# ANALYSIS OF A MEMBRANE TYPE BLOOD OXYGENATOR AND A VENTRICLE TYPE BLOOD PUMP

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# ANALYSIS OF A MEMBRANE TYPE BLOOD OXYGENATOR AND A VENTRICLE TYPE BLOOD PUMP

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(ABSTRACT)

This study presented the development and in vitro analysis of the Arp Membrane Type Blood Oxygenator and a ventricle type blood pump. The system is designed for newborns suffering from Respiratory Distress Syndrome (R.D.S.), especially the 15% who are unable to be helped by the Arp Infant Respirator.

The analysis included oxygen transfer studies and hemolysis studies. The oxygenator was able to transfer as much as 140 $cc O_2/min/m^2$ at a flow rate of 300 ml/min with flow augmentation. Inlet oxygen saturation was between 25-35%.

Both the oxygenator and the ventricle type blood pump caused only very low levels of hemolysis. The pump showed a net increase of 54 mg hemoglobin/100 ml plasma after 5 days of continuous running at a flow rate of 200 ml/min. The complete extracorporeal circuit showed a net increase of only 61 mg hemoglobin/100 ml plasma.

From this study, it is believed that this extracorporeal circuit can supply oxygen (140 $cc O_2/min/m^2$) to a patient over an extended period of total or partial cardiopulmonary by-pass (at least 5 days) without significant levels of hemolysis (61 mg% after 5 days).

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# Chapter 1

## INTRODUCTION

This thesis deals with the design, development, and *in vitro* analysis of a membrane type blood oxygenator planned for use primarily on infants suffering from cardiopulmonary problems. Infants born with "Respiratory Distress Syndrome" (R.D.S.) - a phrase given to a variety of maladies - are of specific interest. The survival rate of the R.D.S. infants was raised from 50-60% to approximately 85% with the development of the Arp Infant Respirator (2). The survival rate, however, could be higher if the remaining 15% of the infants were supported by complete or, at least, partial cardiopulmonary by-pass during the critical days following birth. It is well known that a baby with Hyaline Membrane Disease will recover if it can survive those first critical days (44).

Most extracorporeal oxygenation units in existence today are designed primarily for use with adults. Perfusion of the infant is more difficult. A constant blood volume must be maintained, and the design and the materials must also be developed with great care so that a minimal amount of blood damage occurs (44). For example, there is an increase in red blood cell osmotic and mechanical fragility following by-pass which can lead to sublethal cellular trauma (72). It has also been shown that during by-pass, higher levels of plasma hemoglobin are observed in infant animals as opposed to adult animals (72). This impart may be due to the immature reticuloendothelial system in these young animals (72). Regardless of the cause, blood damage must be held to a minimum.

The most widely used gas exchange devices in heart-lung systems contact the blood directly with the gas phase, even though prolonged exposure of blood to this high-energy interface causes toxic degradation (denaturation) to blood proteins, in addition to high rates of hemolysis (69). As a result, there is a high mortality rate for procedures lasting longer than a few hours (69). However, since the majority of surgical corrections (e.g. heart defects) generally require only twenty to forty minutes of total by-pass (27), the direct contact units have been widely accepted for such factors as reliability, low cost, and convenience (69). For long term support, however, it is a commonly accepted fact that the direct gas contact units cannot be used (69), especially with infants.

Another critical problem with newborns is the fact that high oxygen saturations of the blood are necessary in order for the ductus arteriosus to completely shut off at birth so that blood is not shunted away from or around the lungs (3,23). However, if the lungs are not fully functional due to some type of respiratory distress, the ductus arteriosus does not close and blood is shunted away from the lungs. Immediate support must be provided or death quickly ensues (3,23).

The problem, therefore, is one of finding a unit that will provide adequate oxygenation with tolerable levels of blood damage over a period of several hours or even days. This thesis is intended to provide a strong foundation for final product development in the near future. This study analyzed a membrane type blood oxygenator by looking at two critical areas: 1) hemolysis by measuring plasma hemoglobin

levels and, 2) oxygenation capabilities by measuring oxygen transfer. Various oxygenator designs and an analysis of a ventricle type blood pump are also included.

## Chapter II

## LITERARY REVIEW

The initial studies of extracorporeal circulation began in the 1930's. J. H. Gibbon M. D., using a blood oxygenator, successfully accomplished complete cardiopulmonary by-pass in cats (36). However, the first successful by-pass performed on a human did not occur until 1953 (36).

