Action of Hypoxia on the Pulmonary Vasculature

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The hemodynamic effects of acute hypoxia upon the pulmonary circulation were studied in dogs. The most striking changes were observed on the venous side of the circuit, consisting of a rise in venous (and arterial wedge) pressure greater than that in the pulmonary artery and an increase in the pressure gradient between the venules and the left atrium. These alterations are discussed and interpreted in an attempt to further clarify the response of the pulmonary circulation to hypoxia. It is suggested that there is arteriolar dilatation associated with increased postcapillary vascular resistance.

RECENT work has shown that a rise in pulmonary venous pressure, without a concomitant rise in that of the left atrium, frequently occurs as a consequence of miliary pulmonary starch embolism.1 Venomotor activity was inferred to explain this phenomenon; however, the stimulus for the venoconstriction was not established. Previous work has shown that arterial oxygen desaturation occurred in these dogs.2 Therefore, the possibility was considered that hypoxia may be one of the factors responsible for the observed pulmonary venous constriction and further studies were undertaken.

MATERIALS AND METHODS

Mongrel dogs ranging in weight from 11 to 17 Kg. were anesthetized with intravenous pentobarbital (25 mg./Kg.) The chest was opened at the level of the fourth or fifth intercostal space. The pericardial sac was opened and the atrial appendage was clamped with a Potts' clamp. A no. 7 radio-opaque Cournand catheter was introduced into the left atrium under fluoroscopic control and the left atrial appendage was tied around the catheter. The jugular vein was isolated and the pulmonary artery was catheterized with a double lumen catheter so that its distal lumen was in the wedge position and the proximal lumen was in the pulmonary artery proper. Pressures were also obtained from the carotid artery.

The catheters were perfused during the procedure with a slow drip of heparinized 5 per cent glucose in water. A tracheal tube was inserted and connected to the nitrogen and oxygen mixtures. All pressures were recorded on a Sanborn Twin-viso polygraph and capacitance manometer. Control pressures were taken with the dog breathing room air mixture (78 per cent nitrogen and 22 per cent oxygen). Then, the inhalation of the low (10 or 5 per cent) oxygen in nitrogen mixtures was begun and pressures were recorded periodically for a period of 20 to 30 min. The dog was then returned to the room air mixture. The inhalation of low oxygen mixtures was repeated only when the pressures had returned to control levels.

RESULTS

Fourteen dogs were studied. All were exposed to 5 per cent oxygen in nitrogen (one dog twice) and 6 were also initially exposed to 10 per cent oxygen. Three of the 6 dogs exposed to 10 per cent oxygen showed no pressure variations; one other dog developed left heart failure early as evidenced by a sharp rise in left atrial pressure. Six of the 14 dogs exposed to 5 per cent oxygen also showed early left heart failure. Dogs which developed left heart failure early are not considered in the subsequent analysis. The 3 dogs showing no response to 10 per cent oxygen are also excluded from further discussion, other than to suggest that in them 10 per cent oxygen was not a significant enough stimulus to lead to measurable changes in the parameters studied.

A summary of the results in animals which showed pressure changes and did not develop left heart failure early are given in tables 1 and 2.*

*Copies of these tables will be furnished by the authors upon request.

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HYPOXIA AND THE PULMONARY VASCULATURE

FIG. 1. Average of heart rate (HR) and mean pressures in the carotid artery (CA), pulmonary artery (PA), pulmonary arterial wedge position (PAW) and left atrium (LA) of 6 experiments on 5 dogs before (C) and at various times after induction of hypoxia (arrow H) accomplished by changing inspired air to 5 per cent O₂—95 per cent N₂. It will be seen that when these animals were breathing room air the average mean pressures were: 12 mm. Hg in the pulmonary artery (range 8 to 17), 1.5 mm. Hg in the arterial wedge position (range 0 to 4) and 0.5 mm. Hg in the left atrium (range 0 to 3). The average mean pressure gradient between the pulmonary artery and the pulmonary arterial wedge was 10.5 mm. Hg (range 6 to 15). There was no significant pressure gradient between the arterial wedge and the left atrium.

The mean pulmonary artery pressure rose slightly (4 to 5 mm. Hg) within the first 4 min. of hypoxia and then remained stable at this level. Within 3 min. after the onset of hypoxia, the mean arterial wedge pressure rose to 5 mm. Hg (average) and reached its maximum (average 11 mm. Hg) within 5 to 10 min. (fig. 1). The average mean pressure gradient between the pulmonary artery and the arterial wedge dropped to 5 mm. Hg.

