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Pulmonary Arteriolar Muscularization in Coal Workers' Pneumoconiosis and Its Correlation With Right Ventricular Hypertrophy

Siang-Nian Hu, MD; Val Vallyathan, PhD; Francis H. Y. Green, MD; Kenneth C. Weber, PhD; Werner Laqueur, MD†

• The relationship between the thickness of the walls of small pulmonary arteries (the medial wall thickness as a percentage of external diameter, percentage of medial thickness) in coal miners and control subjects were studied using morphometric techniques and correlated with the degree of right ventricular hypertrophy, severity of coal workers' pneumoconiosis, emphysema, and other chronic lung diseases. Pulmonary arteries less than 100 μm in external diameter were identified and the external diameter, medial thickness, and intimal thickness were quantitatively measured in the lung tissues of 57 coal miners and 15 control subjects with and without other chronic lung diseases. Coal workers' pneumoconiosis, emphysema, and right ventricular hypertrophy were assessed uniformly in all cases. The arterial wall thickness correlated with right ventricular hypertrophy, progressive massive fibrosis, and other chronic lung diseases. Severity of emphysema also showed a weak correlation. Although the functional significance of these findings is not known, we conclude that the muscularization of pulmonary arterioles provides a structural basis for the development of right ventricular hypertrophy in coal miners.

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The prevalence of cor pulmonale in coal miners with progressive massive fibrosis (PMF) is greater than in miners with simple coal workers' pneumoconiosis (CWP) and it is a common cause of death.[1-4] The mechanism whereby cor pulmonale is produced in PMF is a subject of great interest. It has been considered for many years that the severity of destructive changes in the muscular pulmonary arteries in PMF is responsible for increasing right ventricular work load resulting in hypertrophy and cor pulmonale.[5-7] However, measurements of non–circular muscle thickness in CWP vascular lesions do not correlate with right ventricular hypertrophy (RVH).[8]

The pulmonary vessels can be classified into elastic arteries having an external diameter of 1 mm or greater, muscular pulmonary arteries with an external diameter between 1 mm and 100 μm, and vessels less than 100 μm in external diameter, the pulmonary arterioles. The muscular pulmonary arteries have a media containing circularly oriented smooth muscles contained within an internal and external elastic lamina. By contrast the pulmonary arterioles lack a distinct muscular media and have a single elastic lamina that is opposed to the endothelial cells. Transitional zones are present between the muscular pulmonary arteries and the arterioles, and the arteriolar wall may contain small quantities of spiral muscle. These arterioles are considered to be the most reactive and afflicted segments in the pulmonary vascular tree in response to hypoxia, hemodynamic alterations, or other functional and structural changes in health and disease.[9,10]

In coal miners with CWP, a medial muscular coat may develop in the walls of precapillary pulmonary arterioles as a result of parenchymal fibrosis.[8] Significant increases in the pulmonary arterial pressure have been recorded in coal miners at rest and during exercise.[2,11-13] Whether this increase in pulmonary ar-

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From the National Institute of Occupational Safety and Health, Division of Respiratory Disease Studies, Morgantown, WVa (Drs Hu, Vallyathan, Weber, and Laqueur); Department of Histopathology, University of Calgary, Canada (Dr Green); and Pathology Department, Veterans Affairs Hospital, Beckley, WVa (Dr Laqueur).

† Deceased.

Reprint requests to the Pathology Section, Division of Respiratory Disease Studies, National Institute for Occupational Safety and Health, 944 Chestnut Ridge Rd, Morgantown, WV 26505 (Dr Vallyathan).

terial resistance is associated with the development of this newly formed muscular layer in the pulmonary arterioles is not known.[14] Some younger miners without cor pulmonale have shown medial muscular layer hypertrophy in small pulmonary arteries within dust macules.[8] However, quantitative correlations between increasing thickness of arteriolar wall and RVH and severity of CWP have not been demonstrated.

This study was, therefore, undertaken in an attempt to quantitatively evaluate the extent of hypertrophy of the medial muscular layer in pulmonary arterioles and to correlate these changes with RVH and severity of CWP. Because vascular abnormalities are also commonly associated with smoking, aging, and other chronic lung diseases (CLD),[15-18] it is important to distinguish changes related to coal mining from those associated with other conditions. In this study, we attempted to control for this as much as possible and subdivided our coal mining group into those with CWP and those with CWP complicated by other respiratory diseases. We also excluded from analysis all cases with diseases likely to result in passive venous congestion of the lungs.

MATERIALS AND METHODS

The study group consisted of subgroups of 72 autopsies drawn from a series of 120 consecutive autopsies performed in a southern West Virginia hospital serving mainly the coal mining community. Demographic details of the coal miner and control populations were obtained from the hospital records. The occupational histories were obtained by a standard questionnaire sent to the next-of-kin after the death. All the coal miners included in the study had an underground coal mining exposure in coal mines within a 100-mile radius of Beckley, WVa. The number of years worked in the underground coal mines was used as a surrogate of exposure. Autopsy consent on all the cases was voluntary and was provided by the next-of-kin. Control groups consisted of those individuals who had died suddenly as a result of accidents and were consecutively autopsied at the same hospital and found to have no work history in underground or surface coal mines.

