ON THE MECHANISM OF THE EFFECT OF ACETYLCHOLINE ON THE PULMONARY CIRCULATION

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Certain contemporary researchers consider acetylcholine to be one of the substances most actively participating in regulation of the vascular tonus in the pulmonary circulation. However, the known difficulties of studying pulmonary circulation and certain features of the experimental methods employed have given rise to contradictory opinions regarding the action mechanism of acetylcholine in this vascular region.

Acetylcholine's effect on the pulmonary vessels has been studied on isolated lung vessels [1, 17], isolated lungs under conditions of perfusion [3, 7, 11] and animals with an exposed thoracic cage [5, 9]. A review of the literature up to 1933 can be found in Daley's work [6].

In the investigations using perfusion of isolated lungs, acetylcholine was found to have vasocontrictor effect in large doses and a vasodilator effect in small doses. Rose reached the same conclusion in a recently published work experimenting on dogs in which the left ventricle was replaced by a perfusion pump [16].

In investigations they carried out on people and animals without exposing the thoracic cage, Cournand and co-workers [4, 13, 14] and Wood and co-workers [18] concluded that acetylcholine exerts an indirect vasodilator effect on the pulmonary vessels. Other researchers [5, 10, 12], however, believe the pressure changes in the pulmonary circulation to be due to redistribution of the blood.

Our preliminary observations [2] demonstrated that acetylcholine is not the immediate cause of changes in the tonus of the pulmonary vessels. The fall of pressure in the pulmonary artery occurs as a result of change in the systemic circulation.

The purpose of this work was to further investigate acetylcholine's effect on the pulmonary circulation.

EXPERIMENTAL METHOD

The experiments were performed on 21 dogs [106 observations with the animals under morphine (0.0025 g/kg)-chloralose (0.05-0.07 g/kg) anesthesia]. The hemodynamic indices were determined with a multichannel water-mercury manometer and synchronously recorded with a kymograph. The pressure in the pulmonary artery and the pulmonary "capillary" pressure (Wedge pressure) were recorded through catheters introduced through the external jugular vein. In some experiments, catheters with a double or triple lumen were used for simultaneous registration of the arterial and "capillary" pressures in the pulmonary circulation. The central venous pressure (pressure in the venae cavae) was recorded through catheters introduced through one of the femoral veins. The hepatic veins were catheterized in three experiments.

Besides the hemodynamic indices, we also recorded the respiratory variations of the pressure in the trachea and, in special experiments, the intrapleural pressure and the oxygen saturation of the arterial blood in the carotid artery, using a circulating device for the latter. Catheterization of the cardiac cavities and trunk vessels was also used for the administration of acetylcholine. The catheters were introduced through the carotid artery into the aorta and the left ventricle of the heart. In every case, the position of the catheters was determined by the level of the pulse and respiratory pressure waves and by x-ray, and then verified on sections at the end of each experiment.

In addition to the experiments on intact animals, we also performed experiments on dogs with an exposed thoracic cage, using autoperfusion of a vascularly isolated lung lobe with venous blood and recording the pressure in the left auricle.

EXPERIMENTAL RESULTS

Acetylcholine was administered in doses of 0.5-50 γ/kg animal weight. After the administration of acetylcholine in small doses (0.5-5 γ/kg), the pressure in the systemic circulation and the cardiac rhythm did not change in many experiments, but the pressure in the pulmonary artery always rose.

When acetylcholine was administered into veins of the systemic circulation, the pressure in the pulmonary artery rose 12-14 sec later, but the pressure rise occurred after 7.8 (4-11) sec when the substance was introduced into the pulmonary artery and after 4 (2-7) sec when it was introduced into the left ventricle and aorta.

The degree and duration of the pressure rise depended on the dose of the substance administered. There was a greater and more prolonged rise of pressure in the pulmonary artery after the administration of acetylcholine into the left ventricle and arch of the aorta than after the administration of the same dose into a vein of the systemic circulation or directly into the pulmonary artery (Figs. 1, 2).

The average pressure rise in the pulmonary artery was 28.2 (16-48) mm of water following the introduction of acetylcholine into the femoral vein or pulmonary artery, but 40 (25-66) mm of water following its introduction into the aorta. The pressure in the pulmonary circulation returned to the original level after 1-3 min in the majority of observations.

