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THE RATIONALE OF OXYGEN THERAPY DURING FEVER THERAPY *

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THE physiological paradox of oxygen want in the presence of normal arterial oxygen saturation, adequate oxygen capacity, and a competent circulation is a phenomenon usually associated with the interference by drugs with either the ability of the hemoglobin to transport oxygen or the ability of the tissue to utilize the oxygen. Evidence will be presented to support the contention that a similar paradox exists as the result of induced hyperpyrexia.

In a limited number of clinics, the use of oxygen therapy during the period of induced fever has been instituted on the basis that the increase in metabolism coincident with the increase in body temperature requires a greater amount of oxygen than can be acquired from the respiration of air. In view of the fact that there is a 5½ to 7½ per cent increase in metabolism for every degree (Fahrenheit) of elevation in temperature (1), it has seemed logical to provide these individuals with oxygen in excess of that present in the atmosphere. Once instituted as a clinical practice, the beneficial clinical response obtained from the administration of oxygen therapy has resulted in its continued use.

Figure 1 is a graph representing the pulse rates of three unselected groups of individuals receiving artificial fever by means of the Burdick cabinet. The degree of fever and the length of treatment are the same in all three groups. One group of 45 patients was not given oxygen therapy during the treatment, another group of 25 patients received oxygen therapy only after the desired level of fever had been estab-

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lished, and the remaining group of 45 patients received oxygen therapy with or shortly after initiation of the fever therapy.

A striking difference is apparent in the pulse rates of the three groups. In the group receiving no oxygen therapy, the pulse rate climbed rapidly to a high level and continued to increase as the treat-

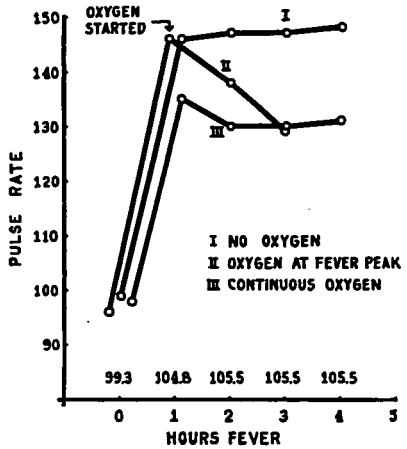

FIGURE 1.

ment progressed. In the group given oxygen therapy after the desired level of fever had been reached, the pulse rate climbed rapidly to the same level as in the first group but slowed after the oxygen was administered, and remained at the lower level during the course of the treatment. In the group given prophylactic oxygen therapy with or shortly after the initiation of fever, the pulse rate became elevated, but never reached the high level of the two previous groups, and it persisted at this relatively low level during the hyperthermia.

It was also observed that restlessness, mental confusion, and excitement were less frequent and less marked in the patients receiving oxygen therapy. Sedation by drugs was required less frequently and in smaller dosages. In the absence of oxygen therapy, treatment had to be discontinued in some patients because of either extreme tachycardia of poor quality or uncontrollable excitement. These same patients tolerated the treatments satisfactorily when oxygen therapy was administered.

The clinical findings just presented represent significant clinical evidence of oxygen want during fever therapy. Laboratory evidence

of the mechanism of this oxygen want and the manner in which oxygen therapy tends to correct the deranged physiology is now presented.

The 13 patients used in the laboratory investigation were, for the most part, receiving treatment for syphilis of the central nervous system or infectious arthritis. As far as could be determined, the patients possessed normal circulatory and respiratory mechanisms, were not receiving drug therapy, and had a normal hemoglobin and red cell count. There were no fluid restrictions before or during therapy, nor were excesses of fluid administered before or during therapy. The average level of fever was 105 F. and the average length of treatment four hours. The hyperthermia was accomplished by the use of the Burdick cabinet. Oxygen, when given, was administered by the oropharyngeal catheter method at a flow rate of 6–8 liters per minute. Twenty experimental studies were conducted on these patients. In 5 of these, the patients received no oxygen therapy during the treatment. In 7, oxygen therapy was given after the desired level of fever had been reached. In 5 others, oxygen therapy was given with or shortly after the initiation of fever. In the remaining 3, approximately 5 per cent carbon dioxide in air was administered after the desired level of fever had been reached.

