Dec. 9, 1969 C. L. CLAFF ET AL 3,482,575

METHOD FOR THE EXTRACORPOREAL OXYGENATION OF BLOOD

Filed Feb. 16, 1967 3 Sheets-Sheet 1

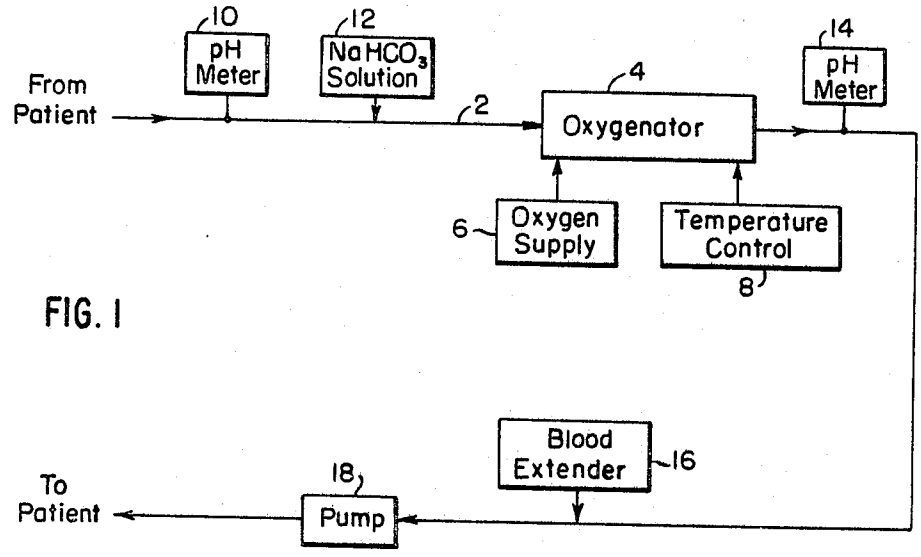


FIG. 1

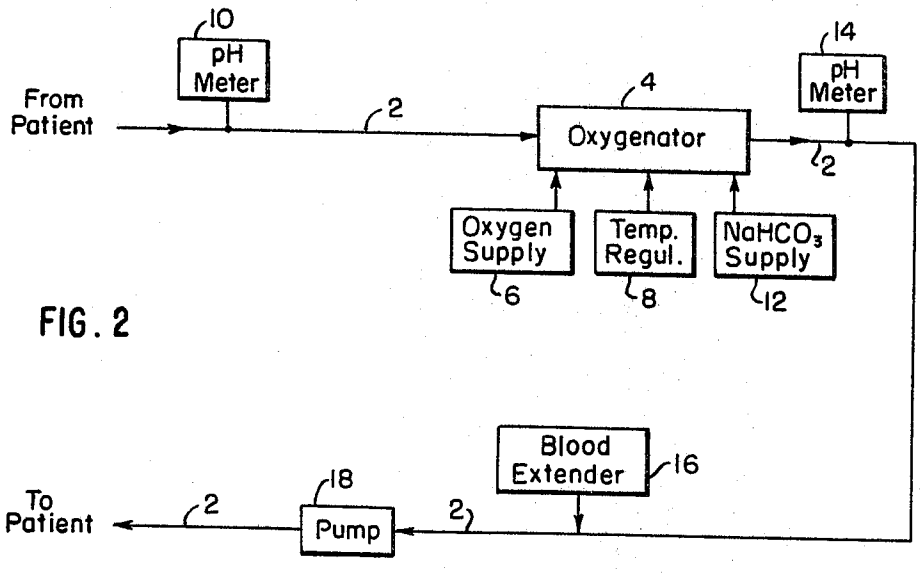


FIG. 2

INVENTORS
C. LLOYD CLAFF
ARMAND A. CRESCENZI
BY
Kenway, Jenney + Hildreth
ATTORNEYS

