CROWELL, JACK W., AND ELVIN E. SMITH. Oxygen deficit and irreversible hemorrhagic shock. Am. J. Physiol. 206(2): 315–316, 1964.—A device was constructed to record continually the oxygen consumption of a dog and to summate as the oxygen deficit the difference between normal oxygen use and oxygen use during hypotension. Dogs were subjected to hypotension of 30 mm Hg and various oxygen deficits were allowed to accumulate. It was found that oxygen deficits of 100 mg/kg or less were not lethal. Oxygen deficits of 120 ml/kg produced an LD50, and oxygen deficits of 140 ml/kg or greater were invariably fatal. Digitalization was beneficial to the dogs. Dibenzylene and conditioning of the animals to periods of hypotension proved to be of no value when the animals were subjected to a definite oxygen deficit equal to that in control animals. Neither epinephrine nor norepinephrine changed the mortality rate for a given oxygen deficit.

quantitative hypoxia oxygen usage during hypotension oxygen deficit and mortality rate in dogs drugs and susceptibility to shock

IRREVERSIBLE HEMORRHAGIC SHOCK can be produced by a wide variety of parametric variations in bleeding volume or arterial pressure levels. Yet, despite rigid criteria the results of such experiments vary considerably, and uniformity from group to group is rare. In fact, a survey of the literature shows that the same type of experiment performed in various laboratories yields different results; variations for seasonal, thermal, and unknown factors also occur (6).

If irreversibility in hemorrhagic shock has a single cause, one possible explanation for this diversity of results is that the actual parameter which must be altered quantitatively to produce irreversibility is not altered in a consistent pattern by the different processes of hemorrhage. It has often been shown that following severe hemorrhage an animal uses less oxygen than he normally uses, but lowering the arterial pressure to some given value does not produce a consistent degree of hypoxia from one animal to another. It seemed possible, therefore, that if one would measure the total oxygen deficit (4) this might be a better criterion for the induction of irreversible shock in animals than are the different hypotensive methods based on time or other factors.

MATERIALS AND METHODS

First, the normal rate of oxygen usage was determined continuously, using the Guyton continuous oxygen usage recorder (3); following hemorrhage the rate of oxygen usage was again determined continuously. Then, the integral of the difference between the rates of oxygen usage was automatically calculated to give the total oxygen deficit.

Figure 1 shows a block diagram of the instrument used to record continually the oxygen deficit. For clarification, it will be described under its various subunits.

Airflow meter. Air was pulled through a long tube by a vacuum and through an airflow meter which could be set at any airflow desired; the amount of air going through the airflow meter was the equivalent of 500 ml/kg dog wt min at standard conditions. The animal, breathing through an endotracheal tube attached to a side arm, removed some of the oxygen from the normal room air flowing in the tube. If it removed 1 ml oxygen/100 ml airflow, the oxygen use of the dog would be 5 ml/kg wt min.

Oxygen analyzer. A Beckman oxygen analyzer was used to determine the percentage of oxygen remaining in the air.

Back emf circuit. The oxygen analyzer has a voltage output proportional to the amount of oxygen in the air flowing through it. Since we wanted a zero signal at various times, an electronic circuit in which voltage reverses to that of the oxygen analyzer was placed in the circuit. Thus, the instrument could be set for zero output with normal air flowing through the tube or could be set for zero output with normal oxygen usage by the dog.

Servoamplifier. The signal passing through the back emf circuit was fed to a servoamplifier. The motor of this amplifier was used to change the y axis of a ball and disc integrator and also to move a potentiometer which measured the amount of deflection of the motor. This latter reading was used to record the change in rate of oxygen usage or the oxygen deficit rate. For example, let us assume that the dog had been using 5 ml/kg min of oxygen normally, and this value was used as a zero

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DEFLECTION MEASURING CIRCUIT

SERVO AMPLIFIER (Deficit Rate)

Ball & Disc INTEGRATOR

INTEGRATOR POTENTIOMETER

OXYGEN ANALYZER

FIG. 1. Block diagram showing the various subunits of the continuous recording oxygen deficit analyzer.

base line; if, after hemorrhage, the dog was consuming only 4 ml/kg min of oxygen the deflection measuring circuit would show a deficit rate of 1 ml/kg min.

