Autoregulation of blood flow by oxygen lack

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Ross, Joe M., Hilton M. Fairchild, Joe Weldy, and Arthur C. Guyton. Autoregulation of blood flow by oxygen lack. Am. J. Physiol. 202(1): 21-24. 1962.—The effect of hemoglobin oxygen saturation upon blood flow through the hind leg of the dog was studied by perfusing the femoral arteries of five normal dogs with blood, the oxygen saturation of which was varied between 100% and 0%, and by perfusing the femoral arteries of nine spinal animals with blood, the oxygen saturation of which was varied between 100% and 10%. The blood saturation was controlled in the following manner: The blood was obtained from the lower lobe of the left lung as it was respired with a mixture of nitrogen and oxygen. By varying the ratio of the mixture, the blood oxygen saturation could be controlled exactly. Decreasing the oxygen saturation stepwise caused a correlated increase in blood flow through the leg. The results have shown that blood flow in the nonspinal dogs increased to an average of 3.4 times the normal value as oxygen saturation fell from 100% to 0%. In the spinal dogs blood flow increased to an average of 3.1 times normal as oxygen saturation fell from 100% to 10%. These experiments demonstrate that the local tissues can autoregulate their blood flow to help maintain an adequate supply of oxygen.

Roy and Brown reported in 1879 that blood vessels supplying nutrients to the tissues contract or expand in accordance with the blood flow requirements of the respective tissues (1). These authors suggested that the quantity of oxygen (or perhaps other blood constituents) transported to the tissues might be the determinant of the degree of vascular dilatation. Since the time of Roy and Brown other investigators have repeatedly suggested that lack of oxygen could be sufficient stimulus by itself to cause autoregulation (1-4), but still others have postulated many additional causes of autoregulation of blood flow, including especially the accumulation of vasodilator metabolites (5-9), H substances (10), histamine (5), choline, or adenosine-like compounds (12).

Also, increased pH (13), excessive CO2 (14), and nervous stimulation (15) have been suggested.

Obviously, local autoregulation of blood flow to the tissues is important because of the necessity of maintaining a sufficient supply of nutrients to the tissues, and yet keeping blood flow low enough not to overtax the heart. The importance of autoregulation in a person whose sympathetic system has been completely removed is especially evident, for blood flow of the different local areas of the body is still controlled accurately in accordance with the needs of each tissue.

The purpose of the present studies has been to elucidate further the basic mechanism by which local blood flow is linked to each tissue's need for nutrients. These experiments support and extend the theory that oxygen lack is a cause of autoregulation of blood flow, and show that the nervous system is not of importance in vasodilatation occurring during oxygen lack.

METHODS

Fourteen mongrel dogs with an average weight of 10.3 kg, anesthetized with 30 mg/kg sodium pentobarbital and heparinized with 5 mg/kg heparin, were used in these experiments. Nine of the dogs were given total spinal anesthesia by intrathecal injection of 20 cc of 0.75% Metycaine. In these spinal dogs the blood pressure first fell to about 45 mm Hg but was brought back to normal by administering a continuous infusion, averaging 0.0052 mg/kg/min, of norepinephrine. In one spinal animal and in one nonspinal animal two sets of data were obtained from each dog, and both sets were incorporated into the results.

In all the experiments the effect on blood flow of changing the hemoglobin oxygen saturation was studied in one of the hind legs which was perfused through the femoral artery cannulated in the femoral trigone. The trachea was cannulated with a double lumen cuffed catheter that provided separate airways to the right and left lungs, then artificial respiration was begun. The right lung was respired with air to provide the animal's body with normally oxygenated blood, while the left lung was respired with varying ratios of oxygen and nitrogen to control the oxygen saturation.
of the blood used to perfuse the hind leg, as will be pointed out below. At this point, the spinal animals were given the spinal anesthesia. In both the spinal and nonspinal animals, the chest was opened between the left fourth and fifth ribs. The ribs were retracted, the left lung exposed, and the hilus of the upper lobe ligated and removed. The pulmonary vein of the lower lobe was cannulated as near to the heart as possible. Thus, all the blood from the remaining left lung was diverted from the normal channel of the circulation and used to perfuse the dog's hind leg, as discussed above.