Extracorporeal blood oxygenators may be classified into three major categories: bubble oxygenators, disc oxygenators, and membrane oxygenators. The first two types oxygenate the blood by exposing it directly to the gas phase. This is an efficient method of oxygenation, but due to the direct blood/gas interface, the oxygenators (the bubble more so than the disc) damage the formed elements of the blood and various plasma proteins. In the membrane type oxygenator, a membrane, of which there are various types and designs, separates the blood from the gas phase. The blood damage is reduced significantly, but there are problems involving oxygenation due to the various flow parameters encountered, especially boundary layer phenomenon.

The first bubble type oxygenator was developed in 1950 by L. C. Clarke and his associates (17). The unit was relatively simple: oxygen was bubbled through a pool of venous blood, and the bubble/blood interface caused the oxygenating surface (17,57). This is the most widely used blood oxygenator for cardiopulmonary by-pass despite its high rate of blood damage, since most surgical procedures involving total by-pass rarely require more than an hour to complete (27).

The disc oxygenator was developed in 1948 by Bjork (in 57). This device consists of a series of flat discs which rotate on a central axis and which are surrounded by a chamber containing an ambient gas mixture which flows over and around the upper one-third of the discs; blood is exposed to the bottom two-thirds of the discs. As poorly oxygenated venous blood flows into the chamber, the rotation of the discs forms a thin film of blood on the upper one-third of each disc increasing the blood/gas interface. This process continues for the entire length of the oxygenator. The outlet blood was well oxygenated (approximately 98% saturated), and also, well hemolyzed because of the direct blood/gas interface and high shear forces.

The development of the first membrane blood oxygenator was in 1955 by G. H. A. Clowes, Jr. This oxygenator consists of a series of flat, ultra thin, plastic (ethyl cellulose) membranes which separate the blood phase from the gas phase. The oxygenating capacity of the oxygenator is dependant upon the diffusion of oxygen and carbon dioxide through the membrane (19). This initial development was followed by various models all operating in the same general manner (47,60,61).

The immediate advantage of the membrane oxygenator was the elimination of the blood/gas interface. Trauma to the formed elements and plasma proteins of the blood was significantly reduced, the oxygenation process being the major problem. A large surface area was needed to oxygenate the blood sufficiently. Consequently, this required many stacks of large, flat membranes that rendered the unit cumbersome. For example, the first oxygenator of Clowes et al. was almost 1 foot by 4 feet with a stack of membrane units nearly a foot thick (19)!

In addition to the bulkiness of the oxygenator, the membranes were thin and flat, and, therefore, extremely fragile. This became especially hazardous with the development of the fragile silicone rubber membranes. Ruptures were frequent which allowed the formation of gas bubbles in the blood (10). The large size of most of these units meant large priming volumes, and so they required greater quantities of foreign blood (19). The major drawbacks, however, were the blood flow geometry, changing blood volumes, and blood mixing.

Membrane oxygenators are divided into two broad and overlapping categories. The first oxygenator type with flat membranes was discussed previously. The second oxygenator type is the capillary membrane oxygenator, in which the membranes are tubular rather than flat. The capillary membrane oxygenator offers several advantages: added strength due to tubular arrangement and the capability of obtaining a large surface area in a relatively small space (28). The mode of operation of the capillary membrane oxygenators is the same as that of the flat membrane oxygenators; i.e., oxygen and carbon dioxide diffuse across the membranes at rates proportional to their respective partial pressure gradients.

Capillary membrane oxygenators are further divided into two classes: those with blood flowing through the tubes and oxygen flowing around the tubes (25,27,33,73), and those with oxygen flowing through the tubes and blood flowing around the tubes (10,64,66,77).

The vast majority of capillary membrane oxygenators are of the first type. However, our interest lies with the latter type. Bodell et al. (1963) were apparently the first to use capillary tubing to carry

oxygen. They used small diameter silicone capillary tubing (inside diameter 0.012 inches and outside diameter 0.025 inches) of lengths reaching one hundred feet. Bodell's model of a capillary membrane oxygenator consisted of a series of repeatable units containing several strands of the tubing wound in a helical loop. The loop formed a lumen through which the blood could flow. Several of these units were assembled in series to form the complete oxygenator. Oxygen transfer was adequate, and hemolysis rates were significantly lower than those of the bubble and disc oxygenators but were still high (66-172 mg Hb/100 ml plasma after ninety minutes of continuous oxygenation). In addition, the unit was difficult to assemble, operate, and sterilize (10).