Ball and disc integrator. The ball and disc integrator had its y axis changed by the servoamplifier motor, and the change was proportional to the difference between the normal oxygen usage and oxygen usage after hemorrhage; this value is the oxygen deficit rate. A constant speed motor was used as a time base for the ball and disc integrator. The output of the integrator was transferred by mechanical means to a ten-turn potentiometer which could, because of its gear ratio, operate for many hours before reaching one end of the potentiometer. This potentiometer had attached a measuring circuit, and this measuring circuit fed a signal to a servorecorder which recorded continually the level of the oxygen deficit.

Method of Operation

After the machinery was warm and stable, with no dog attached to the airflow, the back emf circuit was set for zero signal output from the oxygen usage analyzer. The deficit rate servorecorder was set for 0 deflection, and the oxygen deficit recorder was, of course, showing no change. The dog, anesthetized with 30 mg/kg sodium pentobarbital, was connected to the air tube, and the amount of oxygen flowing through the analyzer correspondingly decreased; a signal proportional to this change was fed to the servoamplifier and through it to the deficit rate servomotor. After the rate of oxygen usage became stable, the back emf circuit was again used to zero the signal to the servoamplifier; the deficit rate servorecorder now showed zero deflection, and the oxygen deficit servorecorder showed no change. The dog was then bled; the rate of oxygen usage by the dog decreased, and the signal to the servoamplifier caused the deficit rate servorecorder to deflect proportional to this difference between present and prior oxygen usage. Simultaneously, the total oxygen deficit was recorded by the integrator system.

The entire system was calibrated before each experiment with appropriate mixtures of nitrogen and air. The dogs were bled until their arterial pressure was 30 mm Hg and they were kept at this hypotensive level until the desired oxygen deficit was attained, whereupon all blood was returned to the animal. A heat lamp was used to keep the animal warm; measurement of the temperature of animals in similar experiments rarely show more than 1 C change in body temperature.

Figure 2 shows a typical experiment. The machine was first zeroed for normal air. Then, the dog was connected to the system and his oxygen usage recorded as 6.5 ml/kg min. The back emf system was then used again to zero the device. At zero time the arterial pressure, indicated by the dashed line, was lowered to 30 mm Hg and the oxygen deficit recording was begun. The rate of oxygen usage temporarily increased, which appeared to result from temporary hyperventilation of the animal. As the arterial pressure fell, the oxygen consumption decreased. In this experiment, the rate of oxygen usage fell from a control value of 6.5 ml/kg min to 2.5 ml/kg min following hemorrhage; thus, the deficit rate was 4 ml/kg min. The oxygen deficit recorder began to show an increase in the oxygen deficit. The rate of oxygen usage of this particular animal increased only a small amount during the experiment. When the oxygen deficit increased to 120 ml oxygen/kg wt. of the animal, the animal's blood was returned; the rate of oxygen usage increased immediately and drastically from its deficit rate of approximately 4 to a positive rate of 7 ml/kg min above the control value (6.5 ml/kg min). Thus, the peak oxygen usage in this case reached 13.5 ml/kg min. The rate of oxygen usage quickly returned to normal, and it can be noted that only a small percentage of the oxygen deficit was repaid. This animal survived.

Oxygen Deficit and Survival

One hundred dogs were subjected to various oxygen deficits and the number of animals surviving in each group was recorded. The continuous line of Fig. 3 shows the results with normal animals and the dashed line...

![Figure 2](https://example.com/figure2.png)
OXYGEN DEFICIT AND SHOCK

Fig. 3. The solid line on this graph shows the survival rate for control animals at various oxygen deficits and the dashed line shows the survival rate for digitalized animals. One hundred and fifty dogs are represented and the number of dogs used to determine each point is indicated by a number adjacent to that point.