Regardless of where acetylcholine was introduced, a decrease of pressure in the systemic circulation was observed either before or, as in several cases, almost simultaneously with the pressure rise in the pulmonary circulation. The cardiac rhythm was usually accelerated. When large doses were administered, especially into the left ventricle and arch of the aorta, acute retardation of the rhythm was observed at the beginning of the reaction. In these cases, there was an acute fall of pressure in the systemic circulation, while there was only a brief decrease of the pressure in the pulmonary artery, followed by its increase.

The pulmonary "capillary" pressure was recorded in five experiments (24 observations). The administration of acetylcholine in small doses did not cause much change in the capillary pressure. The considerable acceleration of cardiac activity following the administration of acetylcholine in large doses was attended by a fall of capillary pressure (Fig. 3). The pressure gradient between the pulmonary artery and the lung capillaries rose in every case.

The two experiments (six observations) performed on dogs with an exposed thorax in order to record the pressure in the left auricle showed little change in the latter. There was usually a fall of pressure in the venae cavae and right auricle, sometimes preceded by a slight rise. An increase was observed in the pressure recorded after a catheter was wedged into a small hepatic vein. The administration of small doses caused no change in the latter pressure.

Large doses of acetylcholine caused a slight increase in the inflow pressure and a decrease in the outflow in a lung lobe being perfused with venous blood, the nerve connections being intact.

The respiratory changes were variable. In most cases, we observed respiratory arrest followed by stronger, deeper respiratory movements. In a few experiments, there was no apnea preceding this intensification of respiration. The administration of acetylcholine in small doses caused little change in the respiration.

The administration of acetylcholine in a dose of 10 γ/kg (21 observations) caused little change in the tonus of the bronchial musculature as observed during the synchronous recording of the respiratory fluctuations