Bodell's development was followed by several modifications (64,66, 77), one of which is currently under study in this lab. Included among these modifications was the placing of many tubes in the flow path of the blood thus significantly increasing the gas transfer capabilities of the unit.

Table 1 gives a brief comparison of the more important developments in the field.

TABLE 1: OXYGENATION AND HEMOLYSIS IN SEVERAL DIFFERENT OXYGENATORS

| WORKER AND DATE | TYPE OF OXYGENATOR | BLOOD FLOW (ml/min) | OXYGEN: TRANSFERRED OR SATURATION % | HEMOLYSIS (mg%) |
|---|---|---|---|---|
| Peirce (1969) | DISC MEMBRANE | ——<br>—— | ——<br>35 $cc O_2/min/m^2$ | 115 after 6hrs.<br>50 after 6hrs |
| Clark (1950) | BUBBLE | —— | 95% | 300-500 after 1 hr. |
| Zingg (1969) | MEMBRANE TUBES | —— | —— | 58 after 1 hr. |
| Katsuhara (1964) | MEMBRANE STACKS | 300-400 | 90% | 200-300 after 5 hrs. (in vivo) |
| Lande (1968) | MEMBRANE STACKS | 500<br>1500 | 40 $cc O_2/min/m^2$<br>75 $cc O_2/min/m^2$ | ——<br>—— |
| Dantowitz (1970) | MEMBRANE LINED CHANNELS | 230<br>920 | 32.2 $cc O_2/min/m^2$<br>92.2 $cc O_2/min/m^2$ | ——<br>—— |
| Cresenzi (1960) | MEMBRANE STACKS | 45 | 4.0 $cc O_2/min/m^2$ | 139 after 1½ hrs. |
| Rush (1969) | MEMBRANE TUBES | —— | 65 $cc O_2/min/m^2$ | 35 after 3/4 hr. |
| Kolobow (1970) | MEMBRANE SPIRAL COIL | —— | 40 $cc O_2/min/m^2$ | —— |
| Dutton (1971) | MEMBRANE TUBES | —— | 60 $cc O_2/min/m^2$ | 40 after 24 hrs. |

## Chapter III

## METHODS AND MATERIALS

### A. Blood Preparation and Collection

Bovine blood, obtained by jugular puncture, was used in all experiments. This blood offers advantages over that from other animals because it has an oxygen uptake value approximately equal to that of humans and is readily available in large quantities. Collapsable plastic sacks, identical to those used by the American Red Cross Blood Bank, allowed blood collection and storage with minimum exposure to the atmosphere. Prior to collection, these sacks were flushed several times with a chlorene bleach solution with the last wash remaining overnight. Finally, after thorough rinsing which normal saline several times, a fresh anticoagulent solution, acid-citrate-dextrose (ACD), was added to the sacks in amounts stipulated by the American Red Cross Blood Bank (67.5 ml/100 ml human blood). This amount was also satisfactory for bovine blood.

ACD was used primarily because it is one of the most widely used anticoagulents in blood banks (24). Therefore, any patient requiring an extracorporeal system would most likely receive blood containing ACD. Also, ACD is used in many areas of research concerning extracorporeal circuits. Finally, ACD is economically and easily made. The constituents of the solution are: 2.20 gms. of sodium citrate (monohydrous), 0.73 gms. of citric acid (dihydrous), 2.45 gms. of dextrose, and normal saline to one hundred milliliters.

Blood sterility was not a major problem because all lengthy tests were done at 2-6°C. As a result, hemolysis due to bacterial or fungal decomposition did not prove to be a threat since the control showed no significant hemolysis during the time period of each test. In vivo tests, of course, will be conducted at normal body temperature.

B. Oxygenator Development

1. Silicone rubber

The oxygenator, designed by Dr. L. J. Arp, is a membrane type oxygenator, i.e. there is no blood/gas interface. The unit consists of five layers of Silastic® medical grade tubing obtained from Dow Corning Corporation of Midland, Michigan. This compound is the material of choice in the development of various membrane oxygenators as well as in numerous areas of biology and medicine. Silicones of this type are possible because silicone can replace carbon in many organic compounds. Therefore, it is possible to combine some of the inertness found in quartz with the pliability and softness of rubber (12).

