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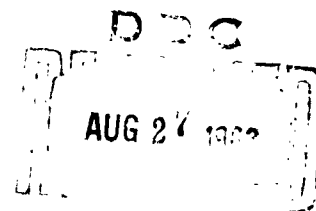
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PHYSIOLOGICAL ADAPTATION TO ENVIRONMENTAL CHANGES

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A B S T R A C T

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Dogs with varying hematocrit ratios were subjected to cardiovascular and respiratory insults designed to determine what cell to plasma ratio was most effective in carrying oxygen to the tissues of the body. It was found that dogs with initial hematocrit ratios of from 35 to 39 were able to carry more oxygen to their tissues after a massive hemorrhage than those dogs with hematocrit ratios outside this range. Furthermore, since the hematocrit ratio tends to increase during hemorrhage, the optimal value for the hematocrit ratio is 40. Normal dogs with this optimal value were subjected to high altitude studies and it was found that these dogs could survive and be active at altitudes lethal to animals with hematocrit ratios outside the optimal range. The optimal range is indicated by the dual nature of the hematocrit ratio as it affects both oxygen carrying capacity and blood viscosity. With low cell content, the viscosity is low but the oxygen carrying capacity is also low. As the cell content of the blood increases, so does both oxygen carrying capacity and viscosity. The inflection of the curve has been at 40 for all types of experiments of this nature. Acclimatized dogs show an optimum at 46, indicating that high altitude polycythemia is detrimental. A mathematical analysis, and a discussion of these facts are included.

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INTRODUCTION

The general object of this study was to determine what role the hematocrit ratio plays in acclimatization, specifically, if the increase in the hematocrit ratio that is known to occur with ascent to high altitudes is beneficial or detrimental and, if beneficial, to determine what changes in the cells or vascular system allow the optimal hematocrit to shift to the higher values. It has been recorded by this author, and also by Richardson and by Guyton, that the maximum amount of oxygen is transported to the tissues if the hematocrit ratio is 40. These experiments relate to oxygen transport in hemorrhagic shock (at low arterial pressure), to polycythemia (at normal arterial pressure), and to blood viscosity and venous return, respectively. Since the transport of oxygen has a cardiovascular component and a respiratory component, experiments designed to evaluate the role of each have been completed, although, certain phases were not completed because of grant termination.

Cardiovascular Component: The amount of oxygen normally taken from the blood is only about 20% of that available. To study the transport system, it is necessary that the animal be put under stress or a condition in which oxygen is flow limited. In these experiments, we bled the animal to a pressure of 30 mm Hg, a pressure at which none of the dogs receive their normal amount of oxygen. It is thus simple to determine which animals are receiving a greater percentage of their normal oxygen needs. Results of the experiments, presented in detail in a later section, show that the hematocrit ratio is a vital parameter in determining oxygen transport under stress conditions and markedly affect survival of the animals.

Respiratory Component: The question of whether the percentage of oxygen in air would act similarly to a reduced cardiac output in stressing the dog was resolved by placing dogs with various hematocrit ratios in a chamber and reducing the oxygen tension in the chamber. It was found that dogs with hematocrit ratios of approximately 40 could withstand much higher altitudes than dogs with lower hematocrits or dogs with higher hematocrits.

Practical Military Importance of Experiments to Date: If it were necessary to send troops to a region of high altitude, screening and selecting personnel with this optimal hematocrit would insure better performance of the troops.

CARDIOVASCULAR COMPONENT

Description of Apparatus: To register the continuous use of oxygen and to record the accumulative oxygen debt required a complex group of mechanical and electrical devices which may be subdivided as follows:

1. Flowmeter. It was necessary that a fixed quantity of air be available per minute and per kilogram dog weight for the dog to breathe. This was accomplished by a servo type flowmeter that operated as follows: A servo motor was connected to a variable valve and a rotameter type air flow meter placed in the air line. When the air flow was too great, the rotameter was not connected to a fixed terminal and the servo motor rotated to close the valve. As the valve began to close, the air flow decreased, the rotameter changed closing a set of contacts which caused the servo motor to open the valve. Thus, the air flow could be adjusted to any desired amount and automatically held at that value. A long tube 3/4 inch in diameter with one end exposed to the outside air and the other to a cannula was used to "trap" the air breathed by the dog. One side of the three way cannula was connected to the trachea of the animal and the remaining opening of the cannula connected to the flowmeter described above. A vacuum system was used to pull air through the tube, by the dog, and through the flowmeter.

