Effect of Acetylcholine on Pulmonary Vascular Resistance in a Patient with Idiopathic Pulmonary Hypertension


Neeropsy studies in cases of pulmonary hypertension of unknown cause show structural changes in the pulmonary vessels that are called irreversible. Acetylcholine chloride was infused at a rate of 2 mg. per minute into the outflow tract of the right ventricle of a 48-year-old woman who had pulmonary hypertension. The mean pulmonary artery pressure decreased from 56 to 25 mm. Hg and the pulmonary flow increased slightly. These findings are consistent with the theory that so-called idiopathic pulmonary hypertension may at some stage be maintained by vasoconstriction.

Much debate has centered around the question of pulmonary vasomotor activity in man. Daly stated that none of the observations on human beings so far reported fulfills all of the criteria that are essential for the demonstration of an active control. It is difficult to measure accurately changes in resistance to flow offered by the pulmonary vessels and to decide whether these changes actually represent significant alterations in vessel caliber. Calculation of this resistance requires the simultaneous measurement of pulmonary artery and pulmonary artery wedge (left atrial) pressure and pulmonary blood flow under conditions in which the state of the subject remains steady.

In patients with idiopathic pulmonary hypertension in whom the left atrial (pulmonary artery wedge) pressure is normal, a large pressure gradient is present across the pulmonary vascular bed. Thus, the absolute errors in measuring changes in perfusion pressure are relatively minor in comparison with the normal situation, in which only a small pressure gradient is present.

The patient was a 48-year-old woman who had 4 children, aged 10 to 18 years. There was no evidence of pulmonary disease or a history to suggest pulmonary emboli. Her main complaint was effort dyspnea with a gradual onset about 3 years prior to the present examination; the dyspnea varied subjectively from day to day, had not manifested recent progression, and caused only slight disability.

The essential findings at cardiac catheterization are summarized in table 1. The arterial oxygen saturation and the pulmonary artery wedge pressure were normal, and the saturation data gave no evidence of any

<table>
<thead>
<tr>
<th>Site</th>
<th>Blood oxygen saturation, per cent (euvette oximeter)</th>
<th>Pressure (mm. Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inferior vena cava</td>
<td>78</td>
<td>3 (mean)</td>
</tr>
<tr>
<td>Right atrium</td>
<td>77</td>
<td>3 (mean)†</td>
</tr>
<tr>
<td>Superior vena cava</td>
<td>76</td>
<td>3 (mean)</td>
</tr>
<tr>
<td>Right ventricle</td>
<td>77</td>
<td>78/4</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>77</td>
<td>78/36</td>
</tr>
<tr>
<td>Pulmonary artery wedge</td>
<td>99</td>
<td>8/2 (mean of 5)</td>
</tr>
<tr>
<td>Radial artery</td>
<td>98</td>
<td>136/78</td>
</tr>
</tbody>
</table>

*Oxygen capacity = 18.1 volumes per cent.
†The "a" wave was prominent and measured 7 mm. Hg.
shunt. A dye-dilution curve obtained by injecting 5 mg. of cardiogreen dye* into the superior vena cava and sampling blood from the right radial artery did not indicate a venoarterial shunt, and the normal contour of the disappearance slope and the first recirculation phases was consistent with the absence of an arteriovenous shunt3 or valvular incompetence4 (fig. 1).

**METHODS**

Catheters were placed into the pulmonary artery just above the valve and into the right ventricle. The pressure in the radial artery was measured by a strain-gage manometer, and the arterial oxygen saturation was determined by an ear oximeter. Tidal volume and oxygen consump-
PULMONARY VASCULAR RESISTANCE

Table 2.—Effect of Infusion of Acetylcholine Chloride (2 mg./min.) into Outflow Tract of Right Ventricle

<table>
<thead>
<tr>
<th></th>
<th>Breathing air</th>
<th>Breathing air</th>
<th>Breathing oxygen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before infusion</td>
<td>During infusion</td>
<td>Before infusion</td>
</tr>
<tr>
<td>O₂ content rt. vent. blood (vol. %)</td>
<td>12.8</td>
<td>13.1</td>
<td>12.8</td>
</tr>
<tr>
<td>O₂ content radial art. blood (vol. %)</td>
<td>17.7</td>
<td>17.7</td>
<td>17.7</td>
</tr>
<tr>
<td>Pulm. blood flow (L./min.)</td>
<td>4.4</td>
<td>4.6</td>
<td>4.4</td>
</tr>
<tr>
<td>Mean pulm. artery pressure (mm. Hg)</td>
<td>56</td>
<td>25</td>
<td>56</td>
</tr>
<tr>
<td>Total pulmonary resistance, dynes sec. cm.⁻²</td>
<td>1020</td>
<td>435</td>
<td>1020</td>
</tr>
</tbody>
</table>

Results

Figure 2 shows selections from the photokymographic record before and during administration of acetylcholine at the rate of 2 mg. per minute with the patient breathing air. During the infusion, no change occurred in the oxygen saturation of systemic arterial blood as indicated by the ear oximeter, in radial artery pressure or in pulse rate. The respiratory rate decreased slightly. The oxygen saturation of the pulmonary artery blood increased, and a pronounced decrease in pulmonary artery and right ventricular pressure occurred.