There are several reasons for the popularity of Silastic®. It is physiologically inert and consequently, non-reactive to body tissues (11,12); also, Silastic® will not support bacterial or common fungal growth (14,16). This was particularly important in this study since all tests were done under clean but non-sterile conditions.

Silastic® is a non-wetting silicone elastomer surface which minimizes much of the hazards encountered when blood contacts foreign substances: contact hemolysis (42), clotting (65), and sticking of red cell membranes to the surface (1,42).

The material also resists fatigue with repeated flexing or stretching. It has an indefinite shelf life, will remain soft and pliable, and will not oxidize or deteriorate during prolonged storage. The compound is easily cleaned with no change in the above desirable characteristics (13).

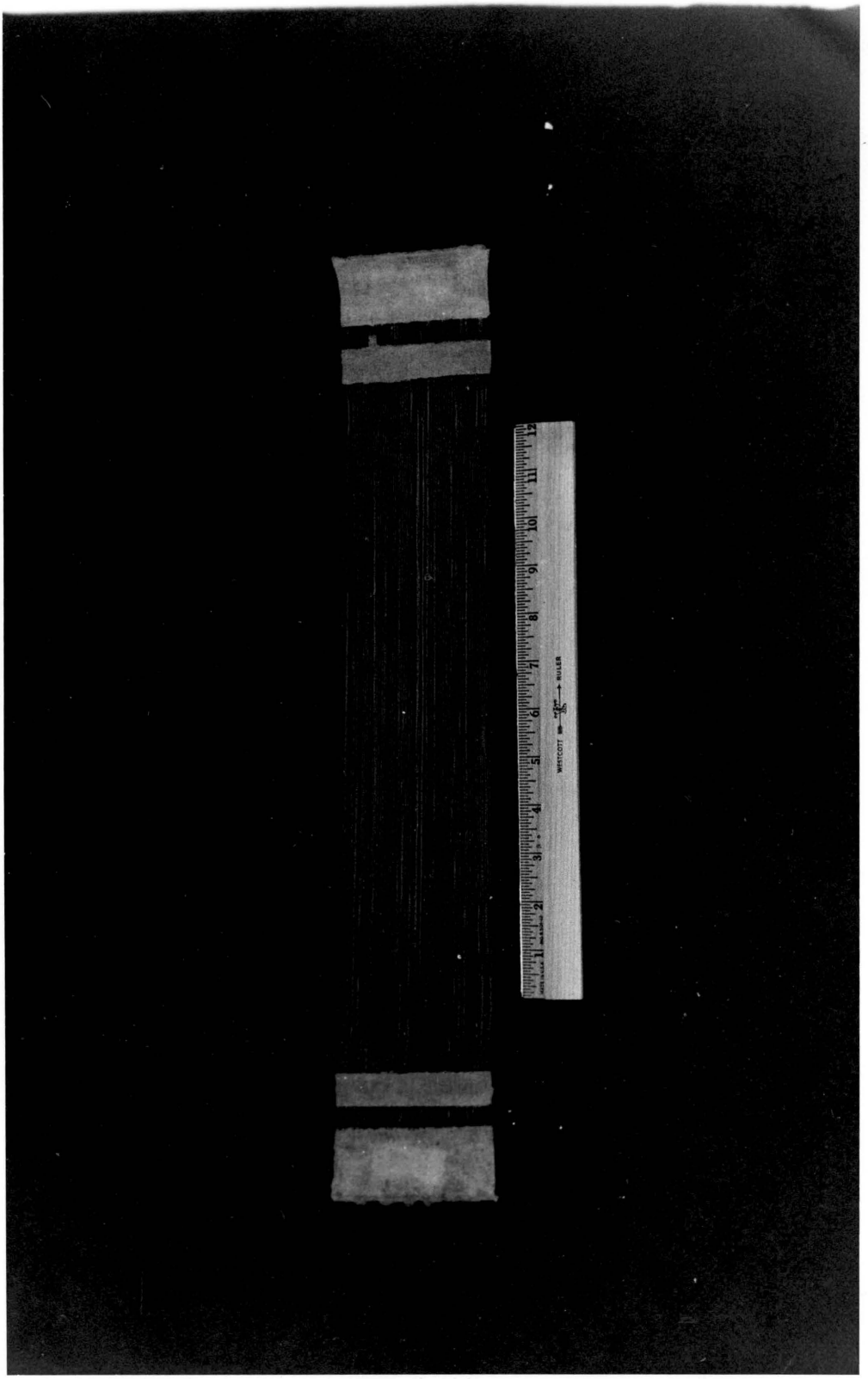
Silastic® compounds, used for medical purposes, contain fillers and vulcanizing agents for added strength but do not contain the wide variety of additives (e.g. color agents) used in organic rubber compounds (12). Therefore, there are no harmful chemicals that need to be leached out.