Forty-eight cases were excluded on the basis that they had cardiac disease likely to result in pulmonary vascular changes. The most common diseases in the category were congestive cardiac failure secondary to ischemic, hypertensive, or valvular heart disease. These conditions were identified from the autopsy protocols and histologic examination of heart and lungs. To evaluate the differential effects of CWP, and other CLDs on pulmonary vasculature, they were grouped into nonminers with no apparent lung diseases (normal control subjects) (n = 5); nonminers with CLDs (n = 10) (abnormal control subjects); coal miners with CWP and no apparent other CLDs (n = 17); and coal miners with CWP and other CLDs (n = 40). The CLD groups included cases showing chronic bronchitis, bronchiolitis, bronchiectasis, lung cancer, interstitial pneumonitis, and granulomatous pulmonary disease. Because emphysema is considered an integral part of the CWP lesion,[19] this parameter was evaluated independently. Complete autopsies were performed in all cases within a period of 24 hours after death. The average age and underground coal mine dust exposure years of each group are presented in Table 1.

Lung Preparation

Whole lungs were removed at autopsy with the major blood vessels and bronchus intact and were inflated and deflated several times with carbon dioxide at a constant pressure of 36 cm of water during inflation. The lungs were then cannulated through the bronchus and infused with 4% buffered formaldehyde solution at a constant pressure of 30 cm of water for 1 hour. The bronchus and blood vessels were then tied and the lungs were floated in a bath of formaldehyde solution for 3 to 4 days. The fixed lungs were cut parallel to the hilum and five (thick 7/8in) slices were made on a flat slicer. The third level thick slice was embedded in gelatin according to the standard procedure of Gough and Wentworth.[20] Three to five paper-mounted thin whole-lung sections from different levels were made from each case for the evaluation of CWP and emphysema. Left lungs were used for whole-lung gross evaluations except in a few cases when a trauma or other visible defect precluded its use. All the autopsies, heart dissection, and measurement of RVH and preparations of lungs were made under the direct supervision of one of us (W.L.).

Analysis of Lung

Each of the whole-lung sections was evaluated independently by two of us (V.V. and F.H.Y.G.); CWP was classified according to the criteria and standards recommended by the College of American Pathologists and the National Institute for Occupational Safety and Health.[9] The following lesions were categorized: collection of coal dust–laden macrophages in a size range of 0.5 to 6 mm within the walls of respiratory bronchioles and adjacent alveoli enmeshed within a fine network of reticulin and occasional collagen fibers associated with focal emphysema were classified as macules. Nodules were classified as lesions up to 20 mm in size with round, irregular, or serpiginous borders with a fibrotic stroma of collagen and reticulin containing dust-laden macrophages. Highly coal–dust pigmented fibrotic lesions measuring greater than 1 cm in size with irregular deposition of collagen fibers were classified as PMF. Nodular discrete lesions up to 1 cm or more in diameter with smooth sharp borders and a laminated appearance or conglomerate of these lesions were classified as silicosis. In addition, the individual lesions of CWP (macules, nodules, PMF, and silicosis), were each graded into four categories of increasing severity. These categories corresponded with increasing size and profusion of the lesions within the whole lung and were based on a series of reference standards established prior to the grading process. Emphysema was classified and graded independently according to the photographic standards established by Thurlbeck et al.[21] In addition to this, we have also graded the focal and scar emphysema. The lung sections were evaluated independently by two of us (V.V. and F.H.Y.G.) and our opinions as to the type and severity grading were recorded. The average of the two scores was used in the analysis. The agreement was within 10 points in 90% of the cases. When the two of us had disagreements over 10 points, the whole lung sections were rereviewed and a consensus reading was derived.

Morphometric Measurements

Representative lung sections selected from the upper and lower lobes of both lungs were studied in all cases. Vascular evaluations and morphometric measurements were made on a minimum of three lung sections stained with Van Gieson's elastic stain. In hypertrophied arterioles with reduplication of elastic laminae the elastic stain was of limited value.

Quantitative morphometric evaluations of the walls of a minimum of 20 pulmonary arterioles with an external diameter less than 100 μm were measured in each case without prior knowledge of age, duration of mining exposure, clinical history, or other anatomic findings. The arterioles in good cross-sections were first identified with a microscope and the images were projected onto a video screen (Zeiss Video Plan II) interfaced with a digitizer and computer. Perimeters of external and internal boundaries of the media for each arteriole were measured at ×400 with the aid of a standard morphometry program. The internal elastic lamina was used to define

the boundary between the intima and the media. In instances when the media of the arteriole was muscularized, the outer boundary of the media was defined by the external elastic lamina. In normal vessels without a distinct external elastic lamina, the outer limit of the media was determined by the innermost aspect of the adventitia of the arteriole. Bronchial arteries were excluded. All arteriolar vessels within the lung sections that were cut in good cross section were evaluated.

The medial thickness as a percentage of the external diameter (percentage of medial thickness [PMT]) of a vessel was calculated from its perimeter measurements using the following equation:

$$PMT = (1 - \frac{\text{Peri Int}}{\text{Peri Ext}}) \times 100\%$$

Where PMT is the percent of medial wall thickness, Peri Int and Peri Ext are perimeters of internal and external elastic lamina, respectively.