Dec. 9, 1969 C. L. CLAFF ET AL 3,482,575

METHOD FOR THE EXTRACORPOREAL OXYGENATION OF BLOOD

Filed Feb. 16, 1967

3 Sheets-Sheet 2

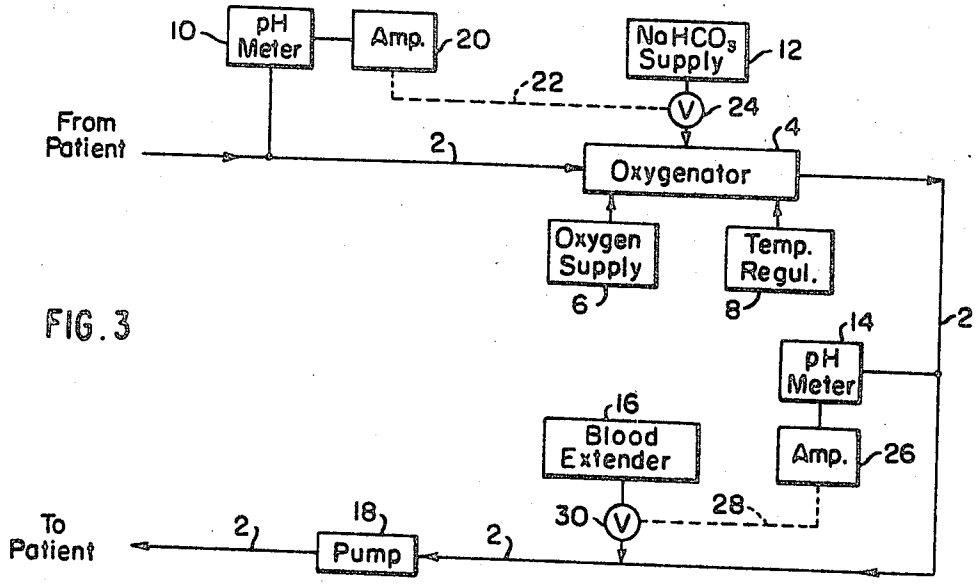


FIG. 3

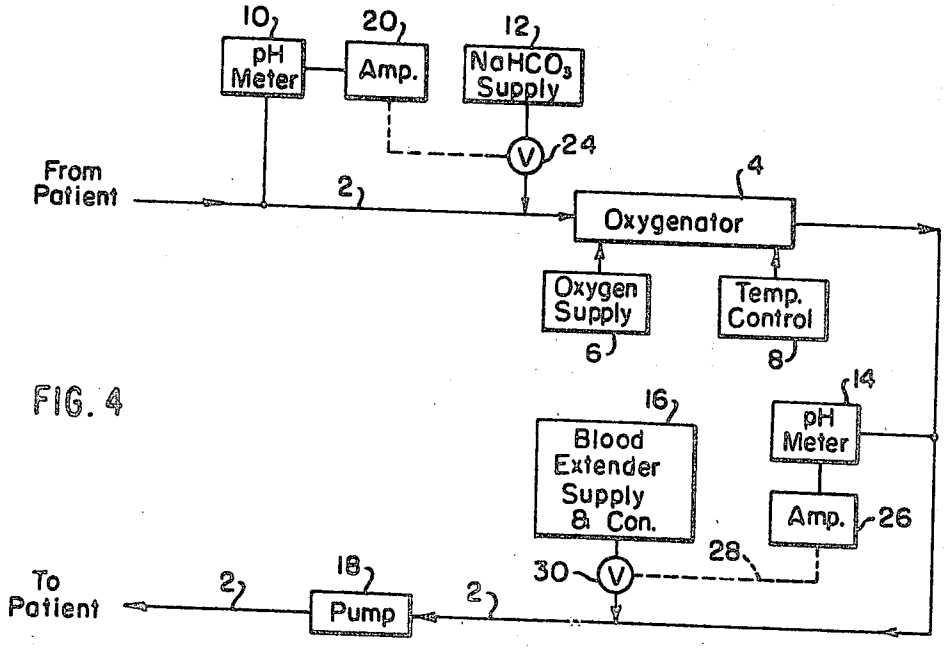


FIG. 4

INVENTORS
C. LLOYD CLAFF
ARMAND A. CRESCENZI

BY Kenway, Jenney & Hildreth

ATTORNEYS

Dec. 9, 1969 C. L. CLAFF ET AL 3,482,575

METHOD FOR THE EXTRACORPOREAL OXYGENATION OF BLOOD

Filed Feb. 16, 1967 3 Sheets-Sheet 3

FIG. 5

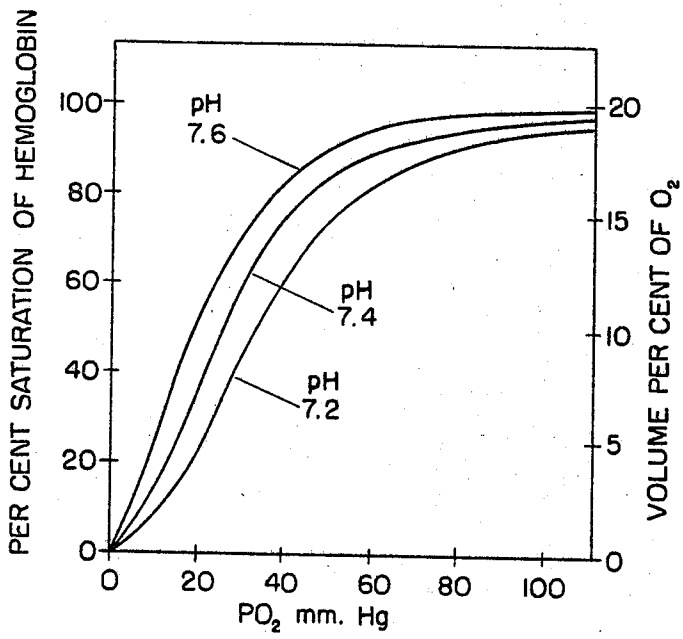
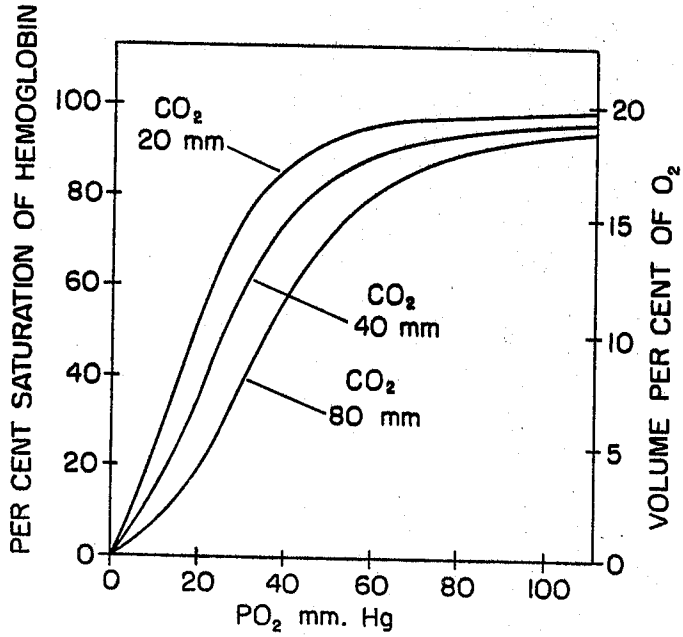


FIG. 6



INVENTORS
C. LLOYD CLAFF
ARMAND A. CRESCENZI
BY
Kenway, Jenney & Hildreth
ATTORNEYS

United States Patent Office 3,482,575
Patented Dec. 9, 1969

3,482,575

METHOD FOR THE EXTRACORPOREAL OXYGENATION OF BLOOD

Clarence Lloyd Claff, Randolph, Mass., and Armand A. Crescenzi, Pleasantville, N.Y., assignors to Single Cell Research Foundation, Inc., Randolph, Mass., a corporation of Massachusetts

Filed Feb. 16, 1967, Ser. No. 616,556
Int. Cl. A61m 5/00, 37/00; A61n 3/00
U.S. Cl. 128—214 8 Claims

ABSTRACT OF THE DISCLOSURE

This invention relates to a method for the extracorporeal oxygenation of blood, and particularly as such oxygenation is done by a membrane-type oxygenator although the invention is applicable to other forms of oxygenators. The invention consists basically of adding enough sodium bicarbonate to blood which has been withdrawn from the femoral vein of a patient with a pH of 7.30 to 7.32 the addition being done directly or by dialysis in an oxygenation apparatus, in sufficient quantity to raise the pH of the blood to a pH of 7.45–7.50 or even higher. The blood, thus alkalyzed by the addition of sodium bicarbonate, is oxygenated, and thereafter, after pH adjustment, if needed, the blood is infused into the patient. Since the pH of the blood will probably be higher after oxygenation than will be acceptable physiologically, the blood pH is brought back to a physiologically acceptable limit, prior to infusion in the patient, by the addition of blood extenders such as a plasma with a suitable extender such as Dextros.

