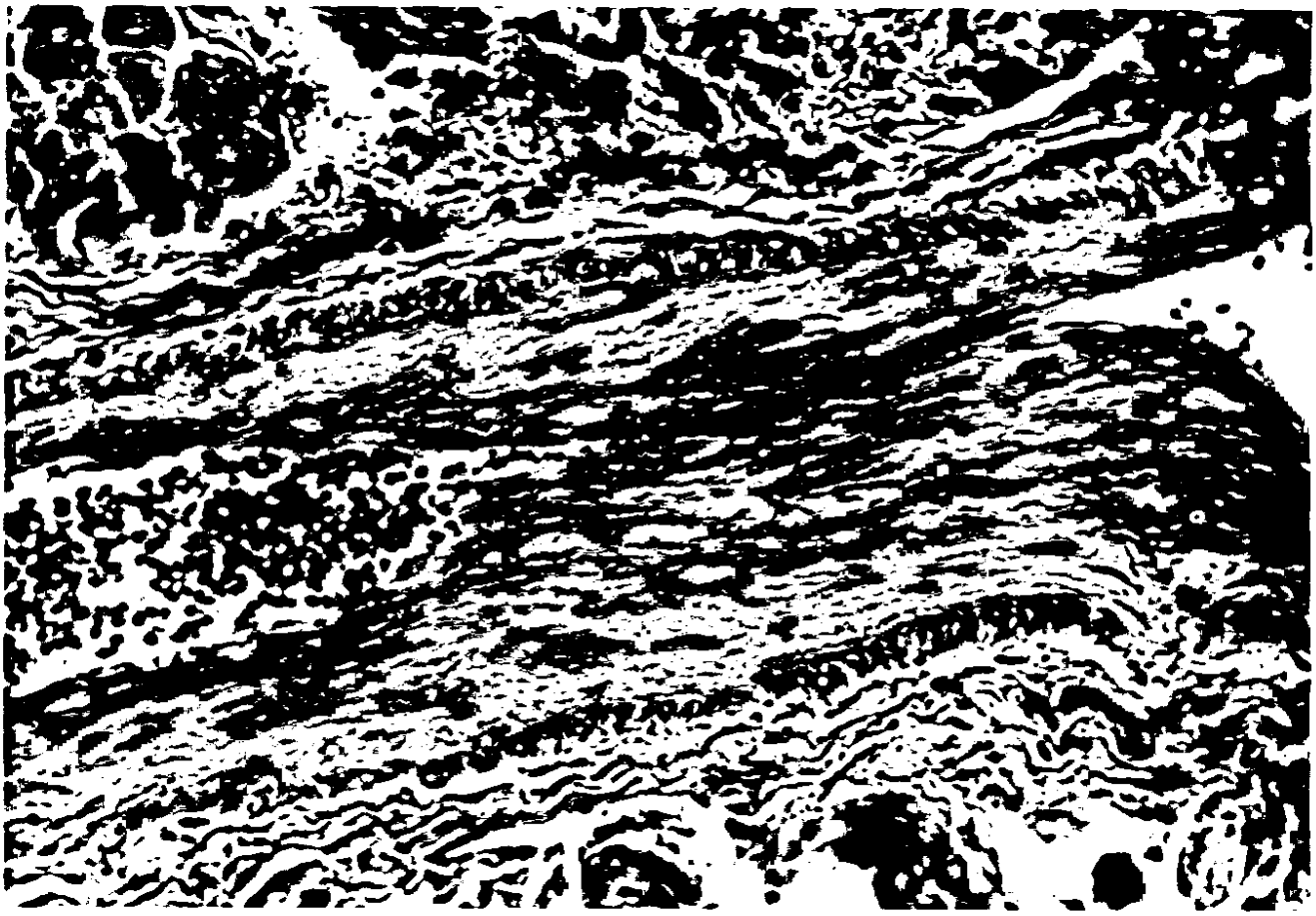

Figure 2. A 65-year-old coal miner with 35-years of underground exposure shows nodular lesions of CWP and silicosis. The severe intimal longitudinal smooth muscle hypertrophy appears to occlude the lumen of a small pulmonary artery. (Masson stain) (380X).

the Appalachian region were recently evaluated with a standard stereology program and showed a high correlation with the RV weight in percentage of LV weight (RV/LV).[22] When the cases were grouped according to the literature of RVH index into normal (RV/LV < 74%), mild (RV/LV = 75–79%), moderate (RV/LV = 80–89%) and severe (RV/LV >90%)[1,23] with comparable average ages and underground exposure years, the mean PMT increased from 23 to 33, 36 and 40%, respectively ($p < 0.001$) (Table I).

