Stretch Reflexes from the Dog's Lung to the Systemic Circulation

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Evidence is presented that reflex systemic vasodilatation occurs after stretching dog's lungs by either mechanical traction or positive pressure ventilation under conditions of separate pulmonary and systemic perfusion. This reflex is mediated by the vagus.

It is generally accepted that the reflex circulatory effects of normal lung inflation and deflation are insignificant. 1 The complex interaction of mechanical and neurogenic effects of lung inflation has made a study of reflex mechanisms particularly difficult. Relevant information can be derived only from experiments in which mechanical factors, such as changes of the pulmonary blood flow and tamponade of the heart and the great vessels, are separated from nervous factors. Anrep 2, 3 is credited with being the first to observe that an increase in airway pressure during isolated lung perfusion causes bradycardia and systemic hypotension. Daly 4 showed that, in separate perfusion of the pulmonary and systemic circulations, an increase in pulmonary arterial pressure leads to a systemic vasodilation and that this effect is mediated by a vagal reflex. The purpose of the present study was to find out whether the reflex systemic responses can be elicited not only by an increase in intraluminal pressure in the pulmonary circulation but also by distension of other pulmonary structures.

METHODS

Two experimental approaches were used in dogs anesthetized with pentobarbital (25 mg./Kg.). In the first type (19 dogs), the systemic circulation was perfused by a heart-lung machine whereas the pulmonary vessels were perfused independently from a pump-reservoir circuit. 5 Hereby the systemic and pulmonary circulations were completely separated except for collateral channels. Pressures were recorded with Statham strain gages on a multichannel oscillograph through semirigid plastic catheters from the femoral artery, the inferior vena cava, a small branch of the pulmonary artery, a small pulmonary vein, and the lumen of a cuffed endotracheal tube. The lungs were rhythmically inflated and deflated either by means of a motor-driven Harvard mechanical respirator, or by means of compressed air and vacuum lines. The pH of the pulmonary and of the systemic blood was frequently tested with a glass electrode and a Beckman Model W pH meter. Whenever indicated by values above 7.50 or below 7.40, rebreathing techniques were used or appropriate amounts of 4.5 per cent lactic acid or of 8.4 per cent sodium bicarbonate were added. The temperatures in the pulmonary and systemic perfusion circuits were kept constant. Observations were made only when eye reflexes and jaw tone of the animals were normal. In 6 animals, the vagi were isolated in the cervical region, where they could be cut or temporarily blocked by the application of small rubber ice bags.

In the second type of preparation (4 dogs), the peripheral circulation was perfused from a heart-lung machine after the vena cavae, the azygos and the pulmonary artery had been ligated. Both atria were drained by siphonage into reservoirs. The chest was closed and the residual air was removed through a pleural pressure registration cannula until near-normal negative pressure values were created. In this preparation, the lungs were not perfused except by the lung collateral circulation. Hereby the effect of spontaneous respiratory movements and of mechanical lung inflation and deflation on the systemic circulation could be tested under conditions of negative pleural pressure.
REFLEXES FROM LUNGS

FIG. 1. Effect of an increase of the airways pressure in an open-chest dog when the systemic and pulmonary circulations are perfused separately at constant flows. At A and D, a sudden increase of the tracheal pressure resulted in a pronounced decrease of the mean systemic arterial pressure with simultaneous rise of the pulmonary artery pressure. At B, an increase of pulmonary artery pressure secondary to an increase of pulmonary venous pressure by constriction of the pulmonary venous outflow tract had a minimal effect on the systemic arterial pressure. At C, the pulmonary artery pressure was raised by a transient increase of pulmonary blood flow without any appreciable change in systemic arterial pressure.

RESULTS

Effects of Stretching the Lungs in the Open-Chest Dog With Separate Pulmonary and Systemic Circulations

When the systemic circulation is supplied by a heart-lung machine and the lungs are perfused from a pump-reservoir circuit, changes of pressures in the arteries and veins cannot be caused by changes of the blood flow through the vessels, since the flows are fixed by the output of calibrated pumps which are not load sensitive in the range of pressures investigated. In 60 experiments of this type, the systemic arterial pressure consistently fell when the lungs were inflated although the systemic circulation was perfused at constant flow. Figure 1 demonstrates a representative experiment: In observations A and D, a pronounced decrease of the systemic arterial pressure began 5 seconds after the lungs had been stretched by raising the inflation pressure from 16 to about 32 cm H2O over 2 ventilatory cycles (8 seconds). At B, a change of the systemic arterial pressure of similar magnitude was not observed when the pulmonary arterial pressure was raised by constriction of the pulmonary venous outflow, thus creating passive pulmonary congestion. In observation C, the systemic arterial pressure was but little affected by an increase in pulmonary arterial pressure secondary to a transient increase of the pulmonary arterial inflow.

