Dispersion Oxygenation for Effecting Survival of Dogs Breathing Pure Nitrogen for Prolonged Periods.*† (17873)

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(Introduced by M. B. Visscher)

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It has been a long endeavor of physiologists and clinicians to find satisfactory methods for temporarily replacing a failing circulation or respiration by artificial means outside the body. All previous efforts have been attempts to simulate the actual conditions encountered in the lung, namely spreading venous blood in thin layers over very large surfaces and exposing the blood to oxygen (1-13). With a new type of blood oxygenator, using the principle of gas dispersion for creation of the large surface contact(14), it has been possible to oxygenate blood at a rate sufficient to maintain life in dogs during acute periods of nitrogen breathing extending to 99 minutes. The present report consists of an extension of these experiments in which complete recovery of the animal is used as the criterion of successful oxygenation. In all cases, blood was pumped from the inferior *vena cava* of the animal, to the oxygenator, and back through the jugular vein to the superior *vena cava* of the animal. It was thought that this simple procedure, free from extensive surgical manipulation, and under the conditions of nitrogen inhalation, would offer a clear-cut test of the efficiency of the apparatus. By using survival of the animal as the criterion of the successful experiment, one could determine whether there were any signs of permanent damage to the brain, or other vital organs, as a result of these unusual experimental conditions.

While the apparatus has been modified only slightly since the previous experiments (14), it seems advisable to elaborate somewhat on the principle of the oxygenator itself. Fig. 1, which is largely self-explanatory, is a schematic representation of the conditions in the instrument. It should be pointed out that "foam", as usually defined (15), is not produced. The term "defoaming" is loosely used merely to indicate that excess

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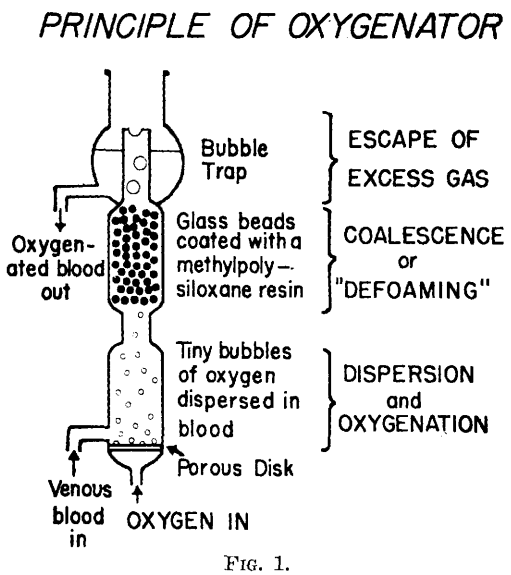

FIG. 1.

gas is removed from the liquid phase. The glass beads should be thoroughly cleaned after about 3 hours use and recoated by stirring the beads with a generous amount of the antifoaming agent. The apparatus was easily sterilized by pumping Dakin's solution and rinsing with sterile saline. Morphine-atropine sedation was used with 1% procaine as a local anesthetic. Paritol (30 mg/kg) was used as an anticoagulant; protamine (about 2 mg/kg) was used to counteract the anticoagulant. Nitrogen was administered from a spirometer and flutter valve system, as previously, through a funnel equipped with a tightly fitting dental dam cuff that extended over the shaved neck of the dog. Arterial pressure, respiratory rate, and electro-cardiac potentials were recorded during the experiments. Blood flow was measured with a rotameter‡, pH with a Beckman Model G meter, and oxygenation of the blood checked by a photoelectric oximeter or Van Slyke determinations(16) as needed. A very satisfactory pump, having a capacity of about 700 ml per minute, and constructed almost

