THE REGULATION OF CIRCULATION

VI. THE EFFECTS OF SEVERE ANOXEMIA OF SHORT DURATION ON THE CARDIAC OUTPUT OF MORPHINIZED DOGS AND TRAINED UNNARCOTIZED DOGS

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In the preceding paper a study of the effects of anemia and hemorrhage on the output of the heart has been reported. Reduction of the hemoglobin concentration was found to be followed by an increase in cardiac output, the degree of increase being relative to the severity of the anemia, and to the rapidity with which it was produced. These findings suggested that the oxygen pressure in the capillaries might be an important factor in the regulation of the cardiac output. Accordingly studies have been undertaken with the object of determining whether deficient oxygenation of the blood, due to anoxic rather than anemic anoxemia, is associated with changes in the circulatory minute volume.

The problem of the cardiac response to deficiencies in the transport of oxygen is an interesting one and previous observations along this line have not been lacking.

Schneider and Truesdell (1) observed an increased pulse rate and increased pulse pressure but no change in the blood flow through the hand, in normal individuals in whom sudden and extreme anoxemia was produced by rebreathing. The same authors (2) reported an increased pulse rate and pulse pressure and decreased blood flow through the hand and peripheral capillaries when gradual severe anoxemia was produced by rebreathing and when constant moderate anoxemia was present. As a result of their investigations Schneider and Truesdell stated: “It is concluded that the circulatory changes in anoxemia do not serve as a means of compensating for a lack of oxygen, but that they may be interpreted as signals of distress.” Doi (3), using the Fick method, found no change in the cardiac output of urethanized cats when the percentage of oxygen in the inspired air was as low as 13.31 and the arterial blood 81 per cent saturated with oxygen.

Dreyer (4) made cardiometric studies on decerebrate cats and found an increased cardiac output after one to three hours of anoxemia, the arterial
blood being 50 to 80 per cent unsaturated. As a result of hemodynamic studies on dogs narcotized with morphine and chloretone, Sands and DeGraff (5) stated: "Increased systolic discharge, an increased rate of the heart, and a reduced peripheral resistance all combine during anoxemia to increase the minute flow of blood through the body." In studying progressive anoxemia these authors found that eventually a "circulatory crisis" occurred, after which the cardiac output was diminished.

These discrepancies are to be attributed to the fact that the methods used were indirect and the animals had been given narcotics and subjected to various operative procedures. Blalock (6) has shown that ether has a very marked effect on the cardiac output, and Marshall (7) found that urethane alters the response of the heart to changes in rate. In view of their findings, it is logical to believe that any observations on the cardiac output of anesthetized or narcotized animals cannot be regarded as entirely applicable to normals, unless checked by similar observations on unanesthetized trained animals. Marshall has demonstrated that such studies are feasible.

As the relationship of anoxemia to the minute output of the heart is a complicated problem, it has seemed advisable to carry out the study from several different points of view. In this paper the results of severe anoxemia of short duration are reported. In subsequent publications the effects of milder degrees of anoxemia of long and short duration will be presented, and the possible clinical application of the findings will be discussed.

Although there is no sharp dividing line between severe and mild anoxemia, in these studies we have arbitrarily classified an arterial saturation of less than 70 per cent as "severe" and have considered saturations of 70 to 90 per cent as "mild."

**Method.** Eight experiments including twenty-four determinations of cardiac output were carried out on morphinized dogs. These animals were given the drug—6 to 10 mgm. per kilo of body weight—approximately one and one-half hours before the start of the observations. Five experiments including thirteen determinations of cardiac output were carried out on trained unnarcotized dogs.

Initial control determinations were made in every instance, the method used being that described in the preceding paper. It was found advisable to make the blood oxygen determinations as soon as the blood was drawn, for some passing of oxygen from the oil into the blood occurs if the samples are allowed to stand.

As soon as the control determination of cardiac output had been completed the Benedict spirometer was filled with room air and the animal attached. The soda lime filter was left in situ and consequently the carbon dioxide was absorbed and the animal breathed an oxygen-nitrogen
mixture in which the percentage of the former gas was steadily decreasing. The duration of rebreathing was varied in different experiments according to the size of the animal and the degree of anoxemia desired. After seven to forty-five minutes of rebreathing the right and left ventricles were punctured simultaneously by two different observers. The blood samples were immediately analyzed for oxygen content and, in some instances, for carbon dioxide content.