The left atrial pressure exhibited only a very small rise within the first 5 min. of hypoxia and then rose little thereafter. In a few instances, however, a further rise in mean left atrial pressure occurred as the hypoxia continued. This added increment was attributed to the development of delayed left ventricular failure. As figure 2 shows, a pressure gradient developed between the arterial wedge and the left atrium (average 8 mm. Hg) during the first few minutes of exposure to the low oxygen mixtures. When left heart failure supervened this tended to decline as left atrial pressure rose.

In order to verify the validity of the wedge pressure as an indirect measure of pulmonary venous pressure, a pulmonary vein was also catheterized through the left atrium in 1 dog. The pulmonary venous pressure was found to be almost identical with the arterial wedge pressure both before and after hypoxia, and significantly higher than the left atrial pressure after hypoxia was introduced.

The carotid pulse contour changed under hypoxia. Both systolic and diastolic pressures rose, the former more than the latter, producing an increase in systemic pulse pressure. These changes were more marked during the first 10 min. after inducing hypoxia, at which time bradycardia was also recorded.

FIG. 2. Average pressure gradients observed in 6 experiments on 5 dogs before and after induction of hypoxia (5 per cent O₂—95 per cent N₂); open bars, gradients between the mean pulmonary artery pressure and that in the pulmonary arterial wedge position; shaded bars, the gradients between the latter and the mean pressure in the left atrium.
In 2 dogs the left ventricle was catheterized at the end of the procedure. The end-diastolic pressures were found to be normal in both, confirming the absence of left heart failure.

**Discussion**

Hypoxia has occupied a prominent position among the stimuli which have been studied for their effect on the pulmonary circulation; however, the results have been controversial and the conclusions discordant. Von Euler and Liljestrand found an acute rise in pulmonary artery pressure in cats which was not affected by vagotomy or ablation of the stellate ganglia, and concluded that hypoxia exerted a direct constricting effect on the pulmonary arterioles. Subsequent claims, to the same effect, have been based on the observation that hypoxia causes a rise in pulmonary artery pressure in the absence of a rise in cardiac output. Others, however, claimed that the pressor response is due to an increase in cardiac output or to the combined effects of increased output and resistance.

Thus, most investigators agree that hypoxia causes an increase in the pressure gradient across the pulmonary vascular bed which is due, at least in part, to vasoconstriction. However, the site of the constrictor activity has not been completely assessed. The venous portion of the pulmonary circulation has only recently been accorded a modest degree of attention in this respect. There has been a widespread tendency to consider the pulmonary veins as inactive tubes which passively transport blood from the capillaries of the lung to the left atrium.

Histologic studies of the pulmonary veins have definitely demonstrated abundant smooth muscle in their walls and a rich supply of ganglionic cells and nerve fibers. The left atrial myocardium in man has been found to extend beyond the pericardium to form a sleeve which overlaps or wedges into the smooth muscle of the pulmonary veins. The pulmonary veins, then, possess a histologic structure compatible with size variation and response to neurogenic or neurohumoral mechanisms. The low pulmonary venous pressure normally makes it easy for a small contraction force to reduce the venous lumen. Like systemic veins, these permit a ready reservoir function for the pulmonary veins. However, the concept of venomotor activity has not been widely accepted. Only recently have these veins come to be considered as an active part of the pulmonary vasculature capable of influencing the response of the entire lesser circuit to various stimuli.

Aviado and Schmidt postulated that the pulmonary venous constriction induced by alloxan is the most important factor in the causation of the pulmonary edema in anesthetized dogs and in the isolated perfused lung. A similar mechanism had been previously invoked by them for the edema that follows steam inhalation. An increased pulmonary venous resistance has also been reported to occur in experimental bacteremic shock. Our recent experiments with unilobar starch emboli indicate a similar venomotor mechanism.

If pulmonary venous constriction occurs in response to various chemical and physical agents, it is conceivable that the pulmonary veins could partake in the reaction of the pulmonary vasculature to hypoxia; however, only limited work has been done in this area. Both pulmonary venous dilatation and constriction have been claimed to occur when perfused lungs are exposed to hypoxia. These contradictory results may be due to the wide range of hypoxia observed.

The development of a significant and striking pressure gradient between the pulmonary veins and the left atrium during hypoxemia, in the absence of left ventricular failure, can best be explained by pulmonary venous constriction.