BACKGROUND OF INVENTION

There are many adverse phenomena that may happen when blood is extracorporeally oxygenated. The medical profession has now worked for several years to overcome many of these, and has done remarkably well in view of the many problems that have been present. Some of the difficulties that arise are the clotting of the blood in the oxygenator itself, the reaction between the materials from which the oxygenator itself is made and the blood, breakdown of the red blood cells due to mechanical action of the oxygenators, foaming of the blood because of too rapid a mixing of gas and blood, maintenance of the blood volume itself, acidosis in the patient due to the use of artificial circulation rather than the normal body circulation, and many others. While the medical profession has overcome many of these difficulties successfully, one factor that remains is that the effective area of the lungs of the average person, as an example, by means of which the persons oxygenates his blood compares roughly to the size of a tennis court, whereas most of the mechanical systems for oxygenating blood extracorporeally provide an oxygenating area which is only a fraction of this. If it is attempted to speed up the passage of blood through such smaller areas in order to get a higher rate of oxygenation, then difficulty is experienced in infusing the blood into the patient without encountering unwanted ill effects (due to stenosis at the side of arterial reentry) such as high velocities of flow, turbulence, and damage to the blood elements. If the oxygenator areas are made physically larger, too much priming blood is needed.

FIELD OF INVENTION

Usually blood from the femoral vein of the patient is flowed by gravity or pumped directly into the oxygenator. In the methods of this invention, the pH of the venous blood is increased from its venal blood pH 7.30 or pH 7.32 to a pH of 7.40 to pH 7.45 or possibly to even 7.55

before or during oxygenation. The preferred form of oxygenator is the Pulsatile Pressure Membrane Oxygenator, such as shown in copending United States patent application of C. Lloyd Claff, Armand A. Crescenzi and Peter F. Ippolito, Ser. No. 269,018, filed Mar. 29, 1963, now United States Patent 3,332,746 dated July 25, 1967, but other forms of oxygenators may be used. This may be done in one of two ways: namely, adding a small amount of a saturated solution of $NaHCO_3$ directly to the blood just before it enters the oxygenator, or by running a saturated solution of $NaHCO_3$ as a dialysis solution alongside of one of the sides of the membrane bag of the oxygenator. In this latter case, the membrane bag would have one side made of a material permeable to the passage of bicarbonate of soda ($NaHCO_3$) into the blood, such as cellophane, and the other side would be made of teflon or silicone rubber membrane. Other types of membranes would be used as they become available.

The reasons for the preferred use of the oxygenator set forth in said copending U.S. patent application are threefold: first is the fact that sixty times a minute a new interphase of red cells lies next to the membrane on either side in the bag. Since it has been proved that there is a relationship between speed of oxygenation and the distance of the red cells of the blood from the source of oxygen, this is an important feature. Secondly, the normal pressure of oxygen in venous blood is approximately 40 mm./Hg as it leaves the patient. Sixty times a minute the blood (plasma and red cells) in the said oxygenator is subjected to a pulsating pressure of 500 mm./Hg (10 lbs. pressure of oxygen). Since there is approximately a pressure of 100 mm./Hg in the lungs of a human. The said oxygenator subjects the hemaglobin of the red cells to five times that pressure. It is a proven fact that there is a definite relationship between pressure and oxygenation, the oxygenation increasing as the pressure increases. And thirdly, it is well known that the diffusion through a membrane of a gas is proportional to the difference in the paritial pressures of that gas on either side of the membrane. In this case, the O_2 pressure in the blood is approximately 40 mm./Hg and the O_2 pressure on either side of the membrane bag is approximately 500 mm./Hg.

SUMMARY OF INVENTION

This invention therefore basically provides a method of greatly increasing the oxygenation of the blood in the oxygenator by treating the blood itself so that it has a higher oxygen acceptance, without the necessity of increasing the size of the oxygenator itself or the velocity of blood therethrough.