On the other hand, medial thickness of small pulmonary arteries with external diameter larger than 100μ (grouped into 101–300μ and 301–500μ) in 25 CWP cases showed less or no correlation with the incidence of RVH ($r = 0.4690$ and 0.0726 respectively), while those of pulmonary arterioles (diameter < 100μ) showed a significant correlation with RVH ($r = 0.8146$) (Figure 6).

Right Ventricular Hypertrophy in Different CWP and Controls

In the same study,[22] progressive massive fibrosis (PMF) caused a higher incidence of moderate and severe RVH than simple CWP did, 60% vs 16%. When they were complicated with chronic airway and lung diseases, both incidences of RVH increased, 87% vs 54% (Table II).

CONCLUSION

Circular smooth muscle hypertrophy in the medial wall of pulmonary arterioles (diameter < 100μ) showed a high correlation with the incidence of RVH in 57 CWP and 15 controls from the Appalachian region. Intimal longitudinal muscle hypertrophy, or medial circular muscle hypertrophy in small pulmonary arteries (diameter > 100μ), did not show such correlation with RVH.

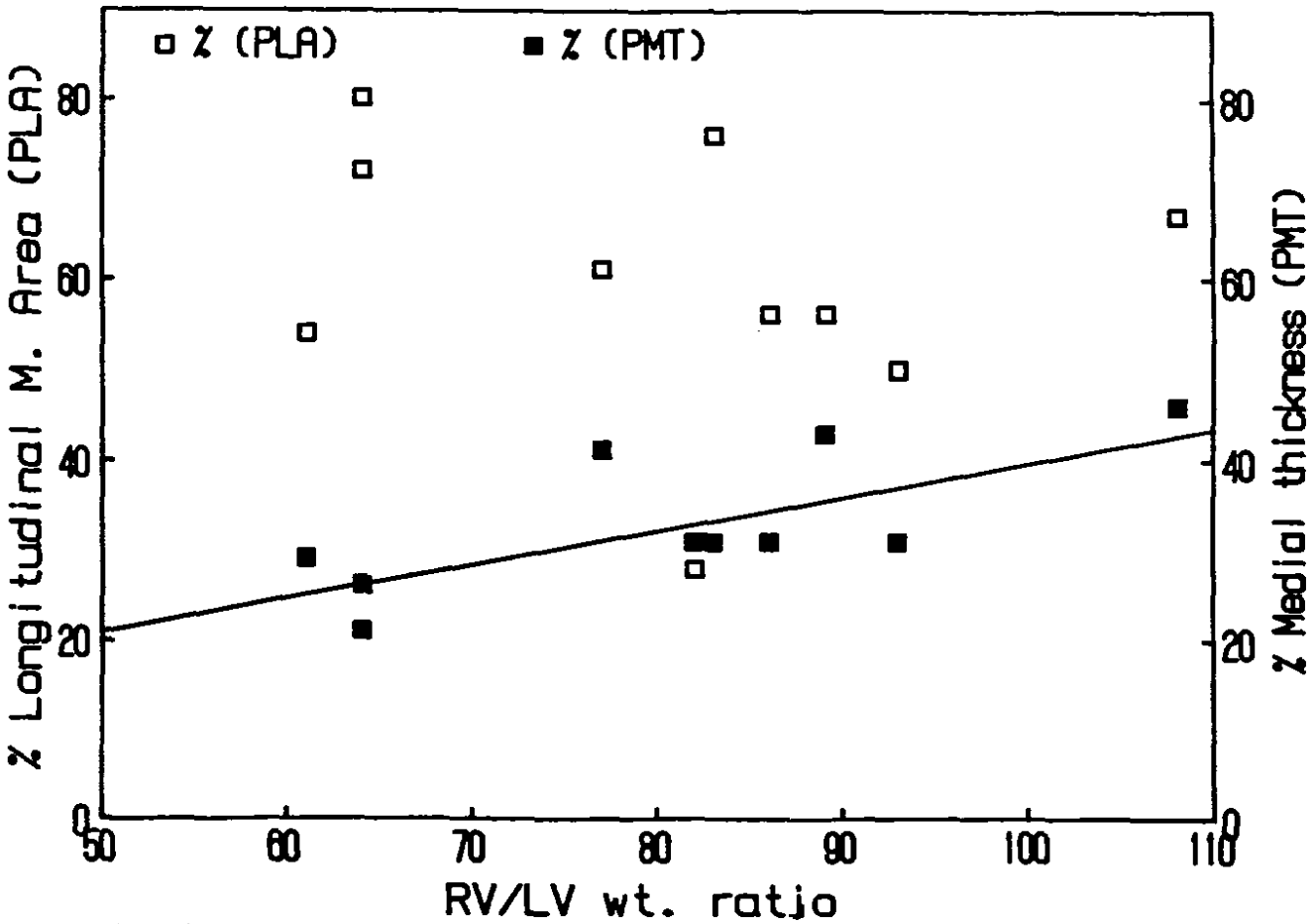

Figure 3. Correlation between RV/LV wt. ratio and percentage longitudinal muscle area (PLA) and percentage medial thickness (PMT) in 10 CWP.