Figure 1 shows a schematic diagram of the final experimental setup. Blood passed from the left pulmonary vein to a reservoir in which a constant volume of blood was maintained. This blood was then used to perfuse one of the hind legs of the same dog. Blood was pumped a) from the reservoir through a Starling's resistor, to control perfusion pressure at exactly 100 mm Hg; b) through a Ludwig type stromuhr to measure blood flow, and c) through a heating coil to maintain constant temperature (37°C) which was monitored just before the blood entered the femoral artery of the perfused limb. Blood could also be directed through a side arm into a cuvette of a Waters-Conerly type oximeter, which measured hemoglobin oxygen saturation.

The Pco₂ of the blood from the left lung was measured four or more times during the course of each experiment by using a Severinghaus Pco₂ meter, and it was always kept within the normal range of 35-45 mm Hg. This could be controlled by altering the degree of respiration of the left lung.

The right jugular vein was cannulated for blood transfusions in the nonspinal animals and additionally for norepinephrine infusion in the spinal animals. The left carotid artery was cannulated to monitor arterial pressure.

RESULTS

Relationship of hind leg blood flow to hemoglobin oxygen saturation. In all experiments, the left lung was respired initially with oxygen to obtain a control blood flow through the hind leg at 100% hemoglobin oxygen saturation. In 13 of the dogs, after control flow was established, the amount of nitrogen respiring the lungs was slowly increased while the oxygen was decreased, until finally only nitrogen was being used. The hemoglobin oxygen saturation gradually decreased from 100% to 0% in the five nonspinal animals and to an average of 10% in the spinal animals. Flow, hemoglobin oxygen saturation, and Pco₂ were measured 4-8 times during the change from pure oxygen to pure nitrogen. The flow in both the normal and the spinally anesthetized animals was found to increase steadily with the decrease in hemoglobin oxygen saturation, which effect is illustrated for a typical animal in Fig. 2. The Pco₂ remained essentially constant as pointed out above in the section on METHODS.

In one animal with spinal anesthesia the hemoglobin oxygen saturation was changed abruptly from 100% down to several different lower saturations, returning to 100% saturation between each successive determination. The results obtained by this procedure were almost identical with those obtained by the above method.

To summarize the results of 14 different experiments, the mean control blood flow at 100% hemoglobin oxygen saturation for five nonspinal dogs was 22.9 cc/min and for nine spinal dogs was 44.9 cc/min. In the nonspinal animals (Fig. 3) the blood flow increased to an average of 3.4 times normal as the saturation of the blood fell to 0%. In the spinal animals the flow increased to 3.1 times normal (Fig. 4) as the hemoglobin oxygen saturation decreased to 10%. As can be seen from Figs. 3 and 4, there was no significant difference between the flow change patterns in the spinal and nonspinal animals.

Experiments using mechanical deoxygenator. Six additional experiments (not included in the above data), using a mechanical deoxygenator system, gave almost identical results down to a hemoglobin oxygen saturation of about 30%. Hemolysis and other complications prevented use of the mechanical deoxygenator system.
AUTOREGULATION OF BLOOD FLOW

at lower levels of oxygen saturation and also made us distrust the results obtained by this method. For these reasons, we went to the pulmonary deoxygenator method reported in this paper.

Calculation of total oxygen carried by arterial blood to tissues. Changes in the amount of oxygen carried by the arterial blood to the tissues each minute can be calculated by multiplying the percent hemoglobin saturation by the blood flow. As an example, the curve shown in Fig. 5 was obtained from the data shown in Fig. 2. At a hemoglobin saturation of 90% the oxygen carried per minute in the arterial blood was 99% of the control value; at 60% saturation, it was 93% of the control value, etc. It can be seen, for instance, that even when the hemoglobin oxygen saturation was decreased to 30%, the amount of oxygen carried in the arterial blood each minute was still 65% of the control value.

The effectiveness of a control system can be depicted by the gain (or amplification) of the system. For instance, at a hemoglobin oxygen saturation of 60%, the oxygen carried to the leg would have been 60% of the control value if there had been no flow increase; actually, in the experiment illustrated in Fig. 5, the oxygen carried per minute was 93% of the control value. By dividing the initial degree of abnormality (40%) minus the final degree of abnormality (7%) by the final degree of abnormality (7%) a gain of about 5 is found \((40 - 7)/7 = 4\frac{3}{4}\). The gains at other hemoglobin oxygen saturations are shown on the graph in Fig. 5. Similar results were observed for the other experiments, the gains averaging about the same as those in this experiment but varying considerably at any single hemoglobin oxygen saturation level.