Since:

$$PMT = 2 \times \frac{\text{Medial Wall Thickness}}{\text{External Diameter}} \times 100\%$$

and:

$$\text{Internal Diameter} = \text{Peri Int}/\pi$$
$$\text{External Diameter} = \text{Peri Ext}/\pi$$
$$2 \times \text{Medial Wall Thickness} = \text{External Diameter} - \text{Internal Diameter}$$

therefore:

$$PMT = \frac{(\text{External Diameter} - \text{Internal Diameter})}{(\text{External Diameter})} \times 100\%$$

The PMT of a case was taken as the mean value of at least 20 measurements of different pulmonary arterioles from a minimum of three different lung sections.

Heart Dissection and Measurement of RVH

Because the measurement of the thickness of the right ventricular wall is an unreliable index of RVH, it is important to assess hypertrophy in relation to mass of right ventricular muscle and relate this to left ventricular mass. Some authors have noted large muscle columns arising from the right side of the septum as clearly being a part of the hypertrophied right ventricle.[5,22,23] If this part of the septal weight is added to the weight of the left ventricle, RVH may be masked, especially in small hearts.[5] Accordingly, we used the technique of right heart dissection developed by Batson.[22] With the aid of this technique Wells and Laqueur[23] in a study of US coal miners were able to demonstrate consistently the effect of chronic pulmonary disease on the right ventricle.

Briefly, the method is as follows: the atria are first opened and removed, and a 2-cm incision is made along the center of the posterior longitudinal sulcus. The interseptal muscular plane created by blunt dissection is then carefully followed until the whole separation of right and left chambers is completed. The ventricles are then opened along their flow tracts, washed, and weighed. The right ventricular weight as a percentage of the left ventricular weight (RV/LV) is determined in each case except for the controls, which had total heart weights within normal range. The RVH was classified into four grades of increasing severity based on the ratio of RV/LV weights. The limits separating one grade from the next were based on published literature on this subject.[5,22-25]

Table 1.—Comparison of Demographic and Pathologic Features of 72 Autopsy Cases From Southern West Virginia*

	Group			
	1, Nonminers, Control Subject	2, Nonminers, CLD	3, Coal Miners, CWP	4, Coal Miners, CWP-CLD
Cases	5	10	17	40
Age, y	37 ± 13†	66 ± 9	67 ± 9	68 ± 8
Underground exposure, y	0	0	34 ± 9	35 ± 9
RV/LV, %	<60	73‡ ± 17	74‡ ± 20	86§ ± 19
PMT, %	10.9 ± 2.5	27‡ ± 10	29‡ ± 10	35§ ± 8
Emphysema score	3 ± 3	19‡ ± 15	37‖ ± 20	44‖ ± 24
CWP score	0	0	3.8 ± 1.8	3.6 ± 2.3
PMF score	0	0	0.5 ± 0.8	0.63 ± 0.9

*CLD indicates chronic lung disease; CWP, coal workers' pneumoconiosis; RV/LV, right ventricular weight as a percentage of the left ventricular weight; PMT, percentage of medial thickness; and PMF, progressive massive fibrosis.
†Mean ± SD.
‡Statistically significant ($P < .05$) from group 1.
§Statistically significant ($P < .05$) from groups 1 to 3.
‖Statistically significant ($P < .05$) from groups 1 and 2.

Statistical Analysis

All comparisons were made using a two-tailed t test and were considered statistically significant if $P<.05$.

RESULTS

Relationship Between PMT Mining Tenure and Categories of CWP

The mean PMT measurements for uninjected pulmonary arterioles with an external diameter of less than 100 μm in control subjects (n=5) was 10.9% (Table 1). Because the control subjects in this study group had a lower mean age (37 ± 13), we have added one SD (2.5%) to all the control PMT values to compensate for this age difference. This is in accordance with the reported differences of less than 2% in PMT values between normal control subjects of less than 35 years and more than 35 years of age.[18] The mean PMT of the CLD (n=10, PMT=27%) and CWP groups (n=17, PMT=29%) were significantly higher than the control values ($P<.001$, $P<.002$, respectively). The CWP-CLD group (n=40) had the greatest value for PMT (35%), which was significantly increased compared with all the other groups ($P<.001$) (Table 1). To determine the relationship between PMT and years of underground mining exposure, CWP score, emphysema score, and RV/LV, the CWP group (n=17) was combined with the CWP-CLD group (n=40) to give a total CWP group of 57. A statistically significant positive correlation was obtained ($P<.05$). A positive correlation between PMT and PMF was also obtained by similar analysis.