One object of the invention, therefore, is the provision of a method for extracorporeally oxygenating blood in which method the blood is rendered more capable of taking up oxygen.

Another object of the invention is the provision of a method for extracorporeally oxygenating blood whereby the blood is first treated to raise its pH above physiologically acceptable limits or even slightly higher, the blood is then oxygenated, and thereafter the pH of the blood is lowered to limits of pH which are physiologically acceptable to the patient by means of plasma extenders and/or buffers.

Yet another object of the invention is the provision of a method for alkalizing the blood prior to oxygenation, and then after oxygenation buffering the blood in order to bring its pH down to acceptable physiological limit before infusing the oxygenated blood back into the patient.

A still further object of the invention is a method for oxygenating blood wherein the blood is alkalized during the step of oxygenation itself to enable the blood to take up a greater amount of oxygen during its passage through the oxygenator, the pH of the blood being measured and

brought back, if necessary, to acceptable physiological range before infusing the oxygenated blood into the patient.

The invention accordingly comprises the steps and sequence of steps and features of opeartion which will be exemplified in the methods hereinafter described, and the scope of the application of which will be indicated in the following claims.

DESCRIPTION OF DRAWINGS

In the accompanying drawings, in which are illustrated schematically four arrangements of conventional apparatus for performing the methods of this invention:

FIG. 1 is a schematic illustration of one embodiment of the invention in which the apparatus is so arranged that the blood is alkalized before entering the oxygenator, and thereafter the pH of the blood is brought back to acceptable physiological limits prior to infusion;

FIG. 2 is a schematic illustration of a second embodiment in which the blood is alkalized during the passage of the blood through the oxygenator, and thereafter the blood's pH is brought down to acceptable physiological limits prior to infusion;

FIG. 3 is a schematic illustration of a third embodiment somewhat similar to that of the FIG. 2 embodiment, but in which further means are provided automatically to control the amount of alkalization of the blood in accordance with the pH of the blood as it leaves the patient but prior to entering the oxygenator;

FIG. 4 is a schematic illustration of a fourth embodiment somewhat similar to that of the FIG. 1 embodiment, but in which provision is made for automatically controlling the amount of alkalization of the blood prior to entering the oxygenator, the reduction of the pH of the blood after it leaves the oxygenator and prior to infusing the patient being also controlled automatically;

FIG. 5 is a disassociation curve of blood showing the effect of pH; and

FIG. 6 is a disassociation curve of blood showing the effect of CO_2 thereon.

Throughout the drawings similar reference characters indicate corresponding apparatus throughout the several views of the drawing.

DESCRIPTION OF THE INVENTION

Referring now to FIG. 1, there is shown in a block diagram a schematic representation of an arrangement of apparatus whereby the basic methods of this invention may be carried out. The flow of the blood throughout the apparatus is indicated by arrows in the drawings.

From a patient, the blood flows along path **2** to the oxygenator **4**. (In the several embodiments shown herein, the blood is conducted throughout the apparatus by tubing which is physiologically acceptable to the blood and inert thereto. Such tubing is well known and the details of it will not be given herein.)

As earlier indicated, the oxygenator **4** may be any one of the several kinds of oxygenators successfully used to date, but it is preferred that it be the pulsatile membrane type set forth in said copending U.S. patent application. As described in said application, the oxygenator **4** comprises a series of membrane bags or envelopes through which the blood passes from the inlet of the oxygenator to the outlet. The bags are surrounded on their out-sides by a constant flow of oxygen, and the whole apparatus is maintained as to temperature by adequate flow of heated water throughout the apparatus for some situations, or by a flow of cold water where hypothermia is indicated. In FIG. 1, the oxygen supply for the oxygenator is indicated by numeral **6** and the temperature control apparatus indicated by numeral **8**.

Prior to entering the oxygenator, its pH is measured by means of a conventional pH meter **10** for this purpose. As the blood leaves the patient, where the technique used is that of tapping the venous bed, its pH will be that of venous blood, that is, in the range of pH 7.3 to pH 7.32 (In cases of acidosis, the pH may be lower, for example, pH 7.29.) In this invention, the pH value of the blood is now raised so as preferably to be that of high normal blood having a pH 7.5 to 7.55. In the FIG. 1 embodiment, a manually controlled saturated solution of sodium bicarbonate ($NaHCO_3$) is dripped into the blood from a supply **12** thereof, the amount needed to be added being determined from the actual pH of the blood as determined by meter **10**, and the rate of blood flow in volume.