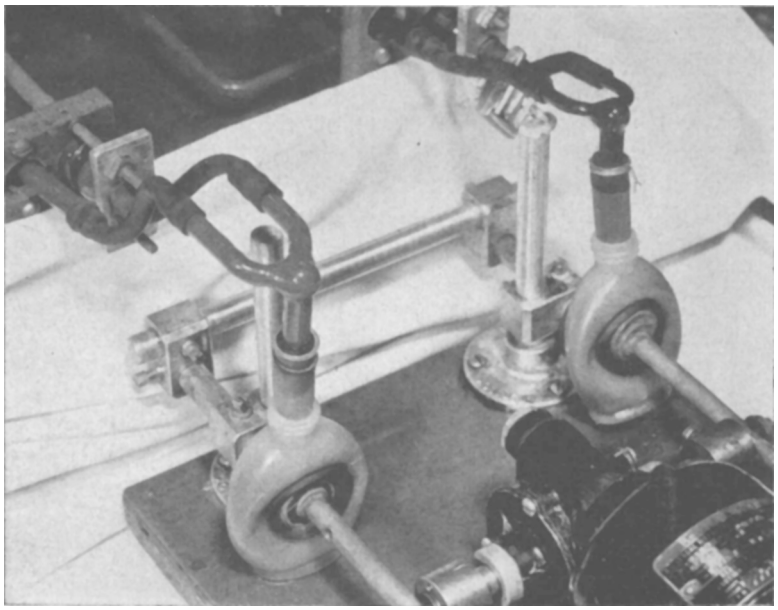

FIG. 2.
Pump constructed of plastic bottles.

‡ The rotameter was not calibrated for each experiment. Therefore, the flow rates given may be assumed to be accurate to only about ±15%. The rotameter provided an extremely valuable and convenient method of making necessary adjustments to obtain maximal or uniform flow during a given experiment, as well as providing absolute flow rates within this limit of error. There still appears to be a disagreement(17,18) as to the method of calibration of rotameters.

TABLE I.
Summary of Experimental Data.

Wt, kg	Mean blood flow, ml/min.	Mean blood flow, per kg ml/min./kg	Duration of breathing N_2 min.	Survival	Cause of death
14.4	600	42	26	+	—
9.1	350	38	60	2 days	Pneumonia
7.0	550	79	25	+	—
7.0	325	46	10	+	—
16.3	300	18	43	10 hr	Pulm. edema
15.8	275	17	61	12 hr	" "
7.7	400	52	60	+	—

entirely of glass and polyethylene, shown in Fig. 2, was used to circulate the blood. It consists of 2 elliptical polyethylene bottles, which were alternately compressed and extended by 2 rods coupled to an eccentric mounted on the shaft of a gear reduction motor (Robbins and Meyers, Springfield, Ohio, 5000 r.p.m., 15-1 gear reduction, 1/20 HP) controlled with a variable transformer. Such a pump is capable of producing negative as well as positive pressures and is rugged enough to function for extended periods of pumping. The pump shown has operated for a total of over 400 hours, using the original set of plastic bottles. Adequate quantities of venous blood can be withdrawn from the inferior *vena cava* by inserting a polyethylene catheter through a femoral vein and placing the tip of the catheter close to the great cardiac vein. This can be accomplished without fluoroscopic guidance by measuring the approximate distance from the femoral incision to the location of the right auricle. The catheter has numerous longitudinal slits for a distance of 6 to 8 cm from the tip to permit the withdrawal of most of the blood flowing along its length. By starting the circulation and oxygenation in the extracorporeal circuit about 5 minutes before the inhalation of pure nitrogen, the respiratory and circulatory signs of acute anoxic anoxia were prevented. When a satisfactory blood flow is maintained, the animals remain conscious throughout the period of nitrogen inhalation, lift their heads if stimulated and retain ocular and bulbar reflexes. The electro-cardiograms which were taken before and during nitrogen inhalation for periods as long as 90 minutes failed to show any signs of general cardiac anoxia.