Correlation Between RV/LV Ratio and CWP Severity

The RV/LV ratio showed the highest correlation with the PMT. When PMT increased from 18% in group 1 to 26% in group 2, 35% in group 3, and 45% in group 4 (Table 2), the RV/LV values showed corresponding increases to 55%, 70%, 80%, and 98%, respectively ($P<.001$). A weaker positive correlation was observed between CWP, PMF scores, and PMT. In Table 3 the mean RV/LV weight ratios of the 57 coal miners have been grouped as normal (<75%), mild (75% to 79%), moderate (80% to 89%), and severe (>89%) RVH. Mean ages and underground tenures were similar for the four groups. There is a highly significant statistical linear

correlation between increasing RV/LV category and PMT. The RV/LV ratio plotted against PMT in CLD, CWP, and CWP-CLD groups are shown in Figs 1 through 3, with correlation coefficients of $r = .908$, $P < .0003$; $r = .902$, $P < .0001$, and $r = .688$, $P < .0001$, respectively. There was no correlation between RV/LV ratios and severity of simple CWP. A significant correlation, however, was noted between PMF score and the highest category of RV/LV (Table 3).

Table 2.—Correlation of Percentage of Medial Thickness (PMT) of Pulmonary Arterioles in 57 Coal Miner Lungs With Other Parameters*

	PMT			
	Group 1, <21%	Group 2, 21%-30%	Group 3, 31%-40%	Group 4, >40%
Cases	7	13	24	13
Age, y	61 ± 5†	70‡ ± 9	68‡ ± 7	67‡ ± 9
Underground exposure, y	28 ± 6	34‡ ± 7	34‡ ± 10	34 ± 9
RV/LV, %	55 ± 11	70‡ ± 13	88§ ± 11	98§ ± 20
PMT, %	18 ± 2	26 ± 3	35 ± 3	45 ± 3
Emphysema score	42 ± 19	24 ± 10	50 ± 24	49 ± 23
CWP score	3.3 ± 1.4	3.4 ± 2.2	3.5 ± 2.2	4.5‡ ± 2
PMF score	0.14 ± 0.4	0.31 ± 0.7	0.58‡ ± 0.8	0.85‡ ± 1

* RV/LV indicates right ventricular weight as a percentage of the left ventricular weight; CWP, coal workers' pneumoconiosis; and PMF, progressive massive fibrosis. For this analysis CWP group (n = 17) and CWP chronic lung disease group (n = 40) were combined and regrouped to four groups on the basis of PMT values.
†Mean ± SD.
‡Statistically significant ($P < .05$) from group 1.
§Statistically significant ($P < .05$) from groups 1 and 2.

Table 3.—The Severity of RVH of 57 Coal Miners Correlated With Other Parameters*

	RV/LV Weight Ratio†			
	Group 1, Normal, <75%	Group 2, Mild, 75%-79%	Group 3, Moderate, 80%-89%	Group 4, Severe, >89%
Cases	17	10	13	17
Age, y	67 ± 9‡	68 ± 11	68 ± 6	66 ± 7
Underground exposure, y	32 ± 8	39 ± 10	37 ± 9	33 ± 7
RV/LV, %	60 ± 10	77 ± 1	85 ± 3	104 ± 16
PMT, %	23 ± 8	33§ ± 5	36‖ ± 5	40¶ ± 6
Emphysema score	35 ± 17	23 ± 17	48# ± 25	54‖ ± 22
CWP score	3.7 ± 1.7	2.6 ± 1.8	3.9 ± 2.3	3.5 ± 2.4
PMF score	0.35 ± 0.68	0.1 ± 0.3	0.54 ± 0.84	0.88‖ ± 0.96

*RVH indicates right ventricular hypertrophy; PMT, percentage of medial thickness; and PMF, progressive massive fibrosis. For this analysis the coal workers' pneumoconiosis (CWP) group (n = 17) and the CWP = chronic lung disease group (n = 40) were combined and regrouped to four groups based on right ventricular weight as a percentage of the left ventricular weight (RV/LV) weight ratios.
†The RV/LV weight ratios categorized into four groups with increasing severity.
‡Mean ± SD.
§Statistically significant ($P < .05$) from group 1.
‖Statistically significant ($P < .05$) from groups 1 and 2.
¶Statistically significant ($P < .05$) from groups 1 through 3.
#Statistically significant ($P < .05$) from group 2.

Effects of Emphysema on RV/LV Ratio and PMT

Emphysema score was positively correlated with occupational group (Table 1). The noncoal miner groups 1 and 2 had the lowest emphysema scores with significantly higher scores in the coal miner groups. The data indicate that both CWP and CLD exert independent effects on the emphysema score. The PMT was not correlated with the emphysema score, except in a subgroup with greater than 50% emphysema score (Table 4).

A positive correlation was seen between the RV/LV weight ratio and emphysema score for the group of miners with the most severe category of emphysema (Table 4). In 10 coal miner cases with the most severe emphysema score (67 ± 13), the mean RV/LV ratio was 100% ± 10%. By contrast, in 10 miner cases with the mildest emphysema (23 ± 11) score, the mean RV/LV ratio was 57% ± 9%. These findings indicate that the more severe forms of emphysema are positively correlated with RVH and muscularization of pulmonary arterioles.

RVH by Type of CWP

The incidences of RVH and mean PMT with different lung diseases are listed in Table 5. The PMF was associated with a higher incidence of RVH (RV/LV, >80%) than simple CWP (60% vs 16%). When CWP was complicated with CLD, both the incidences of RVH increased to 87% in PMF and 54% in simple CWP. When PMF was complicated with CLD, the incidence of RVH rose to 87% and the PMT value increased to 39%, which were the highest among these different lung diseases. When simple CWP with a mean 16% RVH was complicated with CLD, their combined effect increased the incidence of RVH to 54%.