Finally, Silastic® can be bound to itself or other silicone compounds. Thus, giving the material a variety of uses. In these studies, for example, Silastic® tubing of various sizes, flat sheets of silastic, and a thick silicone cement were used in the construction of the oxygenator and the components of the extracorporeal circuit.

2. Oxygenator Construction

The oxygenator itself consists of five layers of Silastic® tubing. The basic geometry of the tube was used because it inherently assists in overcoming the structural weakness of silicone rubber membranes. Also, the tubular arrangement allows for the lowest priming volume/surface area ratio (15,28). Each layer contains sixty parallel tubes twenty inches in length. The inside diameter of each tube is 0.12 inches, and the outside diameter is 0.25 inches. The layers were cemented together by applying silicone rubber cement dissolved in ethyl ether over the final one and one-half inches of both ends of each layer. (fig. 1). In order to prevent gas leakage from the oxygenator

Fig. 1. Individual Layer of the Oxygenator Showing Oxygen Tubes and Air Gaps.


WESTCOTT

into the blood chamber, an air gap was constructed by cementing into place narrow strips as shown in fig. 1.

Five of these layers were stacked consecutively and cemented together at both ends and at the air gap strips. The tubes were opened by cutting approximately one-fourth inch from each end. Thus, the unit consisted of three hundred parallel tubes opened at each end. The total thickness was about one-fourth inch.

An airtight plexiglass housing was constructed around each end of the unit; thus, when oxygen was connected to one chamber, the gas flowed through the tubes to the other chamber. By opening an outlet valve in the other chamber, gas was permitted to flow freely. If this chamber was then closed, oxygen pressure could be controlled inside the tubes (fig. 2). The pressure was varied by adjusting the outlet valve. Normally, oxygen pressure ranged from 15-25 psig (pressure per square inch, gage).

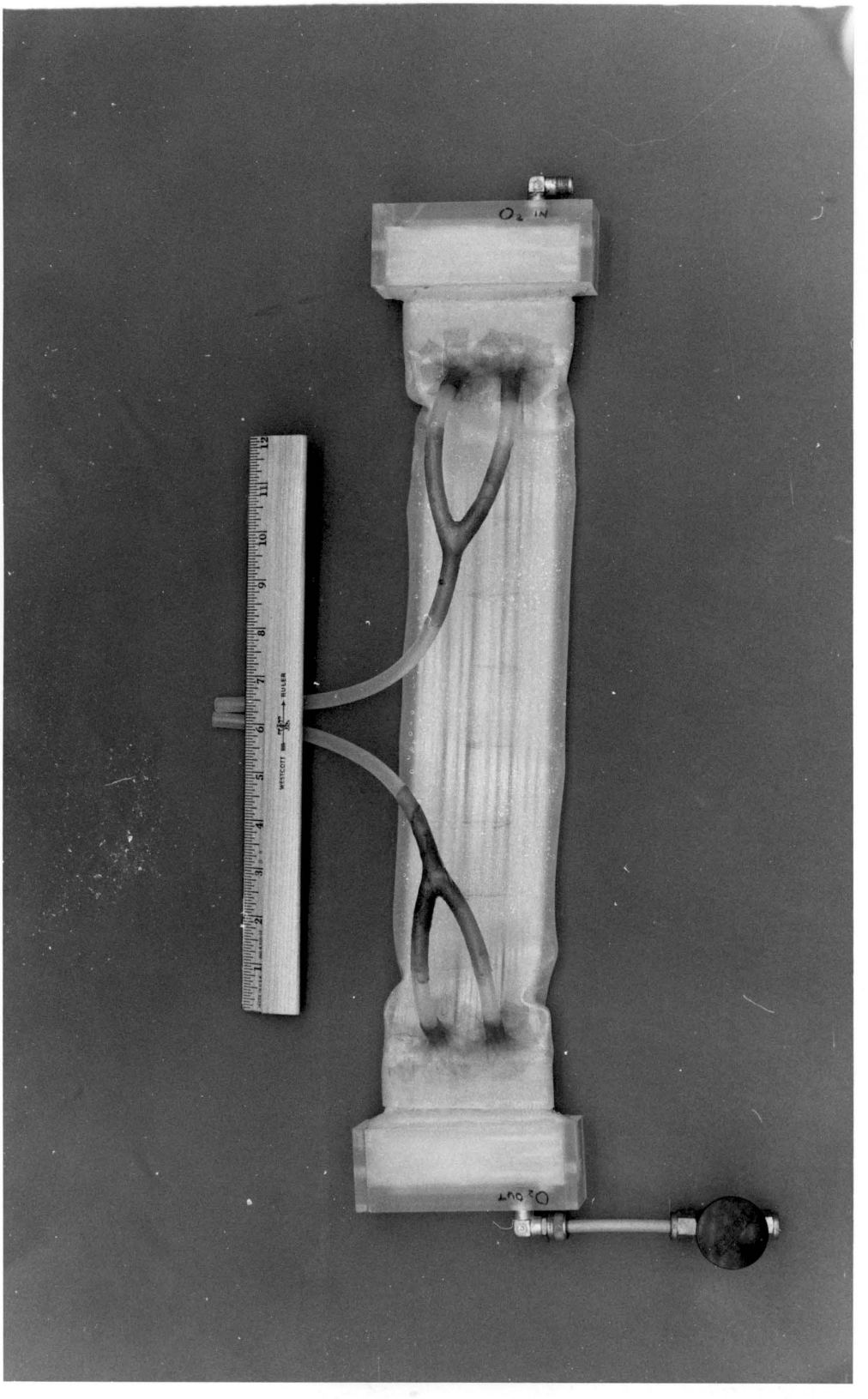
Finally, the blood chamber was constructed around the tubes by wrapping the area between the air gap strips with a thin sheet of Silastic® membrane. This sheet contained the blood inlet and outlet tubes. The priming volume of the unit at completion is only 55 ml.