The importance of this seemingly small shift in pH is realized when it is remembered that the degree of acidity or alkalinity of a fluid (its hydrogen ion concentration) is expressed in terms of pH which is the negative logarithm of the hydrogen ion concentration. Since the pH scale is therefore logarithmic, a solution with a pH of 7.32 has a hydrogen ion concentration 10 *times greater than one with a pH of* 8.32. Therefore a shift in blood pH from the usual venous blood pH of pH 7.30 to a blood pH of pH 7.50 represents approximately a 60% decrease in hydrogen ion concentration. (Physiological limits of pH of blood for man is usually expressed as pH 7.3 (venous) to pH 7.45 or pH 7.5.) Slightly higher and lower limits can be tolerated for short periods.

It has been well known for several years that the transfer of oxygen from hemoglobin in the capillary bed takes place when the environment of the hemoglobin is reduced in pH value. The physiology of this has been measured and described in numerous publications, and an examination of FIG. 5 will illustrate the effect of the pH and carbon dioxide (CO_2) on the disassociation curve of blood. FIG. 5 shows the effect of pH on the disassociation curve of blood, the curves being a plot of the percent saturation of hemoglobin by oxygen against the oxygen tension of the blood, the latter being measured in milligrams of mercury. FIG. 6 shows the effect of CO_2 on the disassociation curve of blood, again the percent saturation of hemoglobin being plotted against the oxygen tension of the blood.

The shifts in the disassociation curves are well known, and usually are called the "Bohr" effect. The curves show that the amount of oxygen combined with hemoglobin depends, among other factors, on the pH value of the blood and also on the carbon dioxide tension of the blood. As the curves show, an increase in the acidity (a lower pH) of the blood tends to drive oxygen off the oxyhemoglobin molecule. So also, as the carbon dioxide tension of the blood increases, the oxygen and the hemoglobin tend to disassociate. This latter is an aid to normal function of the blood in the human body, in the region of the capillaries thereof, as the carbon dioxide tension of the blood is elevated due to the presence of lactic acid and CO_2. This elevated carbon dioxide tension helps the blood to unload the oxygen and to pass it through the capillary.

In the present invention, the reverse phenomenon is utilized, and the alkalinity of the blood is increased prior to being brought into contact in an oxygenator. By increasing the alkalinity of the blood, the reverse of the Bohr effect is obtained, and the hemoglobin's ability to associate with oxygen is greatly increased.

In the method of FIG. 1, the alkalinity of the blood is increased to a pH value of high physiological limits after it leaves the patient, by the addition of $NaHCO_3$ from a supply **12** thereof. The thus alkalized blood is then introduced into the oxygenator, where its red cells and plasma absorb a greater amount of O_2 than would be the case were the blood left at its pH of 7.30 or 7.32. Depending on the pH of the blood when it is traversing the oxygenator, the blood can absorb as much as 100% more oxygen than were the blood not so alkalized.

If, after the blood leaves the oxygenator its pH is higher than what would be acceptable physiologically by the patient, then the pH of the blood must be reduced to

a value which is proper. To do this, the pH of the blood again is measured as by the pH meter **14**, and then manually a blood extender such as plasma or plasma extender (for example, a 5% dextrose in water solution, or low molecular weight Dextran, or Ringers solution) is added to the blood, as from the supply thereof **16**. The blood is then infused into the patient by means of a suitable pump **18** where a pump-type oxygenator is used such as a disc oxygenator or "bubbler." The pump **18** is dispensed with if the oxygenator of said United States Patent application is used. If the patient is acidotic, it may be preferred to use an alkalizer, such as the material commonly known as "Tham" or "Tris Buffer," (hydroxy-methyl) aminomethane (a-amino-2-hydroxymethyl) 1,3 propane diol.