2. Oxygen Analyzer. After the dog had breathed in and out of the flowing air, a sample of this air was fed through an oxygen analyzer to determine the percentage of oxygen remaining in the air. The oxygen analyzer was set to produce 0.5 volts output for each per cent of oxygen in air. Thus, if the air flowing by the dog (500 cc/kg.) had its oxygen percentage reduced by 1%, the dog was using 5 cc of oxygen per kilogram of dog weight, and the oxygen analyzer output would be reduced from 10.45 to 9.95 volts. (Assuming air at 20.9%--actually allowances were made in the flowmeter for the equivalent of 500 cc of air at

normal temperature and pressure and the oxygen percentage adjusted for water vapor).

3. Back EMF Circuit. The oxygen analyzer had a positive voltage output when any oxygen was present and it was desirable to establish a zero baseline. For this purpose, a mercury battery and potentiometer arrangement was placed in series with the output of the oxygen analyzer in such a way that any desired voltage could be used to counter the output of the analyzer--thus, the output beyond this circuit would be zero.

4. Servoamplifier. The output beyond the back EMF circuit was related to changes in oxygen consumption from a preestablished baseline. This signal was fed to a servo amplifier. The motor system of the servo amplifier, in addition to balancing the servoamplifier, rotated a potentiometer for recording the amount of deflection (proportional to the oxygen use change) and also rotated the ordinate arm of a mechanical ball and disc integrator.

5. Oxygen Use Recorder. The potentiometer mentioned in (4) was so connected that its rotation was recorded on a Varian model G-10, with the voltage from the potentiometer adjusted to give a definite calibration that was the same for all records and in terms of oxygen per kilogram of animal weight.

6. Ball and Disc Integrator. The connection of the signal or ordinate axis of the ball and disc integrator has already been mentioned. The time base axis was operated by a Bodine motor controlled by a constant speed electronic device. The output of the integrator was carried through a set of non-backlash reduction gears to a 10 turn potentiometer, and this potentiometer was also electrically wired to operate a Varian G-10 recorder. The output of the integrator was a continuous recording of the oxygen debt of the animal after the animal's oxygen usage had been decreased by hemorrhage.

Operation of Apparatus. After determination of parameters of barometric pressure, temperature, humidity, vapor pressure, etc., the machine was set for the proper amount of air flow at standard temperature and pressure, and the output of the oxygen

analyzer was set for 0.5 volts per percentage of oxygen in the air. The air flow was started and the machine set for zero on the integrator and ratemeter. The dog was attached. The change in oxygen percentage caused the ratemeter to change proportionally and to record the oxygen consumption of the dog. After this recording was made, the back EMF was again utilized to zero the integrator. The machine was then set to record any change in oxygen consumption. The arterial pressure of the dog was lowered to 30 mm Hg. The oxygen consumption decreased because of the inability of the cardiovascular system to transport sufficient oxygen; the ratemeter recorded the amount of decrease and the integrator showed the total amount of oxygen not received by the animal.

Results: Two hundred and ninety five experiments were run, and the effect of hematocrit, epinephrine, nor-epinephrine, dibenzylene, and previous conditioning were studied.

It was found that if the arterial blood pressure of dogs with hematocrit ratios of 29 or less was lowered to 30 mm Hg, they received only 52% of the amount of oxygen they normally use. This results from the inability of the cardiovascular system to transport adequate oxygen because if the cardiac output is multiplied times the arterial oxygen, this total amount of oxygen is insufficient to satisfy the dog's normal demand for oxygen. Dogs with hematocrit ratios of from 30 to 34 receive 64% of their normal oxygen need, and dogs with hematocrit ratios of from 35 to 39 received 74% of their normal need--this is the "optimal" group. Increasing the hematocrit ratio into the 40 to 45 range decreased the amount of oxygen available to 65% and a further increase above 46 of the hematocrit ratio decreased the oxygen available to 59%. Thus, on one end there are insufficient cells for oxygen transport and on the other end of the hematocrit scale the blood viscosity is too high. Peak transport is in the 35 to 39 range. It must be kept in mind that this is the initial hematocrit of the dog before the test, that the hematocrit tends to increase, and that other experiments have shown 40 to be the optimal hematocrit for oxygen transport. Thus, the peak above represents those animals that shift to the optimal range.