The simultaneous spirometric tracing gave no evidence of a change in oxygen consumption. Therefore, these findings suggest a slight increase in pulmonary blood flow associated with the great decrease in pulmonary artery pressure.

The infusion of acetylcholine was repeated with the patient breathing air and subsequently breathing 99.8 per cent oxygen. The results were similar on all 3 occasions (table 2).

Discussion

The pulmonary artery wedge pressure was not measured during the administration of acetylcholine; since the systemic arterial pressure and the pulse rate remained constant, it is unlikely to have changed. Had it increased, the perfusion pressure would have been even less than that calculated. Had it decreased to zero from the preinfusion level of 5 mm. Hg, this would not have affected our conclusions. Hence, the demonstrated decrease in total pulmonary resistance indicates a similar decrease in pulmonary vascular (arteriolar) resistance.

It is difficult to say what degree of decrease in resistance provides certain evidence of vasodilatation. Other workers have
shown that resistance in some patients with idiopathic pulmonary hypertension decreases after single injections of "Priscol" and acetylcholine. In the present studies, in which a steady cardiorespiratory state was maintained by continuous infusion of acetylcholine, the mean pulmonary artery pressure decreased from 56 to 25 mm Hg, while the flow increased slightly. The oxygen saturation of systemic arterial blood, the systemic arterial pressures, and the heart rate were unchanged. Therefore, it is difficult to believe that these findings can be explained other than through a decrease in activity of smooth muscle in vessels somewhere in the lungs.

The breathing of oxygen instead of air can result in a decrease in pulmonary vascular resistance in some patients who have pulmonary hypertension associated with congenital heart disease. In the present case, the breathing of oxygen alone had no effect, nor did it enhance the response to acetylcholine.

The present observations support the conclusion of other workers that active constriction of pulmonary vessels may play an important role in maintaining the pulmonary hypertension in such patients. The nature of this constriction has yet to be elucidated, but it has now been demonstrated in some patients with every disease of the heart or great vessels with which pulmonary hypertension is associated.

**SUMMARY**

Acetylcholine chloride was infused at a rate of 2 mg per minute into the outflow tract of the right ventricle of a 48-year-old woman who had idiopathic pulmonary hypertension. A steady cardiorespiratory state was achieved by this continuous infusion. The mean pulmonary artery pressure decreased from 56 to 25 mm Hg and the pulmonary blood flow increased slightly. The pulmonary vascular resistance was thus reduced from 1020 to 435 dynes seconds centimeter⁻². The oxygen saturation of systemic arterial blood, the systemic arterial pressure, and the heart rate were unchanged. These results demonstrate that constriction of pulmonary vessels played an important role in maintaining the pulmonary hypertension in this patient. The mechanism by which the constriction originates and is maintained is unknown.

**SUMMARIO IN INTERLINGUA**

Chloruro de acetylcholina esseva infundite, a 2 mg per minuta, in le tracto de efflusso del ventriculo dextere de un femina de 48 annos de etate qui habeva idiopathic hypertension pulmonar. Stabilitate del stato cardiorespiratori esseva effectuate per un infusion continue. Le valor medie del tension pulmono-arterial descendeva ab 56 a 25 mm de Hg, e le fluxo pulmonar de sanguine se augmentava levemente. Le resistentia pulmono-vascular esseva reducec assi ab 1020 a 435 dyna-seonda-centimetro⁻⁵. Le saturacion oxygenic de sanguine arterial in le circulation major, le tension del sanguine arterial in le circulation major, e le frequentia cardiac remaneva inalterate. Iste resultatos demonstra que le constreiction es producec e per le qual illo es mantenite remane ineognoscite.

**ACKNOWLEDGMENT**

The authors wish to thank Dr. E. H. Wood for his participation in this study and Drs. R. O. Brandenburg, H. W. Marshall, and R. D. Miller for their cooperation. Roche Products, Ltd., Welwyn Garden City, England, and Hoffman-LaRoche, Inc., Nutley, N. J., kindly supplied us with the ampules of acetylcholine chloride.

**REFERENCES**


Likewise, all studious, good and honest men, do never suffer their mind so to be o’rwhelm’d with the passions of indignation and envy, but that they will patiently hear what shall be spoken in behalf of the truth, or understand any thing which is truly demonstrated to them; nor do they think it base to change their opinion, if truth and open demonstration so perswade them, and not think it shamefull to desert their errors, though they be never so antient, seeing, they very well know that all men may erre, and many things are found out by chance, which any one may learn of another, an old man of a child, or an understanding man of a fool.—William Harvey. De Motu Cordis, 1628.
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