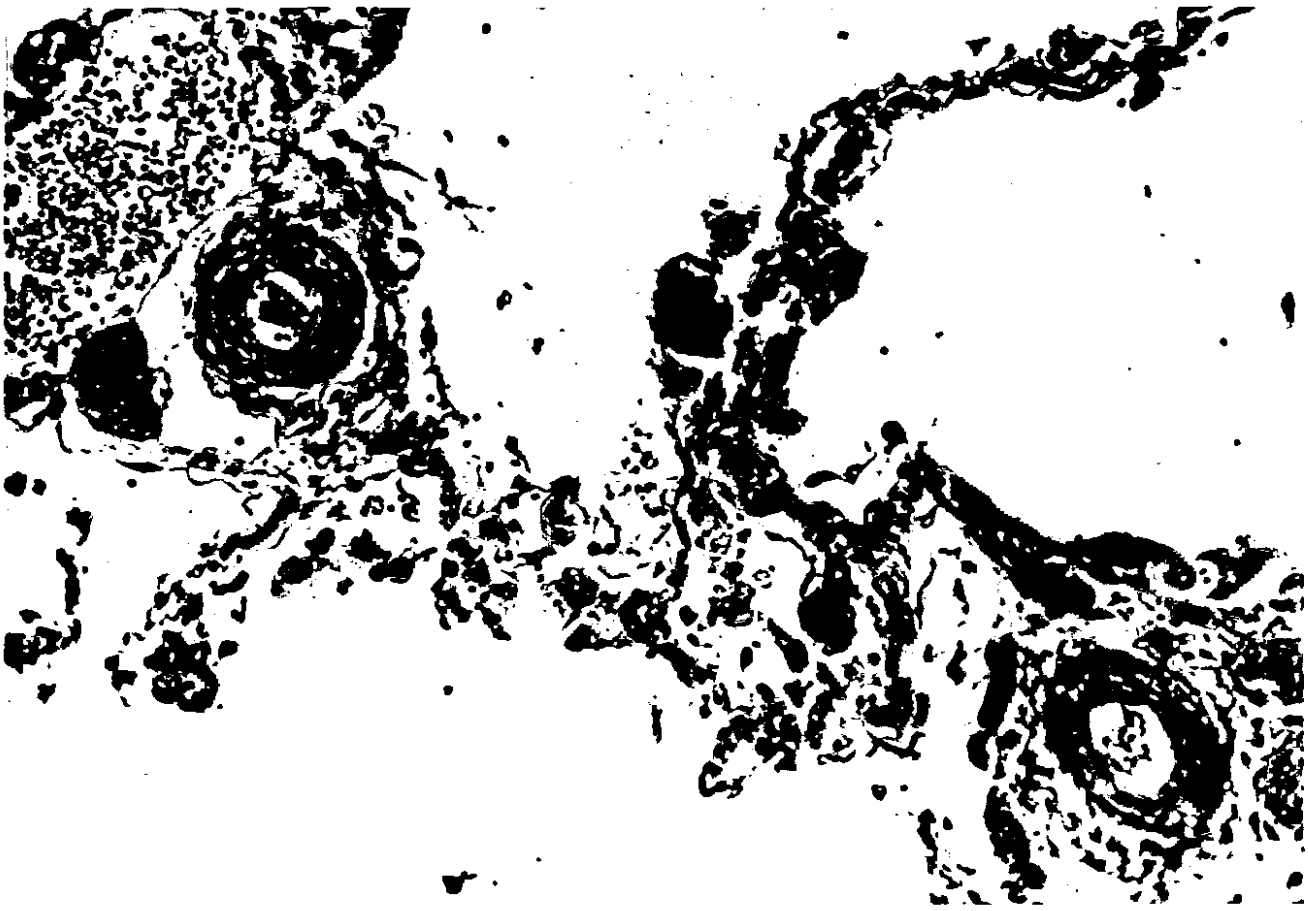

Figure 4. A 78-year-old coal miner with 25-years of underground exposure who had severe PMF and cor pulmonale. Note the medial hypertrophy of his pulmonary arterioles. (Van-Gieson elastin stain) (240X)