The total oxygen deficit incurred during 30 minutes of low arterial pressure was 71 cc/kg dog weight for those animals with hematocrits of 29 or less, 69 for those in 30-34 range, 66 in the optimal range of 35 to 39, 73 in the 40 to 45 range, and 81 in the over 46 range. Thus, the integrated oxygen deficit reflects the fact demonstrated above that animals in the optimal range for oxygen transport receive more oxygen and thus have a smaller incurred oxygen deficit after 30 minutes at low arterial pressure. Thus, taken another way, a person with an optimal hematocrit could withstand a greater hemorrhage than a person not in the optimal range, or could after a hemorrhage go longer before treatment than one in the non-optimal range. Dibenzylene and previous conditioning increased the oxygen transport at a given low pressure. Epinephrine and nor-epinephrine decreased oxygen transport at a given low arterial pressure.

Respiratory Component. A device to simulate the low oxygen content of air at high altitudes was constructed. This device consists of an enclosure made of plywood and sealed with mylar for the sides and bottom, and expanded metal and mylar for the top. The dimensions of the box are 6 ft. wide, 6.5 ft. long, and 24 inches high. The top was especially made for observation of the animals. Control of the internal atmospheres was accomplished by placing dehumidifiers in the air flow system, an air conditioner in the side of the box, a carbon dioxide removal system in the air flow, and an oxygen analyzer system for controlling oxygen percentage. Air from the box was removed via a tube by a Devilbiss pump. The output of the pump went to a pressure valve and if the pressure was high enough, through the pressure valve and back to the box through a second tube. The air flow of the pump was rapid to insure a quick response time. Also, from the output of the pump and before the constant pressure valve, a sample of air was filtered through a Hoke filter and was carried to a gas control panel. From this panel, one had a choice of pure nitrogen for zero calibration, normal air for span calibration, and the sample of air from the box. After the oxygen analyzer had been calibrated, the sample of box air was fed to it for analysis. A large meter recorded the percentage

of atmospheric oxygen in the box air. The meter also had mercury switch controls, and when properly set caused either nitrogen or room air to flow into the box to regulate the oxygen percentage.

Dogs with varying hematocrit ratios, obtained by natural selection, hemorrhage, or transfusion, were placed in the box and carried to a given oxygen content consistent with that at the chosen altitude. The condition of the dog was studied as a function of the hematocrit ratio.

Results: Fifty one dogs were placed in the simulation chamber in groups ranging from 5 to 12. Previously, their hematocrit ratio had been determined. Some dogs were given phenylhydrazine hydrochloride several days previously to lower their hematocrit ratio. After the dogs were inside the chamber, the door and slots were closed and nitrogen gas was allowed to flow into the chamber at such a rate that a simulated altitude of 40,000 feet was reached within approximately one hour. The dehumidifiers and air conditioner apparatus served to keep the gas mixed. After the altitude was reached, all remaining openings in the box were closed, and the gas mixture controlled by the automatic apparatus previously mentioned; the dogs were kept at this altitude for six hours.

Dogs with hematocrit ratios below 24 were usually dead before the simulated altitude of 40,000 feet was reached. Dogs with hematocrit ratios above 30 usually survived although some deaths occurred; the range of survival was from 30 to 65. No deaths occurred in the ranges 37 to 54. Dogs having hematocrit ratios above 66 died, usually before the 40,000 feet altitude was reached. It was also obvious that those dogs in the range 35 to 45 were able to tolerate the high altitude far better than those who survived but were just outside this range. Many of the dogs in the "optimal" range walked out of the box after the experiment was over; the dogs in the fringe area had to be carried out.

A second group of 35 dogs were carried to a simulated altitude of 50,000 feet. In this group, there were no survivors with hematocrit ratios below 36 or above 46, there being one survivor at each of these hematocrit levels and

several dogs with this range of hematocrit died. Two dogs with hematocrit ratios of 40 and 41 not only survived, but were actively walking around the box during the experiment whereas the fringe area survivors were unconscious. One dog with a hematocrit ratio of 41 died.

ACCLIMATIZED ANIMALS

At 50,000 ft. altitude, only animals possessing hematocrits of from 45 to 47 survived for the entire six hour period. Animals on either side of this range survived, without exception, less than one hour. These data indicate a rather critical range for survival of the acclimatized animal at 50,000 ft.

The hematocrits of the animals showed an average increase of 39% during the 120 day acclimatization period. An average decrease of 6% was recorded in the mean corpuscular hemoglobin, showing that the hematocrit had increased faster than did the hemoglobin.