Arterial and venous blood samples were drawn at three points in the procedure according to the method described by Adriani (2). The first pair was drawn before the fever was induced. The second pair was drawn when the desired level of fever was reached. The third pair was drawn approximately an hour after the second pair. The time between the first and second pair varied with the speed of induction of the fever, being on the average one and three-quarters hours. The blood was taken from the ulnar or radial artery for the arterial samples, and from the median vein in the antecubital space for the venous samples. No tourniquet was used during the drawing of the blood. The samples remained in the syringes which were kept on ice until the determinations were made. These determinations were made according to the method of Van Slyke and Neill (3) in the Van Slyke manometric apparatus. On each sample of blood, oxygen and carbon dioxide contents were determined and on one of each pair of samples, an oxygen capacity was run. pH determinations were made on each sample by means of the Beckman glass electrode potentiometer. With these data, the percentage of oxygen saturation of each sample was computed. The tension in mm. Hg of carbon dioxide in each sample was calculated from line charts devised by Van Slyke and Sendroy (4), since the pH and the carbon dioxide contents of whole blood were known. The tension in mm. Hg of oxygen in each sample was then calculated from the ordinary dissociation curves of hemoglobin, since the carbon dioxide tension and the percentage of saturation were known.

At the start of the investigation it was expected that, because of the increased demand for oxygen as a consequence of the elevated metabolic level, there would be an increased arterio-venous difference in oxygen

saturation. Some investigators have reported increased desaturation of the venous blood returning from the brain in the presence of fever (5). As can be seen, however, from the graph in figure 2, there was a marked decrease in the arterio-venous difference in the vessels selected for sampling even in the absence of oxygen therapy, as represented by the readings at the peak of fever. This is easily explained on the basis of acute and marked dilation of the arterioles and capillaries of the extremity due to the heat of the cabinet (6).

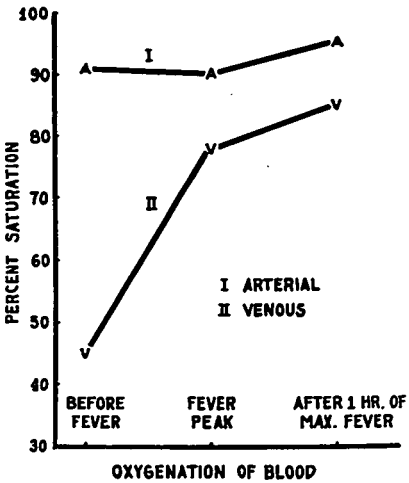

FIGURE 2.

In the absence of oxygen therapy the percentage of saturation decreased slightly, but the oxygen capacity increased, indicating no reduction in the supply of oxygen in the blood stream. The increase in saturation with the administration of oxygen therapy, as represented by the last readings on the graph, was significant, but slight, and seemed not enough to account for the clinical benefit previously indicated. In fact, this information seemed to contradict the clinical evidence of need for oxygen. It was apparent then that there was interference with either the ability of the hemoglobin to make this oxygen available to the tissue, or there was interference with the tissues' ability to utilize the oxygen.

Numerous investigators have reported an increase in pH associated with artificial fever therapy and the presence of an uncompensated alkalosis (7). The graph in figure 3, representing the changes in pH of arterial blood during the course of treatment, indicates that this is

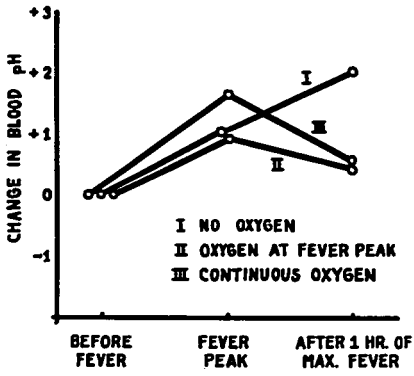

FIGURE 3.

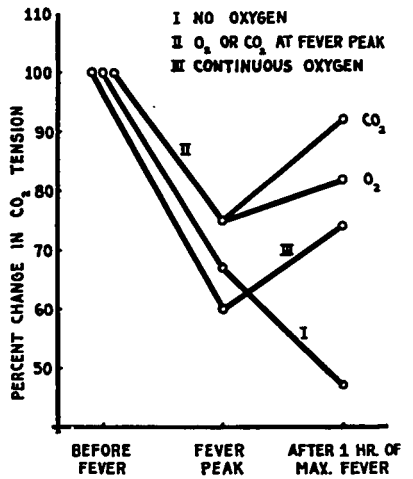

FIGURE 4.

also true of the patients used in this study. The elevation in pH occurs in all four groups. When no oxygen is given the pH continues to rise, whereas there is a tendency toward restoration of pre-fever values in those individuals given oxygen or carbon dioxide in air during the treatment.