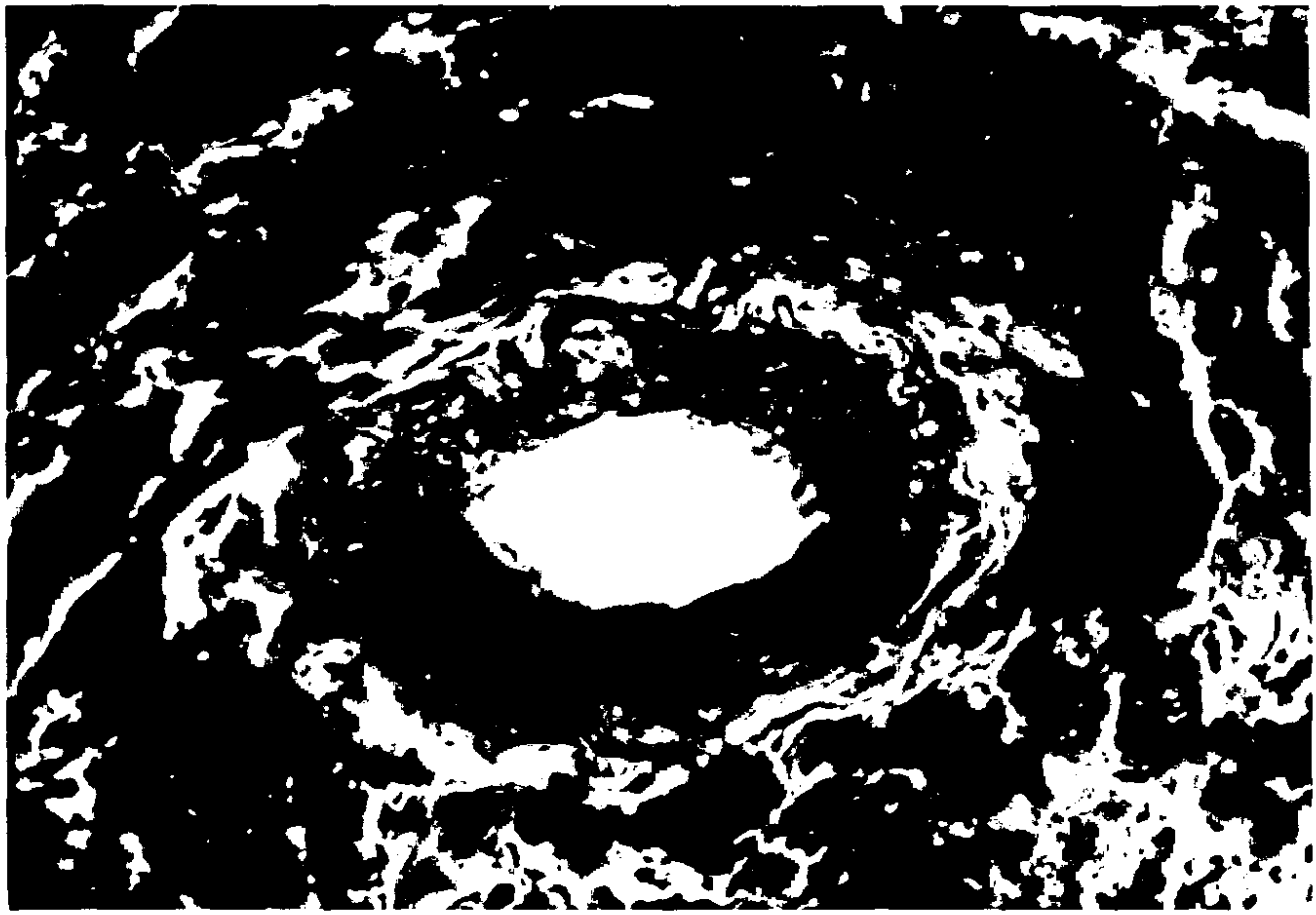

Figure 5. A 69-year-old coal miner with 45-years of underground exposure and CWP, CALD and mild cor pulmonale. Notice the arteriolar muscularization within a macular lesion. (V.G. stain) (960X)

Table I

The Severity of RVH of 57 CWP Cases (in 4 groups) Correlated with Other Parameters

	GROUP I	GROUP II	GROUP III	GROUP IV
COR PULMONALE (RVH)	NORMAL	MILD	MODERATE	SEVERE
RV/LV WEIGHT RATIO:	<74%	75-79%	80-89%	>90%
CASES	17	10	13	17
AGE	67±9♦	68±11	68±6	66±7
UNDERGROUND EXPOSURE (YRS)	32±8	39±10	37±9	33±7
RV/LV (%)	60±10	77±1	85±3	104±16
RV FAILURE (CASES)	0	1	8	15
PMT (%)	23±8	33Δ±5	36†±5	40§±6

♦ mean ± standard deviation

Δ statistically significant ($P < 0.05$) from Group I

† statistically significant ($P < 0.05$) from Group I and II

§ statistically significant ($P < 0.05$) from Group I, II, and III

Table II

Incidences of RVH and Mean PMT in Different CWP and Controls

Diff. Lung Dis.	RVH (RV/LV > 80%) (%)	(cases)	Mean RV/LV (%)	Mean PMT (%) ± (SD)
PMF-CALD	87	14/16	94	38.6 ± 6.6
PMF	60	3/5	83	31.8 ± 9.5
CALD-Simple CWP	54	13/24	79.5	31.9 ± 7.3
CALD	30	3/10	73.5	27.0 ± 9.5
Simple CWP	16	2/12	69.8	27.2 ± 9.5
Normal	0	0/5	< 60	10.9 ± 2.5