The $NaHCO_3$ itself in the blood will limit the fall in plasma bicarbonate during perfusion, and thus assist the intrinsic defense mechanism of the body against a drop in buffer base. This is a great advantage of using the sodium bicarbonate, viz., it provides in the blood a high reserve of blood bicarboante. The effect of this is to lessen the chance of high acidity taking place as a result of a prolonged operation on the patient. Also, when the blood, thus loaded with oxygen because of the high pH, and having the high alkaline reserve, is infused in the patient, it is ready to pour off oxygen in an acid environment that it may find in the patient's body.

It is not necessary that the blood be alkalized prior to entering the oxygenator, and the embodiment in FIG. 2 indicates schematically a system for this. As in the FIG. 1 embodiment, a pH meter **10** is used for measuring the pH of the blood prior to entering the oxygenator **4**. Again, oxygen is supplied from the supply thereof **6** to the oxygenator, the temperature of the oxygenator and blood being controlled by means of the temperature regulator **8**. In this embodiment, the $NaHCO_3$ is supplied to the blood within the oxygenator by the technique of dialyzation. That is, the type of oxygenator that would be used is a membrane one, and one in which the membrane bag has one wall thereof made of a material permeable to oxygen, such as Teflon or silicon rubber, for oxygenating the blood, while the other wall of the bag is a dialysing membrane such as a cellophane material through which may pass the $NaHCO_3$ from a solution thereof in contact with the outside of this cellophane membrane. The strength of the $NaHCO_3$ solution is governed manually in accordance with the reading of meter **10**.

Again, as in the FIG. 1 embodiment, the pH of the blood is measured by pH meter **14** as the blood leaves the oxygenator, and then a sufficient amount of blood extender **16** is added to the blood to bring its pH back to physiologically acceptable limits. Thereafter, by means of the pump **18**, the blood thus oxygenated and having the correct pH value is infused into the patient either on the venous side of the circulatory system or the arterial side, depending on whether the oxygenator apparatus is used as a long period "assist" to the body, or as a short term "open heart surgery" adjunct.

In view of the fact that it may not be desirable to have to regulate by hand the addition of the $NaHCO_3$ prior to or during oxygenation, or the extending of the blood by means of a blood extender, the embodiment shown schematically in FIG. 3 presents a system for the automatic control of these various steps. The illutsration is schematic only, since in view of the teaching of this invention, it is thereafter within the skill of the man of the art to assemble, using conventional apparatus, the system as shown. In this embodiment, the pH meter **10** measures the pH of the blood as it leaves the patient, and the signal from the pH meter then passes to the control amplifier **20** which in turn, by means of conventional circuitry connections **22**, controls a supply valve **24**. The $NaHCO_3$ supply **26** is connected to the oxygenator **4** through the controlled supply valve **24**, and thereby the amount of $NaHCO_3$ needed in order to raise the pH of the blood to a value greater than pH 7.3, and preferably to pH 7.5, added to the dialysing fluid in the oxygenator **4**. After the blood has been oxygenated by the oxygenator, it is again checked by the pH meter **14**, the signal from which is fed to a control amplifier **26** which is turn, through the conventional circuitry **28** controls the supply valve **30**. The supply of blood extender **16** is connected to the tubing carrying the blood by means of the valve **30**, and thus the amount of blood extender necessary to bring the blood back to its safe physiological pH value is determined by the pH meter **14**. The blood then passes to the pump **18** and from thence into the venous or arterial blood system of the patient.

In FIG. 4, the same system of automatic control of the pH of the blood prior—to oxygenation is shown, in this case the $NaHCO_3$ being added to the blood prior to its entry in the oxygenator. The pH meter **10**, as in the prior embodiments, measures the pH of the blood as it leaves the patient, and feeds its output signal to the control amplifier **20**. The amplifier **20** controls the valve **24** which connects the $NaHCO_3$ supply directly to the blood stream of the apparatus. After oxygenation, again as in the FIG. 3 embodiment, the pH of the blood is measured by pH meter **14** whose output signal controls, through the amplifier **26**, the setting of the valve **30**. Valve **30** in turn controls the amount of blood extender being added to the blood stream which is necessary in order to bring a pH of the blood back to a range which is physiologically acceptable to the patient. Thereafter, by means of the pump **18**, the blood is infused into the venous or arterial blood system of the patient, as the case demands.