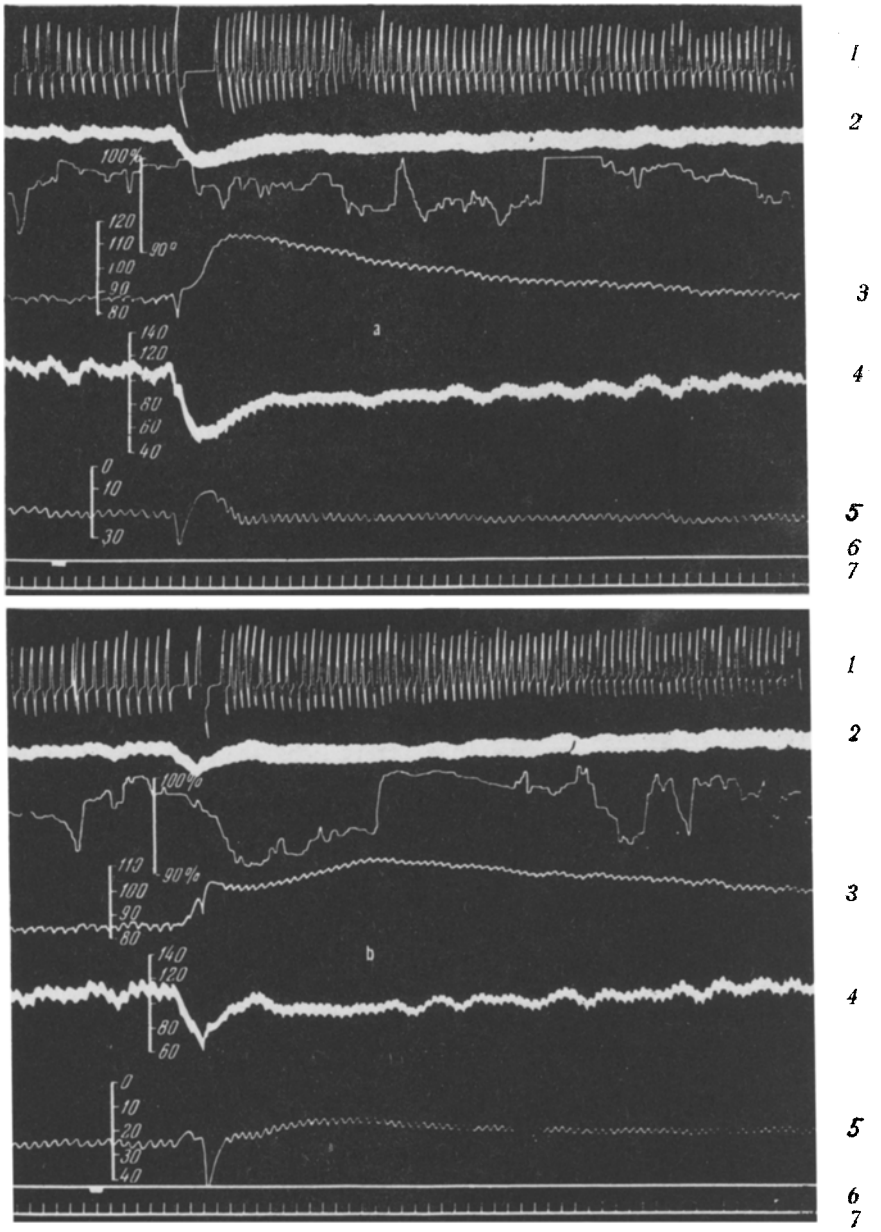

Fig. 1. Reaction to introduction of acetylcholine into pulmonary artery (a) and into thoracic aorta (b). Male dog weighing 24 kg, morphine-chloralose anesthesia. Acetylcholine dose, 10 γ/kg. Curves show: 1) respiration; 2) pressure in femoral artery (membrane manometer); 3) average pressure in pulmonary artery (in mm of water); 4) pressure in femoral artery (in mm of mercury); 5) average pressure in inferior vena cava (in mm of water); 6) indication of stimulation; 7) time in 5-second marks.

and the intrapleural and intratracheal pressures. Acetylcholine's bronchospastic effect was much stronger on a background of neostigmine administration (Fig. 4).

We could not, however, observe any direct relationship between the degree of pressure rise in the pulmonary artery and the intensity of the bronchospasm. The rise of pressure in the pulmonary circulation also occurred in the absence of bronchospasm.

Prompted by the communications of Cournand and co-workers [4, 13, 14] concerning the stronger vasodilator effect exerted by acetylcholine under conditions of hypertonia of the pulmonary circulation, we set up experiments analogous to theirs.

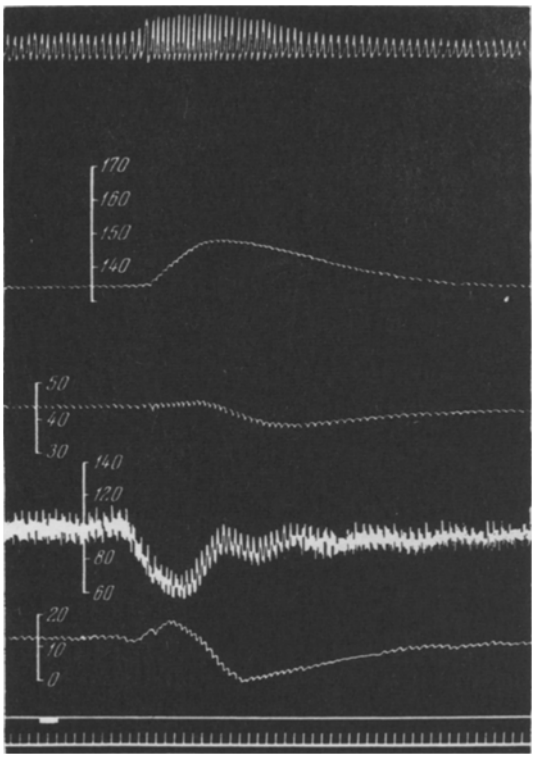

Fig. 2. Reaction to introduction of acetylcholine into pulmonary artery. Male dog weighing 23 kg, Amytal anesthesia. Acethylcholine dose, 10 γ/kg. Curves show (from top to bottom): respiration; average pressure in pulmonary artery (in mm of water); average lung capillary pressure (in mm of water); pressure in femoral artery (in mm of mercury); average pressure at mouth of venae cavae (in mm of water); indication of stimulation; time in 3-second marks.

A rise of pressure in the pulmonary circulation of four dogs (19 observations) was induced by giving the dogs gaseous mixtures with a low oxygen content (6-8%) to inhale. Under these conditions, the pressure in the pulmonary artery rose 20-50%, and other compensatory reactions typical of hypoxia developed: the pressure in the systemic circulation rose; intensified cardiac activity was observed. The compensatory faculties of the organism diminished toward the end of the first or the beginning of the second hour of hypoxia: the blood pressure gradually decreased; stronger tachycardia and decreased pulse pressure were observed; waves of the third order appeared; and the palpebral reflexes diminished and periodically disappeared.