Morphologic Changes in Pulmonary Arterioles

As examples of morphologic changes, photomicrographs of pulmonary arteries from coal miners with simple CWP, CWP with emphysema, CWP with macular and nodular disease, arteriole within coal dust macule, and arterioles in CWP complicated with CLD and RV failure are illustrated in Figs 5 through 8. To compare the morphologic changes, a pulmonary arteriole from a nonminer control subject is illustrated in Fig 4. The major morphologic changes in the coal miners were medial muscular thickening and reduplication of elastic lamina in areas remote from fibrosis (Fig 5), medial muscular hypertrophy with infiltration of coal dust–laden macrophages (Fig 6), and medial muscular hypertrophy with intimal fibromuscular proliferation and narrowing of the lumen (Fig 8).

COMMENT

Factors Influencing the Pulmonary Arterial Resistance in CWP

Coal workers pneumoconiosis is not a single disease process but a composite of

multiple disorders.[26] Multiple mechanisms may be involved in producing changes in the media of pulmonary arterioles in the lungs of miners. These include hypoxia,[27] muscularization of pulmonary arterioles due to the interactions of coal dust macules,[8,28] pulmonary vascular bed loss due to obliterative fibrotic changes in PMF,[5,29,30] and intimal fibromuscular proliferation and thrombosis.[31]

It has been estimated that the pulmonary vascular bed might have to be more than half destroyed before RVH could develop.[32] In response to vascular bed loss, the lungs may develop compensation mechanisms such as recanalization and collateral circulation.[33,34] Polycythemia, a response to hypoxia, may benefit the blood oxygenation, but, on the other hand, increase the flow resistance due to the increase of blood viscosity. In addition, there are individual genetic differences in the pulmonary vascular pressor response to alveolar hypoxia and a wide variability in the responsiveness of the pulmonary circulation to various physiologic and pathologic stimuli[35,36] (S.N.H., V.V., F.H.Y.G., K.C.W., unpublished data). All these mechanisms may modify the pulmonary arterial resistance in CWP.

Chronic hypoxemia and pulmonary hypertension may exert their effects throughout the entire pulmonary arterial tree but especially in the most reactive part—pulmonary arterioles. Chronic alveolar hypoxia, the most potent stimulant, causes the pulmonary arterioles to constrict and give rise to an increased quantity of circular smooth muscle in the medial layer, both in normal and affected areas.[8,27,28] Another stimulant is pulmonary hypertension; the small arteries will also constrict in response to a sudden increase in the pressure.[36,37] Thus, a vicious cycle of constriction, muscularization, and pulmonary hypertension will be formed leading to the development of RVH.

In this study, a newly formed, hypertrophied circular smooth-muscle layer was found in the walls of pulmonary arterioles in most cases with CWP, especially in those with PMF complicated with other pulmonary diseases. A similar, but less severe, muscularization of the pulmonary arterioles was noted in the nonminers with CLDs. Unfortu-

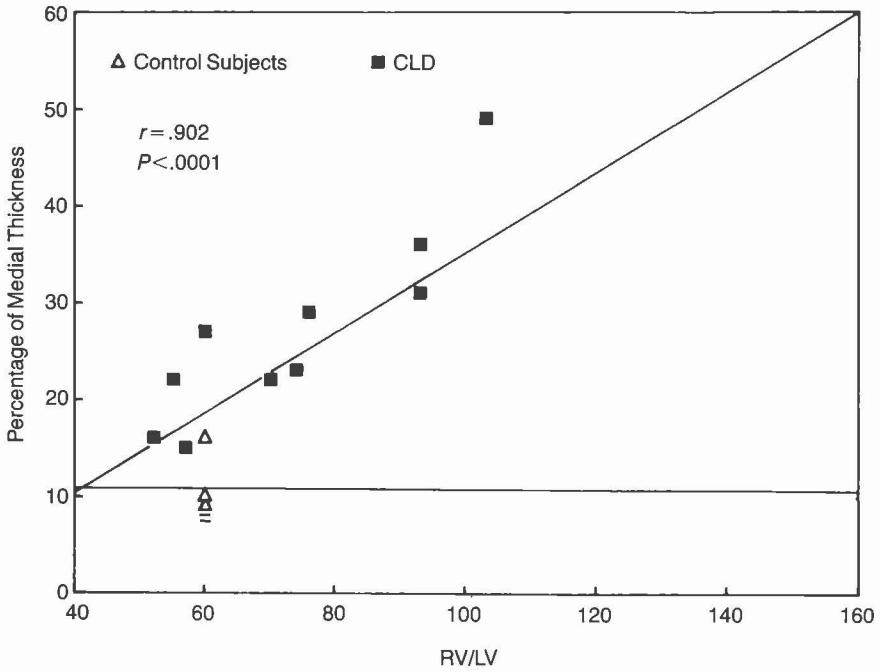

Fig 1.—Comparison of percentage of medial thickness and right ventricular weight as a percentage of the left ventricular weight (RV/LV) in chronic lung disease (CLD) (n=10) and control subjects (n=5). A linear correlation (r=.908) was observed at a significant level of P<.0003.