DISCUSSION

This study supports and extends previous studies by Crawford, Fairchild, and Guyton (2). Our present experiments showed that oxygen lack continues to increase the blood flow down to hemoglobin oxygen saturations as low as 5%, whereas in their experiments the oxygen saturation was carried only down to 30%. Furthermore, the deoxygenated blood used in their studies was obtained from the right atrium so that it obviously contained excess carbon dioxide as well as lacking oxygen, and there could also have been possible venous vasodilator substances in the blood. In the present experiments, the carbon dioxide was exactly controlled, and the blood was arterial blood rather than venous blood even though it was deoxygenated. Nevertheless, the results have been qualitatively and almost exactly quantitatively the same as those of the earlier studies.

Krogh found in rabbit ears that a decrease in oxygen saturation, along with decreased carbon dioxide, produced marked vasodilatation (4); Rothlin found that the tonus of isolated rings from mammalian arteries is a simple function of the oxygen tension of the Ringer's solution in which they are suspended (16). Jalavisto et al. found that the increase in blood flow after stimulation of the gastrocnemius muscle is roughly proportional to the oxygen deficit of the venous blood during the working period (3). These investigations all add support to the theory that oxygen lack can cause vascular dilatation.

Katz and Feinberg have shown that coronary blood flow automatically adjusts to keep the total oxygen carried by the coronary blood each minute constantly in step with the oxygen consumption (17). Others have
also found that blood flow through the heart is roughly proportional to the oxygen usage (18–21).

Still, additional investigators have reported that the blood flow to each local tissue area is proportional to the respective tissue's "rate of metabolism" (22, 23). Freeman and Zeller, for instance, found that the blood flow through the paw of a sympathectomized dog varied directly with the temperature of the bath in which the paw was immersed; therefore, they concluded that the circulation through regions without vasomotor tone is determined by an increase in the metabolism of the tissues (24). These results are compatible with the idea that oxygen lack could cause vasodilatation, for in each instance blood flow increased during increased metabolism and presumably increased oxygen consumption.

In the present experiments the blood flow patterns in spinal and nonspinal animals were not significantly different; therefore, it is probable that the oxygen lack vasodilator effect is entirely independent of nervous control. This concept was also supported by Lewis and Grant, who pointed out that local vasodilatation in response to occlusion of the vessels of the arm is independent of local nervous reflexes because it occurs equally as well when the nerves have completely degenerated (25). This would seem to dispel the belief that autoregulation is controlled by an axon reflex as suggested by Hilton (13).

Accumulation of carbon dioxide certainly was not the cause of the vasodilatation in the present experiments, because even at low oxygen saturations the carbon dioxide was kept within the normal range. Furthermore, Crawford, Fairchild, and Guyton (2) as well as McArdle et al. (26) found no significant or lasting increase in blood flow with an increase in carbon dioxide.

There are two mechanisms by which the lack of oxygen could cause vasodilatation: a) The cells surrounding the vessels could be in competition with the smooth muscle of the vessel walls for the oxygen. If the tissues should use most of the available oxygen, the vessels would dilate because the vascular muscles would have insufficient oxygen to maintain contraction. b) It is possible that oxygen lack could cause some vasodilator substance to be released from the tissues. For instance, ATP, ADP, and AMP have been shown to have vasodilator effects (27, 28); therefore, these substances could be released from the tissues in response to oxygen lack and could cause vasodilatation. However, the previous experiments by Crawford et al. (2) cast considerable doubt on all the theories involving vasodilator substances. In their experiments, mixed venous blood from the right heart always caused vasodilatation while the same blood after passage through the lungs caused immediate return of the vascular size to normal. If any vasodilator substance in the venous blood had been the cause of the vasodilatation, this substance would have had to be removed during its passage through the lungs. Though the lungs are known to remove serotonin, which is a vasoconstrictor substance, they have never been shown to remove any vasodilator substance. Therefore, there is much reason to believe that the increased blood flow observed in the present experiments resulted from simple lack of oxygen and not from the release of a vasodilator substance.

REFERENCES