The reactions to acetylcholine changed as hypoxia increased.

The typical reaction to acetylcholine, i.e., a rise of pressure in the pulmonary artery, was retained during the period of stable compensation with increased blood pressure and moderate tachycardia. In three observations, the pressor reaction was even enhanced. As the hypoxia condition developed and the blood pressure in the systemic circulation decreased, the pressor effect in the pulmonary circulation induced by acetylcholine became gradually weaker and then distorted. Under these conditions, the rhythm of the heart activity became retarded during the reaction period. The direction of the reactions of the systemic circulation remained the same. The respiration became faster and deeper with no preliminary apnea.

We next analyzed the reaction to acetylcholine after preliminary administration of hexamethonium (4-8 mg/kg) or atropine (0.5 mg/kg) and after transection of the vagosympathetic nerves to the neck.

In both the pulmonary circulation and the systemic, the reaction to acetylcholine was less pronounced after the preliminary administration of hexamethonium. Vagotomy did not diminish the reaction to acetylcholine.

In atropinized animals, the intravenous administration of average doses of acetylcholine had either a sharply reduced or an almost nonexistent effect. However, acetylcholine introduced by catheter into the left ventricle and aorta caused a well-expressed reaction.

Therefore, it has been demonstrated that the passage of acetylcholine through the pulmonary vascular bed is not attended by recordable pressure changes in the pulmonary circulation.

A pressor reaction was observed 4-11 sec (an average of 7-8 sec) after the injection of the drug directly into the pulmonary artery. The introduction of acetylcholine into the left ventricle and into the aorta also induced a rise of pressure in the pulmonary circulation which occurred earlier (after 4 sec) than that following the introduction of the drug into the femoral vein or directly into the pulmonary artery. The pressor reaction induced by the introduction of acetylcholine into the left ventricle and aorta was more pronounced than that caused by the administration of the drug into the venous section of the systemic circulation. The initial fall of pressure in the pulmonary artery preceding its rise is due solely to inhibition of the cardiac activity and can be easily reproduced by administering acetylcholine into the pulmonary artery and left ventricle of the heart.

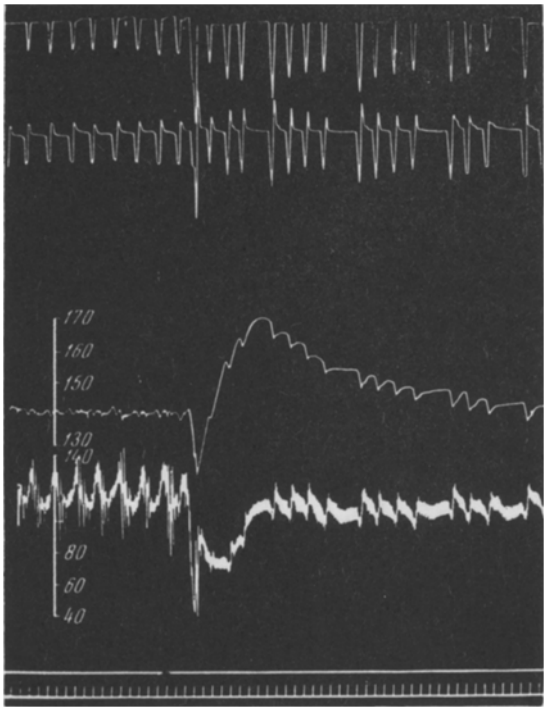

Fig. 3. Reaction to introduction of acetylcholine into femoral vein. Male dog, morphine-chloralose anesthesia. Acetylcholine dose, 10γ/kg. Curves show (from top to bottom): intrapleural pressure; respiration; average pressure in pulmonary artery (in mm of water); pressure in femoral artery (in mm of mercury); indication of stimulation; time in 3-second marks.

It should be definitely established that acetylcholine does not directly cause changes in the hemodynamics of the pulmonary circulation and does not affect the tonus of the pulmonary vessles. The time required for the development of the pulmonary circulation's reaction and the fact that the character of the reaction is the same whether acetylcholine is administered into the venous or arterial section of the vascular bed give reason to believe that the hemodynamic effects in the pulmonary circulation merely reflect the hemodynamic changes in the systemic circulation. The changes which occur in the reaction of the systemic circulation under conditions of hypoxia or experimental hypertonia of the pulmonary circulation are reflected to the same extent by the reaction of the pulmonary circulation.