3. Supporting elements of the extracorporeal circuit

a. Ventricle type blood pump

While the oxygenator is the major element of the extracorporeal circuit in this study, there are other important supporting units. The most significant of these is the ventricle type blood pump used to move the blood around the circuit in a pulsating manner. It is composed of Silastic® rubber with nylon reinforcement at the input and output

Fig. 2. Assembled Arp Membrane Type Blood Oxygenator.


O2 IN
O2 OUT
WESTCOTT
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openings and is enclosed in a plexiglass housing (figs. 3 and 7).

The pump operates by simple pressure alternations controlled by a fluidic control system. When negative pressure is exerted in the housing, the sack expands pulling blood in, while at the same time closing the outflow check valve and opening the inflow check valve. As soon as filling is complete, positive pressure is applied and the opposite occurs. These alternations in pressure give the blood a pulsating flow. Compressed air and a vacuum pump provide positive and negative pressure respectively.

b. The "buffer" bag

This bag, constructed from a silastic sheet, serves as a reservoir for blood (fig. 7).

c. The flow augmentation unit and agitation mechanism

Several methods were attempted to achieve optimum oxygen transfer by the oxygenator. In order to provide turbulent flow to destroy the boundary layer, a senior design team in the Mechanical Engineering Department at Virginia Polytechnic Institute and State University designed and built an agitating unit (fig. 4). A cavity, formed in the top of the agitator held the oxygenator in place. It was further secured and flattened by several plexiglass cover strips. Each individual arm of the unit was adjusted via a cam. This enabled any desired wave form to be delivered to the oxygenator's blood chamber, thereby causing turbulence. Also, by means of a variable speed motor, several rates of rotation, and therefore, agitation were achieved.

Later in the oxygenation trials, agitation was discarded as a means of augmenting flow and oxygenation. The cavity then provided the

Fig. 3. Ventricle Type Blood Pump.

