Dr. Staub: Unusual pulmonary vascular obstruction causes pulmonary edema. This is due to a change in hydrostatic forces locally. This was induced in animals by silicone and mineral oil emboli of approximately 200 micrometers size.

Dr. Matthey: Does the finding of the same effects from different types of emboli mean that mechanical or pressure factors are more important than chemical factors?

Dr. Staub: No. Vane and Piper indicate any embolus to the lung will release vasodilative substances and these effects cannot be ruled out.

Dr. Streng: Do you not think it is rather insecure just to say that there is a change in permeability because the lymph plasma ratio doesn't change? I would have thought you would need positive evidence such as no change in half time for albumin. There are other factors to consider such as the washout of the interstitial space and the stretched pore phenomenon.

Dr. Staub: The parallel increase in protein flux and lymph flux in our model is only compatible with an increased vascular permeability to protein. The simple elevation of hydrostatic pressure does not lead to pore stretching. I favor the theory that linear blood flow velocity is damaging endothelium, as has been demonstrated in the aorta. We do plan to measure protein equilibration. We continued our experiments until washout was complete, that is, a new steady state occurred.

Dr. Permutt: Have you compared raised vascular pressure in animals with decreased vs increased vascular areas for exchange?

Dr. Staub: There is a problem with raising left atrial pressure in embolized lung. The occluded capillaries may be damaged and may leak as we observed when we raised left atrial pressure in the pseudomonas-treated sheep.

Dr. Permutt: Have you raised left atrial pressure to levels equal to those with embolism and found any increase in permeability?

Dr. Staub: We raised left atrial pressure to 50-60 cm H2O and never found a high protein pulmonary edema fluid.

Dr. Bigoni: Can you exclude the role of the bronchial circulation?

Dr. Staub: No. But we are planning experiments on the bronchial circulation.

Dr. Casoni: Have you used blocking agents against the prostaglandins?

Dr. Staub: Brigham has found that prostaglandins protect the lung against leakage and prostaglandin inhibitors increase permeability.

Dr. Matthey: How much of lung vasculature was occluded?

Dr. Staub: Seventy to 75 percent.

Dr. Brody: What sort of lymph flow occurs in frank pulmonary edema?

Dr. Staub: I don't know that.

Dr. Effron: Is there any way to distinguish between that edema which arises from damaged vessels in the embolized portion of the lung and that which is derived from the structurally normal but overperfused vessels?

Dr. Staub: We have planned experiments to answer that question.

CLINICAL AND SPECIAL

The Pulmonary Circulation in Chronic Bronchitis and Emphysema*

Diana M. Shelton, M.B.; E. Keal, M.D.; and Lynne Reid, M.D.

In chronic hypoxia, structural changes occur in the pulmonary circulation, in particular medial hypertrophy of muscular pulmonary arteries as seen in residents at high altitude,1,2 in alveolar hypoventilation associated with obesity,3,4 and in experimental animal models.5,6 In chronic bronchitis and emphysema, increased muscularization of the peripheral arteries has been described, although its degree and role in the development of cor pulmonale has remained controversial.7,8 In cystic fibrosis, muscle hypertrophy of arteries and of small pulmonary veins, as well as peripheral extension of muscle, has been reported.9

METHODS

The pulmonary circulation in 15 patients with chronic bronchitis (6 also with widespread severe panacinar emphysema) was studied in detail using quantitative morphometric techniques10 after the pulmonary circulation had been distended at hypertensive pressure (100 cm water) with a barium sulphate/gelatin mixture. The lungs were inflated and fixed with liquid formalin. Right ventricular hypertrophy (RVH) was assessed by weighing the ventricles separately.11 Since changes occur with age,10 6 patients of various ages were examined to establish control values.