MATHEMATICAL ANALYSIS

To mathematically analyze a biological function, it is necessary to derive formulae for the functions to be analyzed. Fortunately, the relationship of oxygen content to hematocrit ratio is linear and the equation can be determined as $O_2 = m H$, where m is the slope of the line (and contains the values of mean corpuscular hemoglobin, hemoglobin saturation, etc.) and H is the hematocrit. This equation contains no constant factor since plasma has such little oxygen that it may be neglected. A second bit of luck was the finding from our own data, and correlated with published work of Guyton, Richardson, and a replot of that of Whittaker and Winton, that the relation of blood flow to hematocrit is also linear as long as the oxygen present is adequate; in the dog at normal pressure adequate oxygenation occurs with hematocrits ranging from about 15 to 80. Extrapolation to 0 and 100 is made on the assumption that these are the flows that would occur before anoxia causes autoregulation. Thus, this relationship of blood flow to hematocrit may be expressed as $BF = F - kH$, where BF is the blood flow, F the flow of plasma (zero hematocrit blood) in the system, k the

slope of the flow-hematocrit curve, and H the hematocrit. To obtain the oxygen transport curve, the oxygen content per unit volume is multiplied times the volume flow, and the expression $O_t = mH (F - kH)$ is the result. To obtain the optimal hematocrit at which oxygen transport is a maximum, the above equation is differentiated and $H_{max} = F/2k$. In checking this, we obtained a value of 200 for F and 2.5 for k from the work of Guyton, thus $200/5 = 40$, the same value we obtain experimentally. Since the value k is the slope of the flow hematocrit curve, it is equal to f/H_1 , where F and H_1 are the y and x intercepts respectively, thus the value F/k is equal to H_1 , and the expression for the optimal hematocrit becomes $H_{max} = H_1/2$. From the work of Richardson, the zero flow curve in the polycythemic animal occurs at the hematocrit of 80, thus our optimal is again 40. In the acclimatized animal, the optimal hematocrit was 46. The only possible variables are m, F, and k. We found that m had actually decreased somewhat, because in our studies and in the literature it is shown that the hematocrit increases faster than hemoglobin in acclimatizing animals. The value of F and k are related, thus acclimatization is accompanied by either an increase in the number of capillaries functioning or to an increase in the size of those functioning (vasodilation), both of which are well documented in the literature.

By use of the normal equation for blood flow $F = Pd^4/lv$, where P is pressure, d is vessel diameter, L is vessel length, and v viscosity, we can equate this to our flow equation and obtain an expression for blood viscosity which is $v = v_p / 1 - H/H_1$, where v_p is the viscosity of plasma. Thus, at optimal hematocrit, the value of H is 1/2 that of H_1 and for optimal oxygen transport, the viscosity is $v_p/0.5$. or approximately 3 since the most usual value given for plasma viscosity is 1.5.

DISCUSSION

It has always been inherently believed that within wide limits the higher the red cell content the better the oxygen transport. This belief is not correct. By use of the Differential Calculus and by experimentation we have found that optimal oxygen transport occurs is the hematocrit ratio is 40 in normal dogs or

46 in acclimatized dogs. This importance may be divided into its military or "normal person" significance, and into its medical significance. Military Significance: Kolmer's Approved Laboratory Technique lists the normal hematocrit level for men as 41 to 52, other books have a wider variation, 30 to 55. It is not known what the Army's normal range is or whether they measure hematocrit at all-using hemoglobin measurements instead. Thus, it is obvious that in a normal group of people a wide range of hematocrit is present. Yet, when one calculates the reserve oxygen transport capacity of these individuals, those with hematocrits near the 40 mark will have the most, and may be expected to respond better in conditions of extreme stress than their normal colleagues with different though normal hematocrits. Field experiments involving work performance of soldiers at high altitudes as a function of their hematocrit should be carried out.

The second significant figure, the acclimatized optimal hematocrit of 46, shows that the response usually shown by the hemopoetic system to high altitudes is pathological and measures should be taken to control this response, although nothing short of bleeding is known now. It might be added that further studies are needed for although the mean cell hemoglobin concentration was lower in the acclimatized dogs than in the normal, this factor might change with longer periods of acclimatization. This factor does not appear in the formula for the optimal hematocrit but does appear in the formula for overall oxygen transport. Additional research is needed to determine what effect over and beyond that of change in the optimal hematocrit occurs.

Medical significance: Polycythemia is the natural accompaniment of certain types of congenital heart disease. The data shown here shows that this also is a pathological reaction (over stimulation) that is detrimental to the patient. Of special significance is the fact that in premature infants suffering from lung diseases, a great increase in their oxygen use could be accomplished by blood exchange to bring their hematocrits to 40 instead of the 50 to 60 or higher values they have at birth. This "optimization" of the vascular system has worked in every type of experiment we have tried to date and may be presumed to work in others situations.