The oxygen capacity was determined in most of the experiments, but in a few the control arterial blood was assumed to be 95 per cent saturated and the oxygen capacity calculated.

The oxygen consumption during rebreathing was calculated from the spirometer tracing, just as in the control periods. The minute ventilation was calculated from the same tracing, the rate of respirations being multiplied by the average depth of the respirations. The values obtained by this method are only approximately correct. No calculations of the minute ventilation were made for the morphinized dogs.

The pulse rate was counted immediately before blood samples were drawn.

Hydrogen ion determinations were made in several experiments, the method of Hastings and Sendroy (8) being used. In some experiments only one control determination and one determination during anoxemia were made. In other experiments a second control was made thirty to sixty minutes after the cessation of anoxemia. In several experiments anoxemia was again induced.

RESULTS. The dogs remained quiet during most of the observations. Two experiments were discarded because the animals struggled when blood samples were being drawn.

As morphine causes slowing of the heart and affects the breathing of dogs the changes in pulse rate and in ventilation are not considered entirely reliable in the dogs to which the drug had been given. The heart rate of the trained animals was slightly augmented during anoxemia—the average increase being about ten beats per minute. The changes in respiratory rate were variable and usually not striking. During anoxemia the respiratory depth was usually somewhat greater and the minute ventilation was increased in five of the six observations on trained dogs. As the changes in pH were slight and usually in the direction of increased alkalinity, these observations suggest that anoxemia may be of considerable importance in the regulation of the respiration, and are more nearly in accord with the views of Gesell as expressed in his recent review (9) than with other conceptions of respiratory control.

The changes in oxygen consumption are of some interest. Variations of less than 15 per cent are not to be ascribed to anoxemia as animals may vary to at least this degree in the course of one or two hours on the
table. In one experiment a rise of 40 per cent occurred in the oxygen consumption, the arterial blood being 50 per cent saturated. For this no explanation is offered. In general no significant change was noted in oxygen consumption when the arterial saturation was more than 50 per cent. When the arterial saturation was less than 40 per cent a definite diminution in oxygen consumption was found, the degree of diminution being roughly proportional to the severity of anoxemia.

In the control observations the arterial oxygen contents were between 12 and 20 volumes per cent and the arterial blood was 90 to 100 per cent saturated. The venous oxygen contents in the control observations were between 7 and 15 volumes per cent. The utilization of oxygen was not lower than 4.4 volumes per cent in any of the initial control determinations, and was between 5 and 7 volumes per cent in most instances.

The degree of diminution of the arterial oxygen content during the anoxicemic period was variable. The lowest value found was 0.63 volume per cent. This corresponded to an arterial saturation of only 2.9 per cent. In the same experiment the venous oxygen content was 0.02 volume per cent, which may be considered as zero since the mean variation of check determinations of blood oxygen content is, in our hands, about 0.1 volume per cent.

During anoxemia the utilization (A-V) was unchanged in one instance and was less than the control value in fifteen instances. The highest, lowest and average values found for the utilization during severe anoxemia were 5.3, 0.6 and 2.4 volumes per cent respectively.

The oxygen capacity was assumed to be constant in five experiments, but in the others was determined each time blood samples were drawn. The changes found in oxygen capacity were usually only slightly greater than the error of the method of analysis. (In one experiment a decrease of 3.5 volumes per cent was found. This may have been due to error as single determinations of oxygen capacity were considered sufficiently reliable, whereas duplicate analyses of arterial and venous oxygen content were always made.)