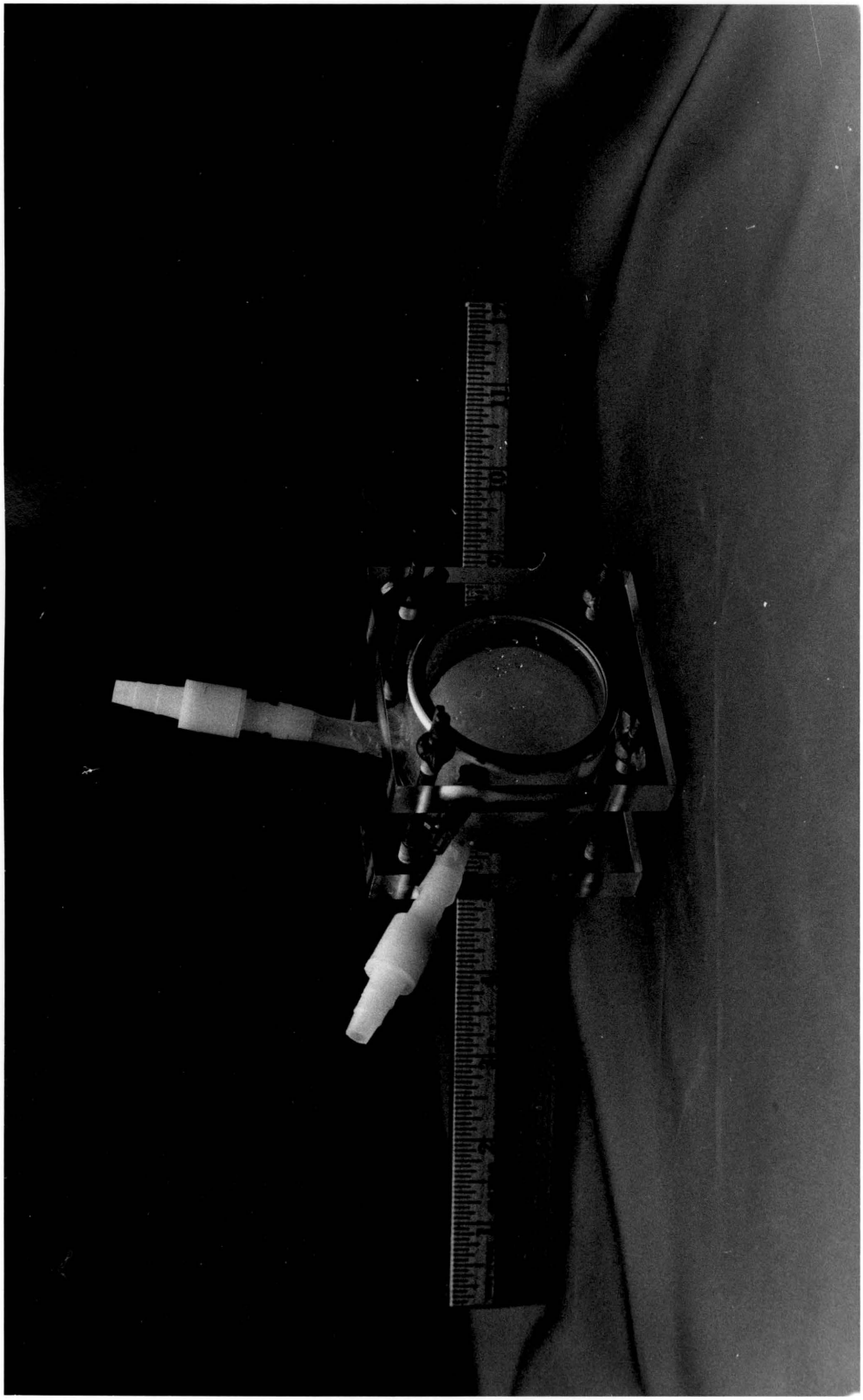
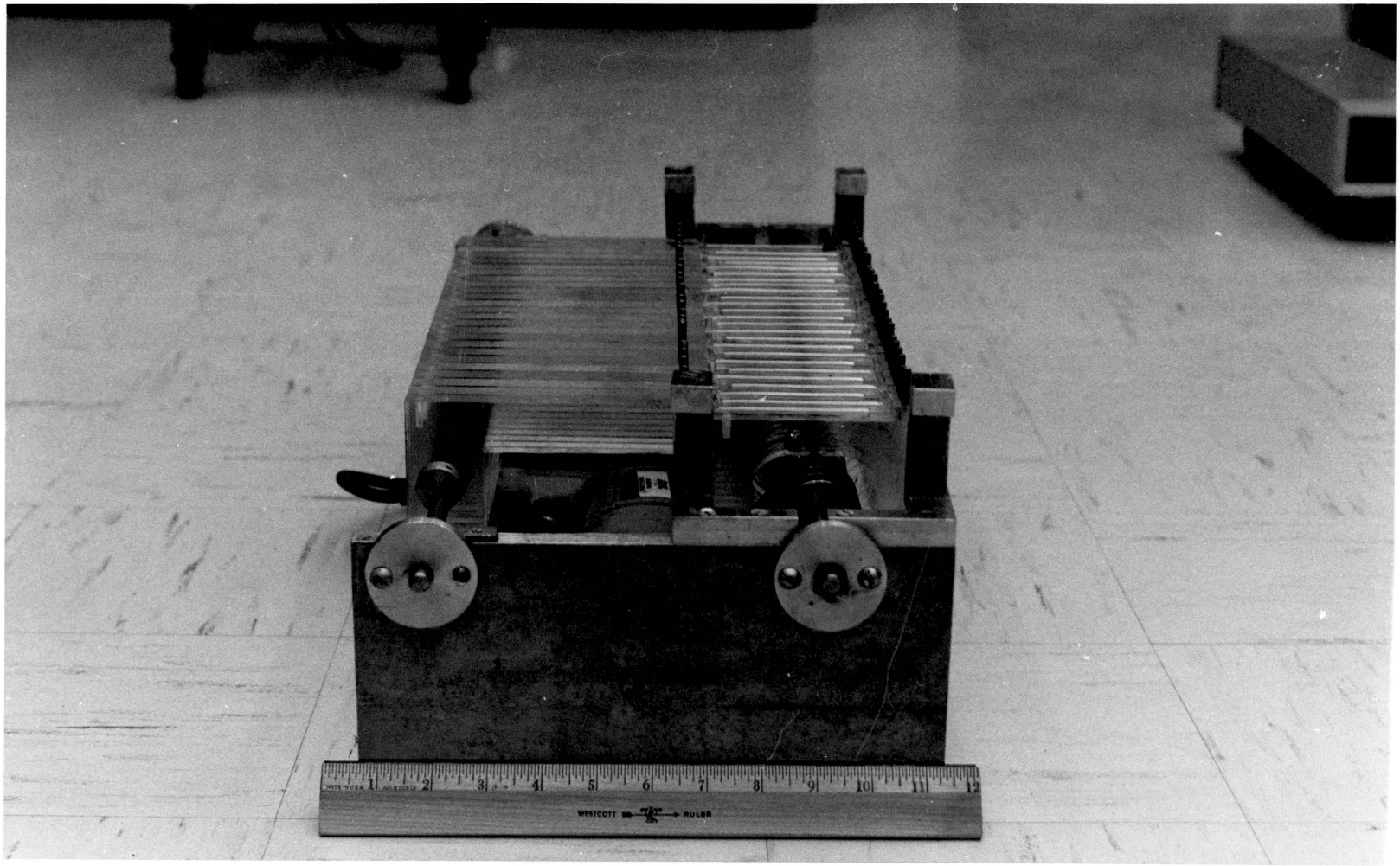