The present series of experiments (Table I) lends itself to an evaluation of the *minimum* blood flow necessary for the survival of dogs, weighing between 7 and 16.3 kg, and breathing pure nitrogen for periods ranging from 10 to 61 minutes. The 2 large animals, Nos. 74 and 75, received a flow of only about 20 ml of oxygenated blood per kg weight per minute, and died 10 to 12 hours after the experiments, in deep coma. Dog No. 52, weighing 9.1 kg and receiving a blood flow of about 40 ml/kg/min seems to be on the border line since the animal stood up, walked around and reacted to visual and auditory stimuli after the experiment, but later gradually became comatous and finally died of pulmonary edema.

The remaining 4 animals remained conscious during periods of nitrogen inhalation ranging from 10 to 60 minutes, and did not show any respiratory or circulatory signs of anoxia. Their blood flow was always above 40 ml/kg/min. The highest flow in dog No. 59 was about 80 ml/kg/min. The largest surviving animal, who inhaled pure nitrogen for 26 minutes, had a weight of 14.4 kg. Except for the drowsiness due to morphine, the animals behaved in a normal way after being lifted from the operating table. They voluntarily responded to call, and failed to show any clinical signs of cerebral anoxia in the

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following 2 or 3 weeks of observation.

Summary. A new method of blood oxygenation by gas dispersion was tested by subjecting dogs, under local anesthesia and morphine sedation, to conditions of complete anoxic anoxia by substituting pure nitrogen for air as the respiratory gas for about one hour. If a *minimum* blood flow of approximately 40 ml/kg/min was maintained, the animals survived the experiment without loss of consciousness, and recovered completely without exhibiting any neurological signs of anoxic damage.

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A Method with Perfused Feline Hearts of Quantitatively Comparing Drugs with Coronary Vasodilating Activity. (17874)

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Hearts perfused by the method of Langendorff(1) have long been employed for detecting coronary vasodilating action in new compounds. This type of assay would appear to suffer particularly from two limitations: 1. The coronary dilating effects are brief and are difficult to quantitate, so that careful comparisons between congeners are impossible; 2. In many experiments the coronary flow initially is so rapid as to make any further augmentation difficult of attaining. To be assured one is obtaining a primary coronary dilating action, increases in flow must occur without changes in the cardiac rate or the amplitude of the myocardial contractions.

Method. It was found that the proper concentration of a suitable vasoconstrictor in the fluid perfusing the heart would significantly diminish the coronary flow, sometimes by as much as 50%, without altering the rate or the amplitude of the contractions. Originally for this purpose we employed surgical Pituitrin in a concentration varying from .005 to .075 unit per ml. We found it unsatisfactory for 2 reasons: 1. Many hearts proved entirely insensitive to its constrictive effect; 2. Not infrequently its predominant action was a positive inotropic effect with little change in the coronary flow. 2-naphthyl-(1')-methyl-imidazoline hydrochloride (Privine) yielded better results. Its addition to the recycled perfusion fluid in a concentration of from 1 to 2 γ/ml usually caused in hearts exhibiting a fast initial flow (greater than 15 ml/min) a progressive reduction in the flow up to as much as 50% without altering the rate or amplitude of the contractions. In hearts with slow initial flow (from 10-15 ml/min) relatively high concentrations of Privine (up to 5 γ/ml) usually failed to reduce it further. This proved no disadvantage since such hearts responded directly to coronary dilators. Fig. 1 and 2 illustrate this action by histamine and sodium nitrite respectively. Obviously it is needless to study by this procedure any drugs that do not exhibit a brief augmentation of the coronary flow after single injections of suitable doses directly into the cannula just above the aorta.

Discussion. The higher doses of Privine not infrequently exerted a mild, positive inotropic effect, later followed by irregularities. The last were most common with "irritable" hearts that had exhibited from the beginning a relatively high rate with occasional extra systoles. The coronary constrictive action of Privine would appear weak not only on the basis of the data presented but also on the basis of Meier's work with cats *in vivo* (2). He found Privine invariably augmented the coronary flow, presumably because the elevated blood pressure following its admin-

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