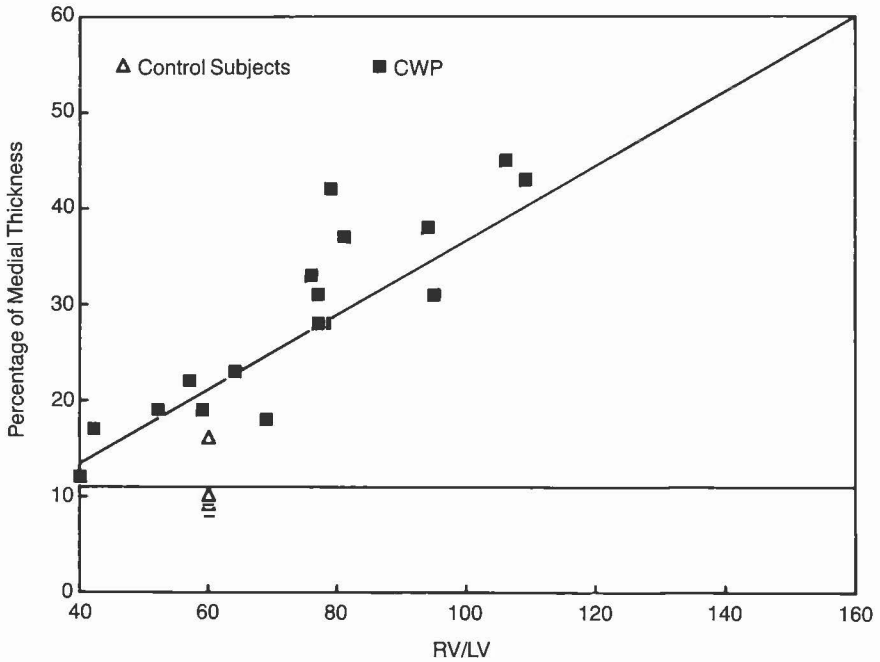

Fig 2.—Comparison of percentage of medial thickness and right ventricular weight as a percentage of the left ventricular weight (RV/LV) in coal workers' pneumoconiosis (CWP) group (n=17) with that of control subjects (n=5). A linear correlation (r=.902) is evident at a significant level of P<.0001.

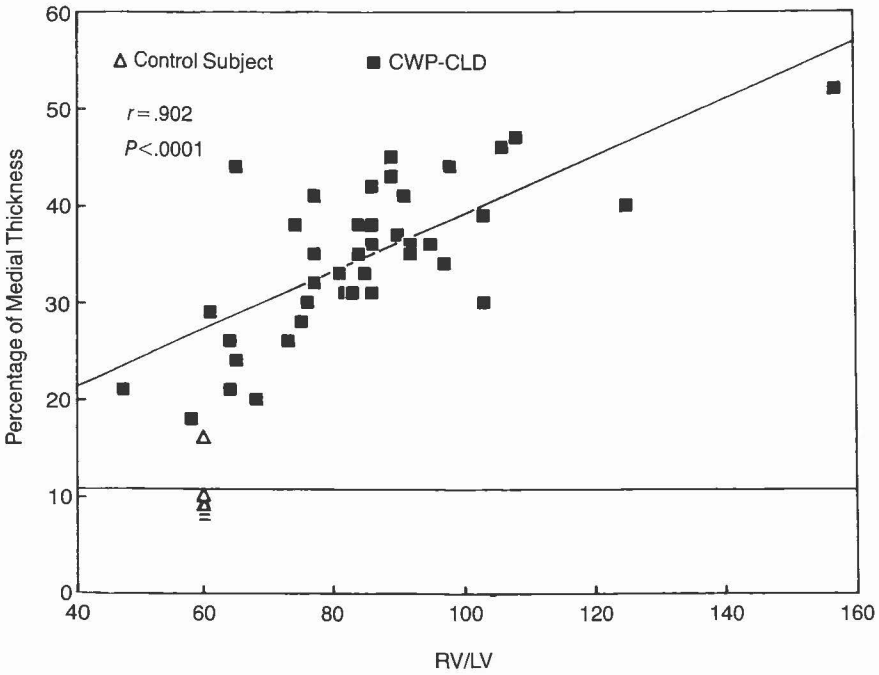

Fig 3.—Correlation of percentage of medial thickness with right ventricular weight as a percentage of the left ventricular weight (RV/LV) in coal workers' pneumoconiosis-chronic lung disease (CWP-CLD) group (n=40) compared with that of control subjects (n=5). A linear correlation was present at $r=.688$ at a significant level of $P<.0001$.

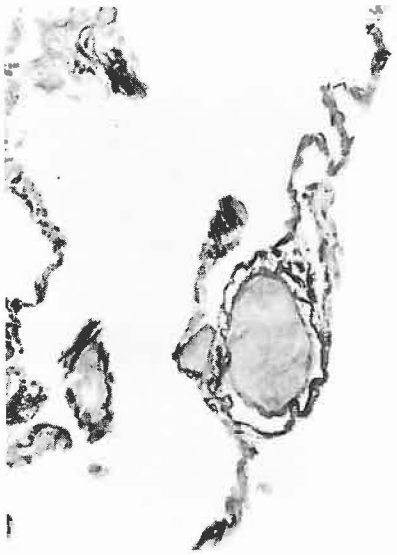

Fig 4.—Photomicrograph of a pulmonary arteriole from a nonminer control subject showing the thin wall and single elastic lamina (Van Gieson elastic stain, ×400).