The carbon dioxide content of the blood was determined in eight experiments. During anoxemia an increase was found in two instances and a diminution in six instances. Although morphine may affect the CO₂ combining power of the blood, the changes in CO₂ content observed in these experiments were similar in the morphinized and in the trained animals and therefore cannot be attributed to the drug. In five of the experiments carried out on morphinized dogs hydrogen ion determinations were made. The control values fell within the limits (7.15 to 7.35) found as normal by Harrison, Wilson and Blalock (10) for dogs to which the drug had been given. During anoxemia the pH increased in five instances and decreased in one. The changes were never very striking, the maximum variation being pH 0.08.
These changes in CO₂ and pH during anoxemia are to be interpreted as indicating a condition of uncompensated acid deficit and correspond to Van Slyke's area "3" (11). Such changes are to be attributed to over ventilation. Koehler, Brunquist and Loevenhart (12) reported a similar slight alkalosis in dogs during the initial stages of anoxemia of long duration. Their animals later developed acidosis, but only after having been anoxemic for a period considerably longer than the duration of the experiments reported in this paper.

Fig. 1. The percentage change in cardiac output is plotted against the percentage of arterial unsaturation. In every instance the cardiac output during anoxemia is above the control—zero—line. In general the output is greater during severe than during mild anoxemia. No striking difference can be observed between the normal and the morphinized dogs.

In the control periods the minute cardiac output fell within the limits which have previously been found as normal for trained and morphinized dogs—100 to 210 cc. per kgm. per minute (7), (10). During anoxemia the output of the heart increased in every instance, but the degree of change was very variable in the different dogs as well as in different observations on the same animal. The maximum and minimum changes found in cardiac output were +539 per cent and +5 per cent respectively.

The degree of increase was, in general, more or less in proportion to the degree of anoxemia. This is shown in figure 1 in which the percentage
change in cardiac output is plotted against the degree of anoxemia, and in figure 2, in which the output per minute per kilogram of body weight is plotted against the degree of anoxemia.

The increase in cardiac output was chiefly due to an augmented stroke volume as the changes in pulse rate were relatively slight.

The cardiac output one to two hours after the end of the anoxemic period was less in every instance than that during rebreathing. In the seven experiments in which second control determinations were made the cardiac output was twice found to be greater and twice found to be less than that during the initial control period, and in the other three instances no change was found. The conclusion is drawn that severe anoxemia of short duration exerts no constant after effect on the function of the heart.

DISCUSSION. These experiments constitute the first studies of the effect of anoxemia on the total minute blood flow of unanesthetized, unnarcothetized animals. In view of the uniform results as contrasted to the conflicting findings of those who studied the blood flow through parts of the body only, or who have used anesthesized animals which had been
subjected to various surgical procedures, it appears justifiable to conclude that the output of the normal dog's heart is always increased when the arterial blood is less than 70 per cent saturated with oxygen.

It has been previously shown (10) that variations in H-ion concentration cause changes in cardiac output. The findings in the present observations can not be ascribed to acidosis, however, because the changes in H-ion concentration were usually in the direction of increased alkalinity, which tends to decrease the total blood flow. Furthermore the variations in pH occurring in the present observations were of smaller magnitude than those which were found to lead to alterations in the cardiac output.

Fig. 3. One hundred per cent hemoglobin is assumed to correspond to 20 volumes per cent oxygen capacity. The oxygen content of the blood is plotted against the oxygen pressure. The percentage saturation of the blood for any given oxygen pressure has been derived from Bohr's dissociation curve—40 mm. CO₂ pressure being assumed—and plotted above. The chart is schematic but represents the condition found in typical experiments. The object of the chart is to contrast the capillary oxygen pressure in anemia (50 per cent hemoglobin) and anoxemia (60 per cent arterial saturation). In anemia of this degree the “mean capillary oxygen pressure” (see text) is slightly decreased and the cardiac output is slightly increased. In anoxemia the changes in both functions are much greater.

The evidence indicates that the changes found in the latter are to be ascribed directly to anoxemia. In the previous paper on the effects of anemia and hemorrhage, the suggestion was made that the capillary oxygen pressure was probably an important factor in the regulation of the circulation. A comparison of the data from the two studies shows that anoxemia caused a very much greater change in cardiac output than did anemia of corresponding degree. This is entirely in accord with the hypothesis concerning the importance of capillary oxygen pressure in circulatory control. In severe anemia the pO₂ in venous blood is decreased
but the arterial oxygen pressure is not altered and consequently the change in mean capillary oxygen pressure is considerably less than in anoxemia in which reduction occurs in both venous and arterial pO₂. These conceptions are shown diagrammatically in figure 3.