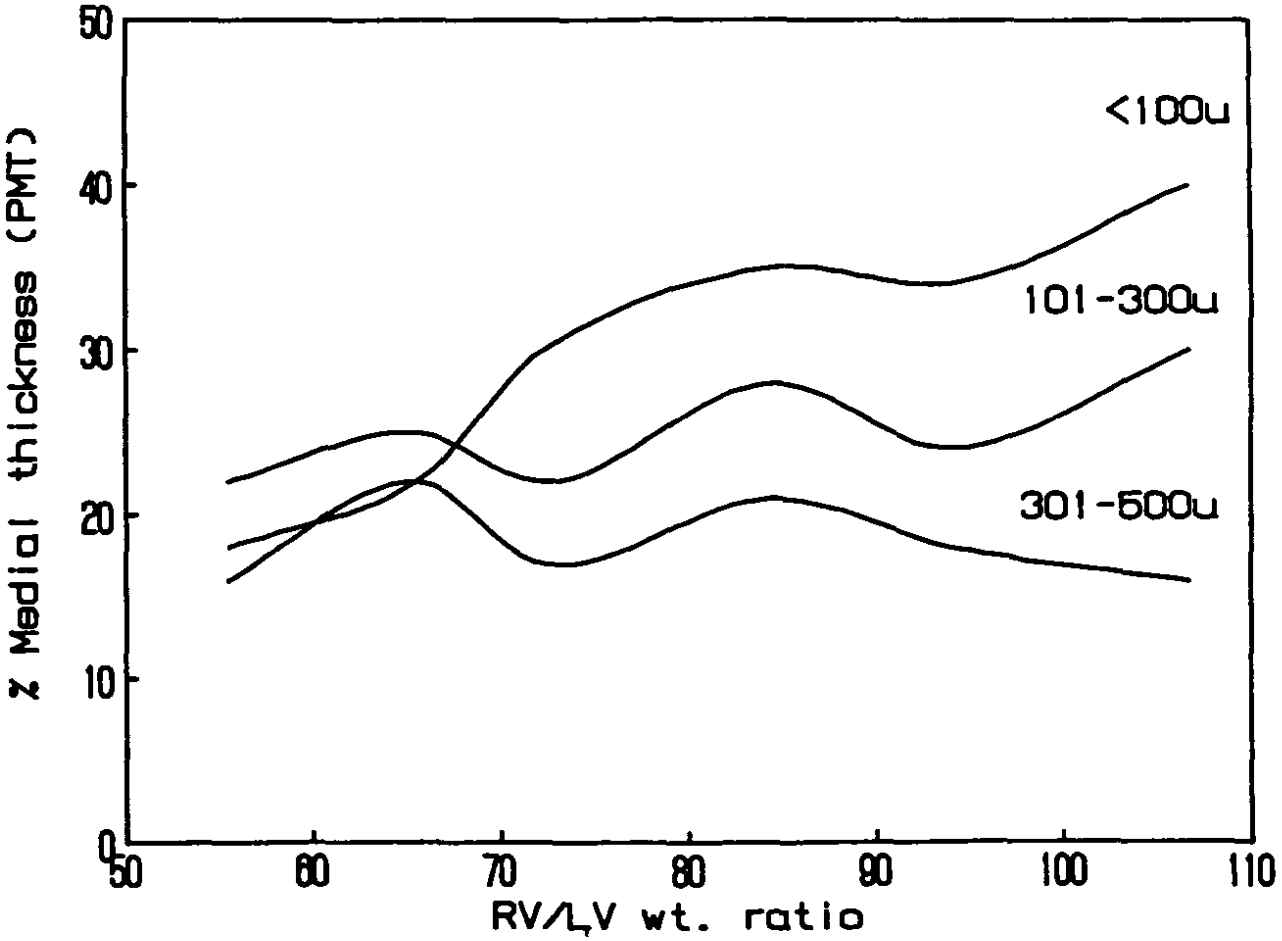

Figure 6. Correlation between RV/LV wt. ratio and percentage medial thickness (PMT) of terminal pulmonary arteries in diameters < 100. 101–300μ and 301–500μ in 25 CWP cases.

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APPENDIX

$$PLA^{*} = \left(1 - \frac{\text{Peri. Lumen}^{2}}{\text{Peri. Int.}^{2}} \right) \times 100\%$$

where, PLA is the longitudinal muscle area in the percentage of original intact lumen area bounded by internal elastic lamina; Peri. Lumen and Peri. Int. are perimeters of the remaining lumen and internal elastic lamina respectively.

Since:

$$PLA = \frac{\text{Longitud. Muscle Area}}{\text{Original Lumen Area}} \times 100\%$$

and,

$$\text{Longitud. Muscle Area} = \text{Original Lumen Area} - \text{Remaining Lumen Area}$$

$$\text{Original Lumen Area} = \left(\text{Peri. Int.} / 2\pi \right)^2 \pi$$

$$\text{Remaining Lumen Area} = \left(\text{Peri. Lumen} / 2\pi \right)^2 \pi$$

therefore,

$$PLA = \frac{\text{Original Lu. Area} - \text{Remain. Lu. Area}}{\text{Original Lu. Area}} = 1 - \frac{\text{Remain. Lu. Area}}{\text{Orig. Lu. Area}}$$

$$= 1 - \frac{(\text{Peri. Lu.} / 2\pi)^2 \pi}{(\text{Peri. Int.} / 2\pi)^2 \pi} = \left(1 - \frac{\text{Peri. Lumen}^{2}}{\text{Peri. Int.}^{2}}\right) \times 100\%$$

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