The influence of the so-called reverse transfer of pressure from the left auricle in the mechanism of acetylcholine's pressor effect in the pulmonary circulation can also be completely negated. The pressure changes in the left auricle are much less pronounced than those in the system of the pulmonary artery and sometimes in the opposite direction.

Acetylcholine is known to raise the tonus of the bronchial musculature considerably. In Rodbart's opinion [15], spasm of the bronchioli causes the intraalveolar pressure and capillary resistance to increase.

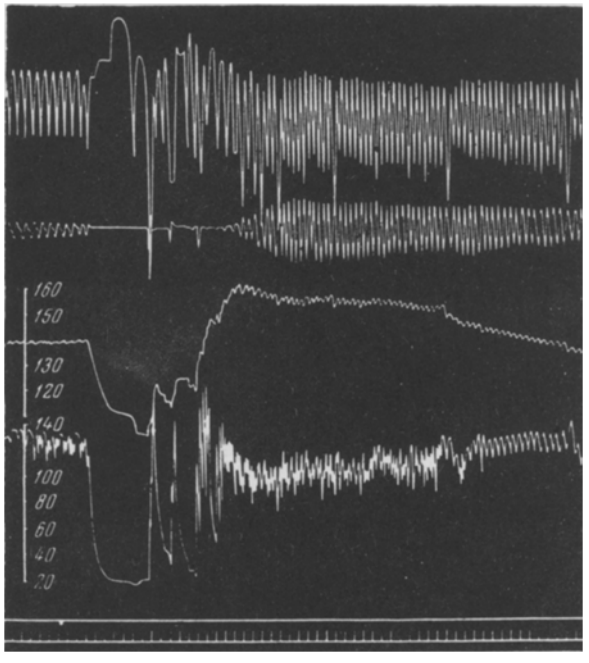

Fig. 4. Reaction to introduction of acetylcholine into femoral vein on a background of neostigmine action. Symbols the same as in Fig. 3.

However, a rise of pressure in the pulmonary artery can also occur without any changes in the bronchomotor tonus. Rose also [16] was unable to detect any direct relationship between changes in the tonus of the bronchial musculature and hemodynamic changes in the pulmonary circulation.

The above analysis gives reason to believe that the pressure rise effected by acetylcholine in the pulmonary artery is basically a secondary result of hemodynamic changes in the systemic circulation. After the administration of acetylcholine, a complex of reflex compensatory reactions develops immediately after dilatation of the systemic vessels to counteract the fall of arterial pressure and acetylcholine's effect on the vascular interoceptors. Cardiac activity is accelerated, the pulse pressure rises and the outflow from the portal vein system increases, probably because of the contraction of the muscles of the gastrointestinal tract. Under these conditions, the pressure gradient between the pulmonary arteries and the capillaries also increases. In all probability, this is due to reflex changes in the tonus of the pulmonary vessels as well as to the increase in the inflow.

SUMMARY

It was shown in experiments on dogs that during the circulation through the pulmonary vascular system of acetylcholine added to the blood no recordable pressure changes were noted in the pulmonary circulation. Pressor reaction began in 4-11 seconds after the administration into the pulmonary artery. Injection of acetylcholine into the left ventricle and aorta also leads to the pressor reaction in the pulmonary circulation; this occurs earlier than when the substance is injected into the femoral vein or directly into the pulmonary artery (in 4 seconds). Besides, pressor reaction is more marked in administration of acetylcholine into the left ventricle and aorta than in injection into the venous part of the systemic circulation. Pressure reduction in the pulmonary artery, preceding its rise, is directly connected with the inhibition of the cardiac activity and is also well reproduced with acetylcholine administered into the pulmonary artery and the left ventricle of the heart.

Thus, acetylcholine does not provoke direct changes in the hemodynamics of the pulmonary circulation, and, evidently, does not influence the tone of the pulmonary vessels.

Period of reaction development in the pulmonary circulation and the same type of reaction occurring in acetylcholine administration into the venous and the arterial portion of the circulation lead to the conclusion that the hemodynamic effects the pulmonary circulation reflect the hemodynamic shifts in the systemic circulation.

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