These data concerning the qualitative and quantitative effect of anoxemia on cardiac output support the idea that capillary oxygen pressure plays an important rôle in the regulation of circulation, but such an hypothesis can not be regarded as proven until observations concerning the effect of anoxemia of lesser severity and longer duration have been made. Such studies are in progress at the present time.

It is of some interest to consider the mechanism whereby variations in oxygen pressure may conceivably alter the circulatory minute volume. Observations on acidosis (10) suggested that the increased cardiac output was probably dependent, in part at least, on capillary dilatation and diminished peripheral resistance. Krogh (13) found that oxygen lack produced dilatation of the capillaries of the frog’s tongue, and it is possible that such an action may play a rôle in increasing the cardiac output in anoxemia.

Another possibility is the existence, in addition to the vasomotor center, of a medullary circulatory center, analogous to the respiratory center, which effects the cardiac output through the nerves to the myocardium. Evidence for such a mechanism is lacking at present.

The third possibility is that changes are brought about by a direct myocardial action of the blood passing through the coronary vessels. Anrep and Bulatao (14) have shown that an increased coronary flow causes an increased cardiac output, while Hilton and Eichholtz (15) demonstrated that anoxemia increases the coronary flow. Present evidence indicates therefore that anoxemia increases cardiac output by a direct myocardial action. The question as to whether in the final analysis this effect is due to oxygen lack per se or to the presence of unoxidized acid metabolites remains unanswered.

The maximum increase in cardiac output observed in these experiments has been approximately 300 to 500 per cent, or an increase to fourfold and sixfold respectively. Ordinarily in healthy dogs the coefficient of utilization is 25 to 35 per cent of the total arterial oxygen content. If an animal is able to quintuple his cardiac output and can use all the reserve oxygen in the blood then the greatest possible oxygen intake should be fifteen to twenty times the resting oxygen consumption. Such a conclusion is substantiated by the observations of Hill and Lupton (16) who found that the maximum oxygen consumption of men during running was 3500 to 4000 cc. per minute, which is about fifteen times the resting oxygen consumption. From their findings these investigators calculated a maximum cardiac output during exercise of about 30 liters per minute.
for the normal male. As 5 liters per minute is, according to the investigations of Burwell and Robinson (17), approximately the average normal cardiac output of adult men, this represents a maximum increase of 500 per cent. This corresponds well with the maximum cardiac output which we have found for dogs with anoxemia, and indicates that findings in these animals can probably be applied with some accuracy to men.

Great increase in the minute output of the heart, with relatively little change in the pulse rate, necessarily postulates an increased cardiac diastolic volume, and Takeuchi (18) has shown that anoxemia causes such a change in the size of the heart.

In order to consider the application of these results to human physiology it is necessary to assume that anoxemia affects the hearts of man and dog in the same manner. The foregoing discussion has been based on such an assumption.

SUMMARY

Anoxemia has been produced by rebreathing, the CO₂ being absorbed. The effects of arterial oxygen saturations of 3 to 70 per cent on the cardiac output of morphinized and trained dogs have been studied by the Fick method. Anoxemia of severe degree (greater than 30 per cent unsaturation) causes the following changes:

1. Slight increase in pulse rate.
2. Increased minute ventilation.
3. Diminished oxygen consumption (when the arterial saturation is less than 50 per cent).
4. Uncompensated acid deficit (diminished CO₂ content and decreased H-ion concentration).
5. Increase of 5 to 500 per cent in minute cardiac output.

These findings support the hypothesis that capillary oxygen pressure is an important factor in the regulation of the circulatory minute volume.

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BIBLIOGRAPHY

(1) Schneider, E. C. and D. Truesdell. This Journal, 1924, lxxi, 90.
(2) Schneider, E. C. and D. Truesdell. This Journal, 1923, lxv, 379.
(3) Doi, Y. Journ. Physiol., 1922, lvi, 43.
(5) Sands, J. and R. C. DeGraff. This Journal, 1925, lxxiv, 416.
(6) Blalock, A. In press.
(13) Krogh, A. The anatomy and physiology of capillaries. New Haven, 1924, 133.