RESULTS

The Pulmonary Arteries

The thickness of the media of the muscular pulmonary arteries was expressed as a percentage of wall thickness (2 × wall thickness/external diameter × 100). In chronic bronchitis and emphysema with RVH, percentage wall thickness was increased above the normal for the aged lung, the difference being highly significant (P < 0.001) for arteries less than 250 μm external diameter and significant (P < 0.05) at all diameters up to 600 μm, above which no significant increase was seen. Cases without RVH also showed an increase in mean percentage of wall thickness, but this was less and was predominantly in the smaller arteries where it reached significant

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levels (Fig 1). The difference between the cases with and without RVH achieved statistical significance (P < 0.02) in arteries less than 250 μm diameter.

Normally the smallest muscular arteries have relatively the thickest walls and in the abnormal cases, the smallest arteries showed the greatest increase. Medical hypertrophy appeared to be uniform throughout the lungs. In normal and diseased lungs, wall thickness showed no significant difference between lobes of individual cases despite variation in amount of alveolar damage.

In the normal patients, pulmonary arteries of less than 300 μm diameter consist of a mixed population of 3 structural types—with muscular, partially muscular (having a spiral of muscle along the wall) and non-muscular walls. Extension of muscle peripherally into smaller arteries than normal is demonstrated by 2 methods: in all diameter groups the percentage of arteries with muscle in their walls was increased, and was greatest in the cases with RVH. The diameter ranges of the arterial types are shown in the table.

Extension was also shown by identifying an artery according to the accompanying airspace. The percentage of arteries with muscle in their walls associated with either alveolar walls, alveolar ducts or respiratory bronchioli, was increased both in cases with and without RVH, but was greater in the cases with RVH (Chi square test P < 0.001), although the diameters of the arteries in either group did not differ significantly from normal.

The Pulmonary Veins

The medial thickness of the muscular pulmonary veins was greater than normal in the cases with RVH (P < 0.01 for veins less than 900 μm). The mean wall thickness of the cases without RVH showed a lesser increase. In both the normal and diseased patients, the smaller

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<table>
<thead>
<tr>
<th></th>
<th>Largest Non-muscular Artery (μm)</th>
<th>Range of partially Muscular Arteries (μm)</th>
<th>Smallest Muscular Artery (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>126</td>
<td>35-228</td>
<td>87</td>
</tr>
<tr>
<td>No RVH</td>
<td>96</td>
<td>36-184</td>
<td>68</td>
</tr>
<tr>
<td>With RVH</td>
<td>62</td>
<td>25-131</td>
<td>40</td>
</tr>
</tbody>
</table>
veins had relatively the thickest walls (Fig 2). There was no difference in wall thickness between upper and lower lobe veins in the patients studied.

Extension of muscle into the peripheral pulmonary veins was also seen, though the change was less pronounced than in the small arteries. The increase in veins with muscular walls was most apparent at diameters of 125-200 μm, and was greatest in the cases with RVH; for example, in veins of 176-200 μm, the percentage of wholly muscular veins was between 28% and 50% compared to a normal value of 12%.

**Discussion**

Experimental animal work has demonstrated that both prolonged and intermittent hypoxia induces pulmonary hypertension and RVH, associated with medial hypertrophy of the muscular pulmonary arteries and the appearance of muscle further to the periphery.\(^1\)\(^-\)\(^3\) Electron microscopic studies in our department have shown that the appearance of "new muscle" in the peripheral arteries is due to further differentiation of cell types, the pericyte and "intermediate cell," normally present in the walls of the non-muscular region (personal communication, B. Meyrick).

Studies of patients with chronic bronchitis have shown a rise in mean pulmonary artery pressure associated with increasing hypoxia.\(^4\)\(^-\)\(^6\) and prolonged oxygen therapy administered to patients suffering from chronic airways obstruction with progressive pulmonary hypertension has been found to decrease pulmonary artery pressure and vascular resistance.\(^7\)\(^-\)\(^9\)

It is suggested that a chronic, although variable, degree of hypoxia in patients with chronic bronchitis produces pulmonary vasoconstriction leading to hypertrophy and extension of muscle in the pulmonary arteries before hypertrophy of the right ventricle develops. The pulmonary veins also seem to respond to hypoxia by muscle hypertrophy.