The relatively small rise in mean pulmonary arterial pressure during hypoxia is in accordance with what has been generally reported in the literature. However, this rise was much smaller than the mean arterial wedge pressure rise. The pressure gradient between the two sites falls to $\frac{1}{2}$ of the control value. It is suggested that this drop in pressure gradient across the pulmonary arterioles may actually be due to arteriolar dilatation and that the mildness of the pul-

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Pulmonary hypertension is a reflection of the increase in postcapillary resistance (and perhaps of increased blood flow), rather than of an arteriolar constriction. It is conceivable, however, that small variations in either the arteriolar tone or cardiac output will lead to the different degrees of pulmonary artery pressure rise reported in the literature. In order to explain the rise in pulmonary artery pressure as being due to increased arteriolar resistance, with its associated decrease in the gradient between artery and wedge, it would be necessary to postulate a reduction of the cardiac output to less than 50 per cent of the control levels, which is unlikely. However, in the absence of pulmonary blood flow measurements, the cause of vascular resistance changes must remain a matter of interpretation.

Teleologically the alterations in pulmonary hemodynamics induced by hypoxia may play a role in enabling the organism to best prepare itself against the adverse effects of low oxygen tension. Arteriolar dilatation, if it occurs, by decreasing the resistance in the pulmonary circulation, will lessen the increase in work load imposed upon the right ventricle in an oxygen poor atmosphere and permit a greater flow. Also, greater pulmonary blood flow could be provided in the body’s attempt to oxygenate as much blood as possible under extreme degrees of hypoxia. Similarly, venous constriction in poorly oxygenated areas of the lung could affect a mobilization of blood for greater pumping. It will thus influence the venous return to the heart by transiently squeezing blood from the veins into the left atrium when the constriction begins. This apparently is the cause for the initial rise in left atrial pressure.

The specific manner by which hypoxia exerts its action on the pulmonary vasculature is beyond the scope of this report. It may be caused either by a direct effect or indirectly through a neurogenic or a neurohumoral mechanism. 

It is true that if a marked increase in pulmonary blood flow occurred (say to approximately 10 times the control) it might explain many of the pressure changes observed, but this degree of augmented flow seems unlikely. At any rate, it can be definitely stated that the gradient from the pulmonary veins to the left atrium could not develop during hypoxia if the veins were just passive conducting tubes. It follows from this that active venoconstriction plays a significant role in adjusting to hypoxia.

SUMMARY

A study of the effect of hypoxia on the pulmonary vasculature was undertaken because evidence of pulmonary venous constriction and arterial oxygen desaturation was found in some dogs following experimental miliary pulmonary embolism. Anesthetized dogs were exposed to low oxygen mixtures in the inspired air (5 and 10 per cent oxygen), and the pressure changes in the pulmonary circuit were recorded. The most striking change during hypoxia (in the animals which responded and did not develop early heart failure) was a rise in the pulmonary arterial wedge and pulmonary venous pressures, with only a very slight rise in left atrial pressure. This is interpreted as indicating active pulmonary venous constriction induced by hypoxia. The pressure gradient from the pulmonary artery to the pulmonary arterial wedge decreased during hypoxia to 50 per cent of the control level in these dogs at the same time that the arterial wedge to left atrial mean pressure gradient rose strikingly; this was interpreted to indicate arteriolar dilatation. The mild rise in pulmonary artery pressure is explained on the basis of the increased postcapillary resistance (and increased pulmonary blood flow) despite the presumed arteriolar dilatation. The beneficial aspects of the pulmonary vascular changes induced by hypoxia in the pulmonary hemodynamics are discussed.

SUMARIO IN INTERLINGUA

Un studio del effecto de hypoxia super le vasculatura pulmonar esseva interprendite proque signos de constriction venose e de dissaturation oxygenic arterial habeva esseva
trovate in le pulmoni di un numero di cani post le induction experimental in illos de embolismo pulmonic miliar. Canes anesthesiate esseva fortiate a inspirar aere a basse admixtures de oxygeno (5 a 10%), e le alterationes del pression in le circuito pulnionic esseva registrate. Le plus frappante alteration occurrente in stato de hypoxia—in le animales que respondeva e que non disvelop-pava precoce insufficientia cardiac—esseva un augmento del cuneate pression pulmono-ar-terial e del pression pulmono-venose in le presentia de solmente un levissime augmento del pression sinistro-atrial. Isto pote esser interpretate como mdication del facto que un active constriction pulmono-venose es indu-cite per le hypoxia. Le gradiente de pression inter le arteria pulmonar e le cuneo pulmonoarterial se reduceva durante le hypoxia a 50 pro cento del valor de controlo, durante que le gradiente inter le cuneate pression arterial e le pression sinistro-atrial medie se augmentava frappantemente. Isto esser interpr-tate como indication de dilatation arteriolar. Le leve augmento del pression pulmonoarterial es explicate super le base del augmentate resistentia post-capillar e del augmentate fluxo de sanguine pulmonar) occur-rente in despecto del supposition de dilata- tion arteriolar. Es discuite le aspectos benefic de alterationes pulmo-vascular que es induciti per hypoxia in le hemodynamica pul-monar.

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