Repeatability of Experiments and Effect of Various Drugs and Procedures

Figure 4 shows under the heading “control 1” the LD₅₀ of 17 normal dogs from the previous experiments. A second group of 10 dogs “control 2” were subjected to this same oxygen deficit of 120 ml/kg, and their percentage survival was not significantly different from that of the first control group. Another group of 11 dogs was given Dibenzyline 1 mg/kg 8 hr before the experiment and then subjected to an oxygen deficit of 120 ml/kg. Again the per cent survival of the animals did not differ significantly from that of the controls. Epinephrine and norepinephrine drips during hypotension in 20 dogs did not significantly change the lethality of this LD₅₀ oxygen deficit. A third control group of 15 dogs did not show any significant difference in mortality rate from previous control groups. A group of 11 dogs was subjected to a sublethal oxygen deficit of 80 ml/kg and two days later subjected to an oxygen deficit of 120 ml/kg. Their mortality rate was not different from that of normal animals. Two days following this experiment the five survivors of the conditioned series were subjected to an LD₁₀₀ oxygen deficit and, despite double conditioning, none of these animals survived. Figure 5 shows a possible explanation of these effects. The line is a mathematical drawing of all points representing an oxygen deficit of 120 ml/kg. Control dogs showed an average deficit rate of about 2.7 and required approximately 45 min to develop this oxygen deficit. Giving the dogs epinephrine increased the deficit rate slightly and shortened the time. Conditioning and Dibenzyline caused a decreased deficit rate of the animals at 30 mm Hg arterial pressure and, therefore, a longer time was required for these animals to develop the LD₅₀ oxygen deficit.

DISCUSSION

For an experimental technique to be valid it is necessary that the stimulus be quantitatively constant from animal to animal (6). Certainly hypoxia can be produced by bleeding an animal. However, removing a certain quantity of blood or lowering the animal’s arterial pressure to some given value does not produce the same degree of hypoxia in one animal as in another (2). Thus, when one lowers the pressure of an animal to 30 mm Hg, he does produce hypoxia, but there is no way of knowing how much unless it is measured. Unless the stimulus parameter is constant, the influence of drugs or other procedures may alter the stimulus instead of the properties of the system.

It must be pointed out that our experiments are not different from those we have previously used or those used by many investigators. We removed the animal’s blood into a reservoir, and this reservoir was so elevated.
that the animal's arterial pressure was 30 mm Hg. However, we did not measure, as a parameter of shock, the time that the animal was at low pressure; instead, we measured the oxygen deficit. We found in our experiments that the time required for an animal to produce a given oxygen deficit varied tremendously. For example, if a dog's normal oxygen consumption was 6 ml/kg, the minimum time required to produce an oxygen debt of 120 ml/kg, even if the animal used no oxygen whatever, would be 20 min. Obviously, no dog had this rate. The dogs during hypotension actually showed very different percentages of their previous oxygen usage, and the tremendous variability from one animal to another was quite sufficient to explain why some animals can survive a longer period of hypotension than others. It would appear from the present experiments that measuring the oxygen deficit may be a way of producing quantitative information in the field of shock.

Many drugs and methods have been suggested as changing the susceptibility of an animal to shock. Among those that are supposed to increase the animal's susceptibility to shock are epinephrine and norepinephrine (7). We found that if the experiment is based on time alone, one can show that catecholamines are detrimental. Dibenzyline (1, 5, 8) and conditioning to hypotension have been suggested for preventing hemorrhagic shock. We found in our experiments that they do increase the time required for the animal to develop irreversible shock. If the total oxygen deficit required to cause death was used as a criterion, none of these had any effect.

Beyond the idea of producing quantitative hypoxia, the possibility exists that some other factor is also produced quantitatively. It is not difficult to imagine that a quantitative lack of oxygen would cause a quantitative amount of anaerobic metabolism, resulting in the production of a quantitative amount of lactic acid, for example, or a quantitative decrease in adenosine triphosphate, or its conversion to some other adenosine compound. Furthermore, there are undoubtedly many other reactions that occur quantitatively in response to a quantitative oxygen deficit. Thus, this type of experiment may have a meaning far beyond that of allowing us to produce reproducible degrees of shock.

REFERENCES