**References**

Vascular Obstruction Causes Pulmonary Hypertension in Severe Acute Respiratory Failure*

Warren M. Zapols, M.D., Koichi Kobayashi, M.D.; Michael T. Snider, M.D., Reginald Greene, M.D.; and Myron B. Lauer, M.D.

A cute respiratory failure (ARF) of diverse etiologies is a frequently lethal syndrome with severe gas exchange and hemodynamic dysfunction. We obtained measurements of pulmonary hemodynamics and correlated them with morphologic changes of the pulmonary vasculature. We found evidence for both reversibly obstructed and destroyed microvasculature producing an elevated pulmonary vascular resistance (PVR).

We have studied hemodynamic performance in 20 previously healthy patients with severe ARF using a No. 7 French, flow-directed Swan-Ganz pulmonary artery catheter and serial thermodilution cardiac output measurements. During mechanical ventilation with positive end expiratory pressure, Pao 2 was >50 mm Hg and Pco 2 was >28 mm Hg. In ARF patients, a cardiac index (CI) of 3.4 L/min was accompanied by significant pulmonary artery hypertension (mean ± SD, 31 ± 8 mm Hg), an elevated PVR (3.48 ± 1.25 mm Hg/min/L), and increased right ventricular stroke work index (850 ± 170 gm-cm/kg-stroke/min^2). In all patients, calculated

PVR decreased at high CI, but always remained elevated above normal (Fig 1, normal data obtained from Barratt-Boyes et al.). There was no difference in pulmonary capillary wedge pressure in normal and ARF patients. The increased PVR was not closely correlated with total lung water, lung hydroxyproline content, or mixed venous oxygen tension.

MATERIAL AND METHODS

We used a perfusion technique similar to Sohlin et al to stereoscopically visualize the pulmonary circulation. Low viscosity silicone polymers were filled with radiopaque colored compounds and 500 ml infused after catheterization at 50-100 mm Hg through the pulmonary artery of six patients anticoagulated at death. No flushing was performed. The trachea was intermittently inflated to 40 cm H2O peak pressure with 10 cm H2O positive end expiratory pressure (PEEP) during perfusion. In order to recruit vessels, after 400 ml of silicone had flowed from the pulmonary veins, they were clamped and the vasculature maintained at a fixed distending pressure of 50 mm Hg. Polymerization occurred within 3 hours with the lung statically inflated at 10 cm H2O PEEP.

Two cm^3 samples of lung from random areas were cleared in alurol and photographed through a Wild M8 microscope. Additional samples were gelatin-embedded, cut into 200 nm sections on a freezing microtome and stained with cresyl violet. Mounted sections were photographed by transmission light microscopy.

RESULTS

Figures 2 and 3 illustrate the dense capillary networks of normal human lungs inflated at 50 mm Hg. Figures 4 and 5 illustrate common pathologic findings of a patient with three weeks of ARF and an elevated pulmonary vascular resistance. Figure 4 demonstrates a small infarct (black) due to pulmonary arterial obstruction. In addition, the alveolar capillary network is diffusely diminished. Figure 5 illustrates the destroyed capillary networks of ARF. There are virtually no capillary networks in this lung inflated at 100 mm Hg.

Progressive destruction of pulmonary microvasculature was morphometrically observed in five ARF patients by Bachofen and Weibel. We believe our hemodynamic and inflation studies confirm and expand these observations. Diffuse occlusion, external compression or destruction of the pulmonary vascular bed appear to be major pathologic processes in severe acute lung injury. Bedside hemodynamic measurements of PVR with Swan-Ganz catheters suggest recruitable and destroyed components are present frequently in severe ARF.

REFERENCES

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