The same drop of systemic arterial pressure was obtained by manual traction of the lung tissue as by overinflation. Quantitative expressions for mechanical stretching are not easy to define. "Pulling" consisted of grasping one lobe of a lung at the periphery, using
all fingers of one hand, and exerting an estimated force of 300 to 400 Gm. This maneuver not only stretched the lung tissues, but also compressed them between the grasping fingers. A typical observation is shown in figure 2, where the pulmonary circulation was stopped before the manual stretching of the lungs, to avoid interference from the pulmonary circulation.

Fig. 2. Effect of manual "pulling" (duration 8 seconds) of a nonperfused lung (arrow) on the systemic arterial pressure during constant systemic perfusion. The separate pulmonary circulation was arrested shortly before the mechanical stretching of the lungs, to avoid interference from the pulmonary circulation.

Traction of one lobe caused a decrease of the systemic arterial pressure irrespective of the control values of this parameter: the phenomenon was observed at mean arterial pressures as high as 160 mm. Hg and as low as 40 mm. Hg. When the lungs were stretched at the lower levels of systemic arterial pressure, the resulting blood pressure fall was often irreversible, even after massive increases of the systemic flow. When the systemic arterial pressure had fallen to shock levels for more than 1 minute, it could usually be restored only by pressor drugs (levarterenol, 5 to 20 μg./min.). The magnitude of the systemic arterial pressure fall was not correlated with the level of positive airway pressure. For instance, transition from no ventilation to inflation with as little as 12 cm. H₂O positive pressure caused the systemic arterial pressure to fall markedly.

Both the extent and the duration of the arterial pressure fall were highly variable. The drop which occurred after one single positive pressure inflation amounted to 5 to 40 mm. Hg and lasted from a few seconds to an indefinite period. At times such peripheral vasodilations were followed by peripheral vasoconstriction overshooting the control values. When the lung inflation was continued for more than one cycle or for prolonged periods, the systemic arterial pressure might remain depressed, or return to normal after variable periods of time, or overshoot in a positive direction.

The lung stretch systemic arterial pressure relation was abolished after cutting the vagi in the neck (4 experiments) or after blocking them by cold (3 experiments). The phenomenon reappeared, however, when the cold-blocked vagi were permitted to rewarm.

**Effect of Stretching the Lungs in the Closed-Chest Dog without Pulmonary Perfusion, but with Systemic Perfusion**

In 4 experiments, the peripheral circulation was maintained by the heart-lung machine, while ligatures of the great veins and of the pulmonary artery and siphon drainage of both atria prevented any significant contribution by heart-ejected blood to the systemic arterial flow and pressure. The chest cavity was closed tightly and negative pleural pressures were obtained.

When the dog was breathing spontaneously, fluctuations of the systemic arterial pressure were observed. Our registering devices, however, were not designed to correlate these arterial pressure variations with the phasic
fluctuations of the intrapleural and airways pressures, and no conclusions could be drawn.

When positive pressure ventilation was resumed, a sudden increase of the inflation peak caused a fall of the systemic arterial pressure which was in all respects (delay, extent, duration and recovery) similar to the phenomena observed in open-chest animals.

**DISCUSSION**

The phenomena reported here present evidence for the occurrence of systemic vasodilation caused by stretching the lungs which is reflex in nature. Although the possibility that ventilation might produce associated changes of peripheral vasomotor tone has been considered by Brodie and Russell and Visscher et al. Anrep was the first who succeeded in showing unequivocally some direct cardiovascular effects of lung inflation. Vasodilation in the perfused hindleg was associated with respiration or increased tracheal pressure. In the conditions of intact circulation, however, it is generally agreed that the fall of systemic arterial pressure which occurs under positive pressure respiration is due to mechanical interference of lung inflation with venous return and secondary decrease of cardiac output. (For review see reference 10.)

In the open-chest animal, direct measurements of right cardiac output have shown that lung inflation decreases the venous return mainly by increasing pulmonary vascular resistance, the tamponade of the heart and great vessels being only of minor importance.

To eliminate these mechanical factors, cardiac arrest and constant flow perfusion techniques were used in our experiments. Since the volume flow is fixed by the pump output, any change in systemic arterial pressure must be caused by variation of the peripheral resistance and consequently of the peripheral vasomotor tone. The only influence of the pulmonary circulation on the systemic circulation known under conditions of separate perfusion concerns the reflex fall of systemic arterial pressure when the pulmonary arterial pressure is increased, as demonstrated first by Daly and confirmed by Aviado et al. However, in the descriptions of these authors and in our own observations (fig. 1, B and C), this effect is small in magnitude when compared with the changes of systemic arterial pressure seen after lung stretching. Furthermore, although traction or insufflation of the lungs usually produced associated elevations of the pulmonary arterial pressure, the systemic vasodilation was observed to the same extent in cases in which the pulmonary blood flow remained either unchanged or was stopped during the observation.