Table 4.—Severity of Emphysema in 57 Coal Miner Lungs Correlated With Other Parameters*

	Emphysema Score		
	Group 1, <11	Group 2, 11-50	Group 3, >50
Cases	4	32	21
Age, y	70 ± 9†	66 ± 9	69 ± 7
Underground exposure, y	33 ± 3	32 ± 7	39 ± 11
RV/LV, %	76 ± 2	79 ± 22	86‡ ± 17
PMT, %	31 ± 3	31 ± 9	36§ ± 7
Emphysema score	8 ± 1	31 ± 12	69 ± 12
CWP score	1.8 ± 0.4	3.7‡ ± 2.1	4.3‡ ± 2
PMF score	0	0.5 ± 0.9	0.6 ± 0.8

*RV/LV indicates right ventricular weight as a percentage of the left ventricular weight; PMT, percentage of medial thickness; CWP, coal workers' pneumoconiosis; and PMF, progressive massive fibrosis. For this analysis CWP (n = 17) and CWP = chronic lung disease group (n = 40) were combined and regrouped into three groups based on emphysema score.

†Mean ± SD.

‡Statistically significant ($P < .05$) from group 1.

§Statistically significant ($P < .05$) from groups 1 and 2.

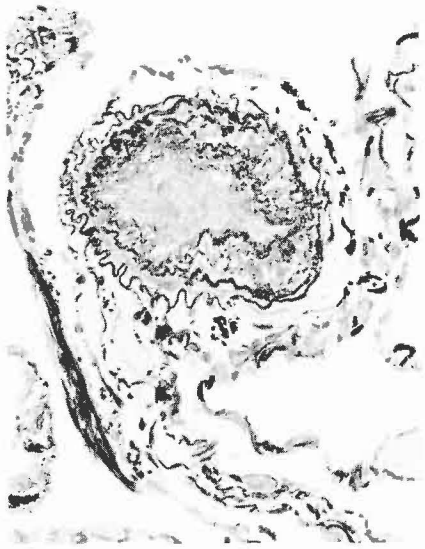

Fig 5.—Photomicrograph of a pulmonary arteriole from a coal miner with macular coal workers' pneumoconiosis and emphysema. Arteriole shows muscular medial thickening and reduplication of the elastic lamina (Van Gieson elastic stain, ×400).

Table 5.—Incidences of RVH and PMT in Different CWP and Complications*

Different Lung Diseases	RVH, %	RV/LV, >80%, Cases	Mean RV/LV, %	Mean PMT, % ± SD
PMF-CLD	87	14/16	94	39 ± 6.6
PMF	60	3/5	83	32 ± 9.5
CLD-simple CWP	54	13/24	80	32 ± 7.3
CLD	30	3/10	73	27 ± 9.5
Simple CWP	16	2/12	70	27 ± 9.5
Normal	0	0/5	60	11 ± 2.5

*RVH indicates right ventricular hypertrophy; PMT, percentage of medial thickness; CWP, coal workers' pneumoconiosis; RV/LV, right ventricular weight as a percentage of the left ventricular weight; PMF, progressive massive fibrosis; and CLD, chronic lung disease.

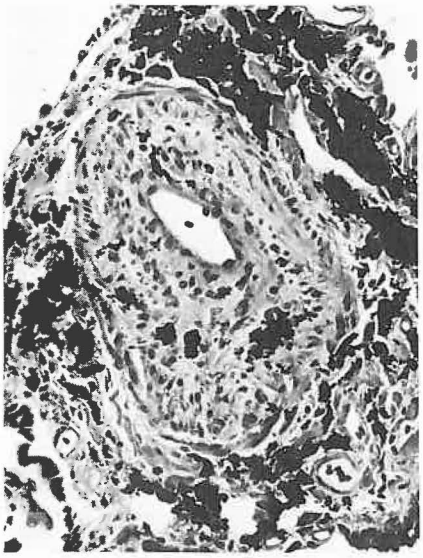

Fig 6.—Pulmonary arteriole from the lung of a coal miner with simple, macular, and nodular coal workers' pneumoconiosis. The arteriole is surrounded by a mantle of coal dust and shows marked medial hypertrophy with infiltration of coal dust–laden macrophages into the wall of the media (hematoxylin-eosin stain, ×400).

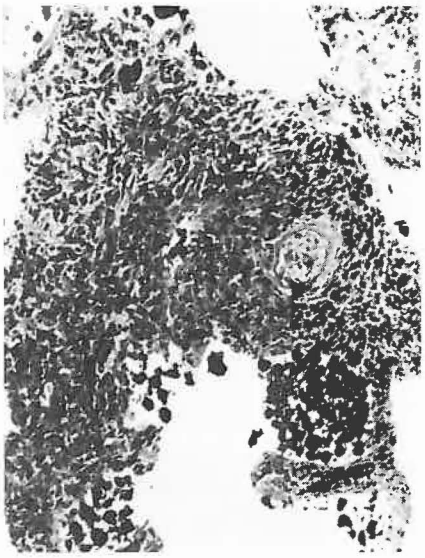

Fig 7.—Coal dust macule showing partially obliterated and muscularized pulmonary arteriole within the macule (arrow) (hematoxylin-eosin stain, ×150).