The rise in pH is probably chiefly due to the loss of carbon dioxide through the hyperventilation accompanying the fever (7*a*). The patients in this study had an average drop of 15 per cent in the carbon dioxide content of their blood, and, as can be seen in figure 4, they have

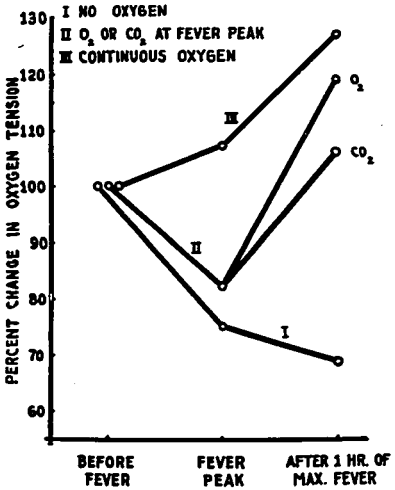

FIGURE 5.

reduced carbon dioxide tensions. This reduction in carbon dioxide tension progresses in those individuals receiving no oxygen therapy during treatment. In the groups given oxygen or carbon dioxide, the opposite is true.

It has been suggested (8) that alkalosis may so interfere with the liberation of oxygen by hemoglobin that insufficient oxygen is released to supply the needs of the tissues. The fundamental factor in the supply of oxygen to the tissues is the difference in tension between arterial blood and tissue. Any interference with the maintenance of a normal oxygen tension will seriously reduce the amount of oxygen available to the tissue. The data obtained in this study show that the alkalosis present during fever effects a significant reduction in the arterial oxygen tension even in the presence of a normal arterial oxygen saturation.

The graph in figure 5 represents percentage changes in the tension of oxygen in the arterial blood of the four groups. In the group receiving no oxygen therapy during treatment, the arterial tension falls as much as 25 per cent with the development of the desired level of fever, and continues to fall as the treatment progresses. In the group

receiving oxygen therapy after the desired level of fever had been reached, the arterial tension first falls 18 per cent, but with the administration of oxygen, it rises to a point 19 per cent above the original level. In the group receiving oxygen during the whole treatment, there is no drop in tension, but rather a continuous rise. In the group given approximately 5 per cent of carbon dioxide in air after the desired level of fever had been reached, the clinical responses obtained were apparently equally as beneficial as those obtained with oxygen. Although the oxygen tension returned to above the pre-fever level, the increase above that level was not as great as with the administration of oxygen. The drop in tension observed in the groups receiving no oxygen until the peak of fever is comparable to that obtained by ascending to an elevation of 17,500 feet.

DISCUSSION

The fall in arterial oxygen tension provides a reasonable explanation for the clinical evidence of oxygen want. The interference with the supply of oxygen to the tissues is probably due to the decreased rate of diffusion of oxygen accompanying the fall in arterial tension. Two factors, at least, operate to emphasize the deficiency in oxygenation of the tissue: one, the decreased rate of diffusion, and two, the increased demand for oxygen by the tissue because of the elevated metabolic level.

The administration of oxygen benefits the patient chiefly by physical methods. That is, an increase in the alveolar concentration increases the partial pressure, thereby increasing the saturation of the blood with a consequent increase in tension in spite of the elevated pH. The break in the vicious cycle of low tension, high pH, and tissue hypoxia may also be effected by the increased amount of oxygen in physical solution in the plasma, which oxygen is readily available to the tissue and not dependent on dissociation of hemoglobin.

Although carbon dioxide seemed equally effective in controlling the oxygen want in this type of case, oxygen is the method of choice. One cannot clinically estimate the concentration of carbon dioxide required. Too little carbon dioxide, to be effective, may then be given, but more hazardous would be the administration of too high a concentration with consequent narcotic or convulsant manifestations of toxic concentrations reaching hypoxic tissue. It may also be necessary to carry a higher than normal oxygen tension in the presence of the accelerated metabolic state. For this reason and the fact that excesses of oxygen can do no harm, oxygen is preferred to carbon dioxide as therapy.

SUMMARY

In the presence of hyperpyrexia there is a reduction in arterial oxygen tension. The administration of oxygen therapy prevents this re-

duction and may explain the clinical evidence of benefit from oxygen therapy.

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COMING EXAMINATIONS

The Part II (Oral) Examinations for certification by the American Board of Anesthesiology, Inc., will be held at the Ritz-Carlton Hotel, Atlantic City, New Jersey, June 6 and 7, 1942. Applications should be filed at the headquarters' office by March 7, 1942. If the Part I (Written) Examinations has been passed successfully, or if an application is on file at headquarters, it will not be necessary to make separate application for the oral examinations. Sec., Paul M. Wood, M.D., 745 Fifth Avenue, New York City.