In a human being, the normal pH value of blood lies in the range of 7.3 to 7.45. Oxygenated blood lies on the high side of this range, and venous blood lies on the low side of the range. In the instant invention, sufficient $NaHCO_3$ is added to the blood either before or during oxygenation to raise the pH of the venous blood from a pH of 7.30 to 7.32 to a value greater than 7.4, and preferably in the range of pH 7.45 to pH 7.55.

In view of the above, it will be seen that the several objects are achieved and other advantageous results attained.

As many changes could be made in the above methods without departing from the scope of the invention, it is intended that all matter contained in the above description or shown in the accompanying drawings, shall be interpreted as illustrative and not in a limiting sense, and it is also intended that the appended claims shall cover all such equivalent variations as come within the true spirit and scope of the invention.

Having described the invention, what we claim is:

1. The method of continuously extrocorporeally oxygenating blood which comprises: continuously withdrawing blood from a living mammal, adding to the blood a physiologically acceptable chemical in sufficient quantity to alkalize the blood so that its pH lies within the range of 7.40–7.55; exposing the alkalized blood to oxygen in order to oxygenate the blood; treating the oxygenated blood to reduce its pH to lie within the range of 7.35–7.40; and thereafter continuously introducing the oxygenated blood into the mammal.

2. The method of claim **1** in which said chemical is $NaHCO_3$.

3. The method of claim **1** in which the alkalized blood prior to being oxygenated has a pH lying within the range of 7.45–7.55.

4. The method of claim **1** in which the step of treating the blood after oxygenation comprises extending the blood with a plasma extender.

5. The method of claim **1** including the steps of testing the blood to determine its pH prior to alkalinization thereof; and of testing the blood after oxygenation but before said treating to determine the pH after oxygenation.

6. The method of continuously treating the blood of a living mammal, the mammal being in an acidotic condition, comprising the steps of continuously withdrawing venous blood from the mammal; measuring the pH of the withdrawn blood; increasing the carbonate content of the blood to increase its pH to a value above 7.32; extracorporeally oxygenating the blood while at said value; measuring the pH of the oxygenated blood; extending the oxygenated blood with an alkalizing extender selected from the group consisting of Tham or Tris buffer to bring its pH value to lie within the range of 7.35 to 7.4; and thereafter continuously introducing the treated and oxygenated blood into the circulatory system of the mammal.

7. The method of continuously extracorporeally oxygenating the blood of a living mammal comprising the steps of continuously withdrawing venous blood from the mammal; measuring the pH of the withdrawn blood; increasing the carbonate content of the blood to increase its pH to a value above 7.32; oxygenating the blood while at said value; measuring the pH of the oxygenated blood; treating the oxygenated blood to bring its pH value to lie within the range of 7.35 to 7.4; and thereafter continuously introducing the oxygenated blood into the circulatory system of the mammal.

8. The method of continuously extracorporeally oxygenating blood which comprises:

continuously withdrawing blood from a mamal whose blood can be oxygenated extracorporeally;

measuring the pH of the withdrawn blood;

passing the blood into and out of a permeable membrane bag one layer of which is permeable at least to oxygen and carbon dioxide but not to blood, and the other layer of which is a dialysing membrane;

contacting said one layer with oxygen while the blood passes through said bag in order to oxygenate the blood;

contacting said other layer with a solution of $NaHCO_3$ to increase the pH of the blood to a value greater than 7.32;

measuring the pH of the oxygenated blood after it leaves said bag;

reducing the pH of the oxygenated blood to within the range of 7.35 to 7.4 prior to infusing said mammal with said oxygenated blood; and

continuously introducing the oxygenated blood into the mammal.

References Cited

UNITED STATES PATENTS

2,792,002	5/1957	Malmros et al.	23—258.5
3,212,498	10/1965	McKirdy et al.	23—258.5
3,332,746	7/1967	Claff et al.	23—258.5

OTHER REFERENCES

Malm et al.: Trans. Amer. Soc. Artif. Int. Organs, Vol. IX, 1963, pp. 216–218.

Meredino et al.: Surgery, Vol. 42, #6, December 1957, pp. 996–999.

Poth et al.: Amer. Surgeon, Vol. 23, #11, November 1957, pp. 1056–64.

DALTON L. TRULUCK, Primary Examiner

U.S. Cl. X.R.

23—258.5