We could not correlate the magnitude of the systemic arterial pressure fall with the level of positive airway pressure. It was our impression that the degree of expansion of the lungs in itself was a more important factor than the level of inflation pressure at which the phenomenon was observed. In other words, the relative volumetric increase seemed to be more effective in eliciting the reflex than the extent of airway pressure variation. Therefore one may speculate that the effect described by Daly, for which no specific receptors have been found in the arterial wall, could have resulted from stretch transmitted to the lung stroma. This effect possibly represents only one aspect of a more general phenomenon of systemic vasodilation as a consequence of stretching all the lung structures.

The clinical implication of these observations is readily apparent for conditions in which the functional pulmonary circulation is temporarily excluded, such as during cardiopulmonary bypass. If in such cases the lungs are not ventilated, then the reflex causing systemic hypotension might possibly be evoked when the lung inflation is resumed. Since the systemic vasodilation caused by stretching of the lungs has been confirmed in the closed-chest preparation, this phenomenon may be of importance during spontaneous respiration. The depression of the systemic arterial pressure to shock levels for indefinite periods as observed occasionally in our experiments, correlates with the clinical observation of Beecher et al. that an increase of positive pressure in the airways may be dangerous in patients...
in poor circulatory conditions. It has been shown that positive pressure ventilation is especially detrimental in the presence of hypovolemia.\textsuperscript{15, 16} Since the reflex is elicited not only by insufflation, but also by mechanical stretching, the need for gentleness in the surgical manipulation of thoracic organs is reemphasized.

As for the significance of the lung stretch-systemic resistance relationship in conditions of normal respiration, our experiments do not offer any solution to the conflicting findings of the plethysmographic technic.\textsuperscript{17-19} It must be pointed out that plethysmographic data are of purely descriptive nature and are very complex to interpret because the volume changes of inflow and outflow are measured simultaneously. They represent the integrated effect of several reactions of mechanical and possibly reflex nature, and factors bearing on the different time lags of these effects must be introduced for any critical approach.

The circulatory effects of lung stretching are mediated by the vagi, as demonstrated by section or transitory cold blocking of these nerves. This reflex appears to be identical with the one originally described by Churchill and Cope\textsuperscript{20} as far as reflex time (6 to 7 sec.) and pathways are concerned.\textsuperscript{21} It seems to follow the same afferent pathways as the classically described respiratory reflex to lung inflation (Hering-Breuer). With regard to the receptor sites in the lungs,\textsuperscript{22} no attempts were made in our experiments to differentiate between the pleural surface and the lung stroma. Previous physiological studies\textsuperscript{23} demonstrated that at least 60 per cent of the lung stretch receptors are localized in the pleura or very close to it.

**SUMMARY**

The peripheral circulation of open-chest dogs was perfused at constant flow from a heart-lung machine while the pulmonary circulation was isolated in situ and left either without perfusion or perfused at constant flow from a separate pump reservoir circuit. Stretching of the lungs by manual pulling or by positive pressure inflation produced marked peripheral vasodilation, which often resulted in marked sustained hypotension. Systemic hypotension was also induced by positive pressure ventilation in closed-chest dogs in which the systemic circulation was carried on a heart-lung machine and cardiac ejection and pulmonary perfusion were prevented. This reflex systemic vasodilation was prevented by vagotomy or by cold blockade of the vagi.

**SUMMARIO IN INTERLINGUA**

Le circulation peripheric de canes con thoraces aperte esseva perfusione a un fluxo constante ab un machina corde-pulmon durante que le circulation pulmonar esseva isolate in sito e remaneva sin perfusion o esseva perfusione a fluxo constante ab un separate circuito de pumpa e reservoir. Distension del pulmones per traction manual o per inflation a pression positive resultava in unmarcate vasodilatazione peripheric que esseva frequentemente le causa de marcate e persistente hypotension. Hypotension systemic esseva etiam inducite in canes con thoraces claudite in que le circulation systemic esseva mantenite per un machina corde-pulmon, durante que ejectiones cardiac e le perfusion del pulmon esseva prevenite. Iste reflexo de vasodilatazione systemic esseva prevenite per vagotomia o per cryoblocage del vagos.

**REFERENCES**

REFLEXES FROM LUNGS

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