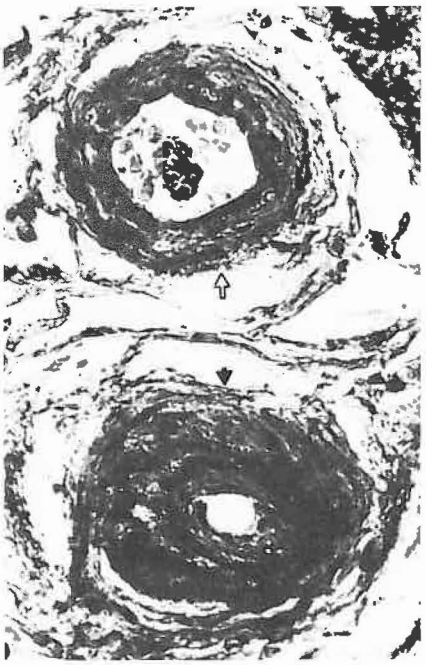

Fig 8.—Photomicrograph showing two pulmonary arterioles from a coal miner with severe coal workers' pneumoconiosis and emphysema complicated with chronic lung disease and right ventricular failure. One arteriole shows prominent medial muscular hypertrophy (arrow), while the other arteriole shows severe intimal fibromuscular proliferation and narrowing of the lumen (arrowhead) (Van Gieson elastic stain, ×770).

nately, the nonminer control group with normal lungs was too small with a younger age range. Therefore, meaningful comparisons with this group were not possible. However, it should be noted that the values obtained for PMT in these normal younger control subjects are very similar to the reported values for PMT in literature.

In all the groups, the thickness of the hypertrophied muscle layer in the pulmonary arterioles was highly significantly correlated with the degree of RVH (Tables 2 and 3). The PMT was also positively associated with two independent variables: the CLDs (without CWP) and CWP. The muscularization of lung arterioles thus provides a structural basis for the development of RVH in coal miners.

The role of emphysema and its correlation to marked muscularization of the media of pulmonary arterioles in coal miners is difficult to evaluate. Loss of lung capillary bed, expressed in reduction in total internal surface area, or total alveoli in emphysema, does not correlate with the weight of the free wall of the RV.[38] Emphysema without airway obstruction reportedly does not cause cor pulmonale.[39] The percentage of lung destroyed by emphysema is not always well correlated with the weight of the right ventricle.[40] In this study, severity of emphysema in 57 coal miner cases was plotted against the RV/LV ratios with an r value of .2. It appears that chronic alveolar hypoxia and pulmonary hemodynamic changes are the essential pathogenetic factors for the arteriolar muscularization and RVH in emphysema.[41] It would thus appear from our data that there are weak independent correlations between RV/LV ratios and emphysema and between PMT and emphysema. However, it is evident from the data that emphysema is not the sole cause of the pulmonary arteriolar thickening in this study group of coal miners.

Role of Simple Pneumoconiosis and PMF in Cor Pulmonale

It is well known that simple pneumoconiosis without complication of chronic obstructive pulmonary diseases rarely causes RVH. Among the 36 simple pneumoconiosis cases in this study, however, there were four cases with RVH with little, if any, other lung complications. The key histologic findings in these cases were extensive perivascular dust deposition–associated macules (Fig 7). The RVH and increased PMT were more severe in the coal miners with PMF. The mantle of coal dust and associated collagen fibers or fibrotic nodules might slow the diffusion of oxygen into the walls of the arterioles leading to chronic hypoxia. The latter increases both vasoconstriction and medial muscle mass of the arterioles.[42] Moreover, the artery's adventitia and surrounding connective tissue, where the normal vasomotor response to hypoxia is mediated, are full of coal dust that might modify this response, thereby increasing the reactivity of the vessels to the hypoxia[43] (Fig 6).

Role of CLD Other Than CWP on the Pulmonary Vasculature

Chronic obstructive pulmonary diseases are known to occur more frequently in coal miners and play an important role in the development of cor pulmonale.[44] This view was supported by our study. When CWP was associ-

ated with other lung diseases, especially chronic bronchitis or bronchiolitis, the medial muscular layer of small pulmonary arterioles was significantly increased resulting in a higher incidence of RVH (Table 5, Fig 8).

The thickness of a newly formed, hypertrophied, circular-oriented smooth-muscle layer in the medial walls of pulmonary arterioles of less than 100 μm in diameter was positively correlated with RVH in 57 coal miners and 15 control subjects from an Appalachian coal mining region. The degree of medial thickening of pulmonary arterioles also correlated positively with severity of PMF but not with simple CWP. Emphysema was found to be an important confounding variable.

All the autopsies were collected from the Pathology Department, Veterans Affairs Hospital, Beckley, WVa. Without Dr Laqueur's contribution, this study would not have been possible.

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