Fig. 4. Mechanical Agitation and Flow Augmentation Unit.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base for a channeling arrangement to increase the velocity of blood flow in the oxygenator perpendicular to the center line of the tubing. This channeling was achieved by simply cementing lengths of one-eighth inch diameter tubing on alternate sides of the bottom surface of the cavity. The oxygenator was then clamped into position, and it was "sandwiched" between the flow directing tubes and the clamping arms. At points where a tube and a clamping arm were in close proximity, a constriction was formed which diverted the blood flow back and forth across the membrane tubing. Fig. 5 shows a portion of this arrangement. A schematic representation of the system shown in fig. 6 illustrates the route of the blood flow through the oxygenator.

d. Blood Flow Rate Determination

In order to determine flow rate, a Statham Physiological Flow Meter (Model E-200, serial number 3102) was used, in conjunction with a Statham Physiological Flo-Probe sensor (Model E-3006, serial number 30369).

e. Complete Extracorporeal Circuit

A schematic representation of the complete extracorporeal circuit is shown in fig. 7.

4. Hemolysis Studies

First, it was necessary to determine the levels of hemolysis caused by the extracorporeal circuit minus the oxygenator. Secondly, the hemolysis levels were determined for the entire system. The differences between these measurements then determined the actual damage caused by the oxygenator. Bovine blood was collected as described previously. All blood used for each individual test came from the same animal in

Fig. 5. Close-up View of a Section of the Flow Augmentation Unit.

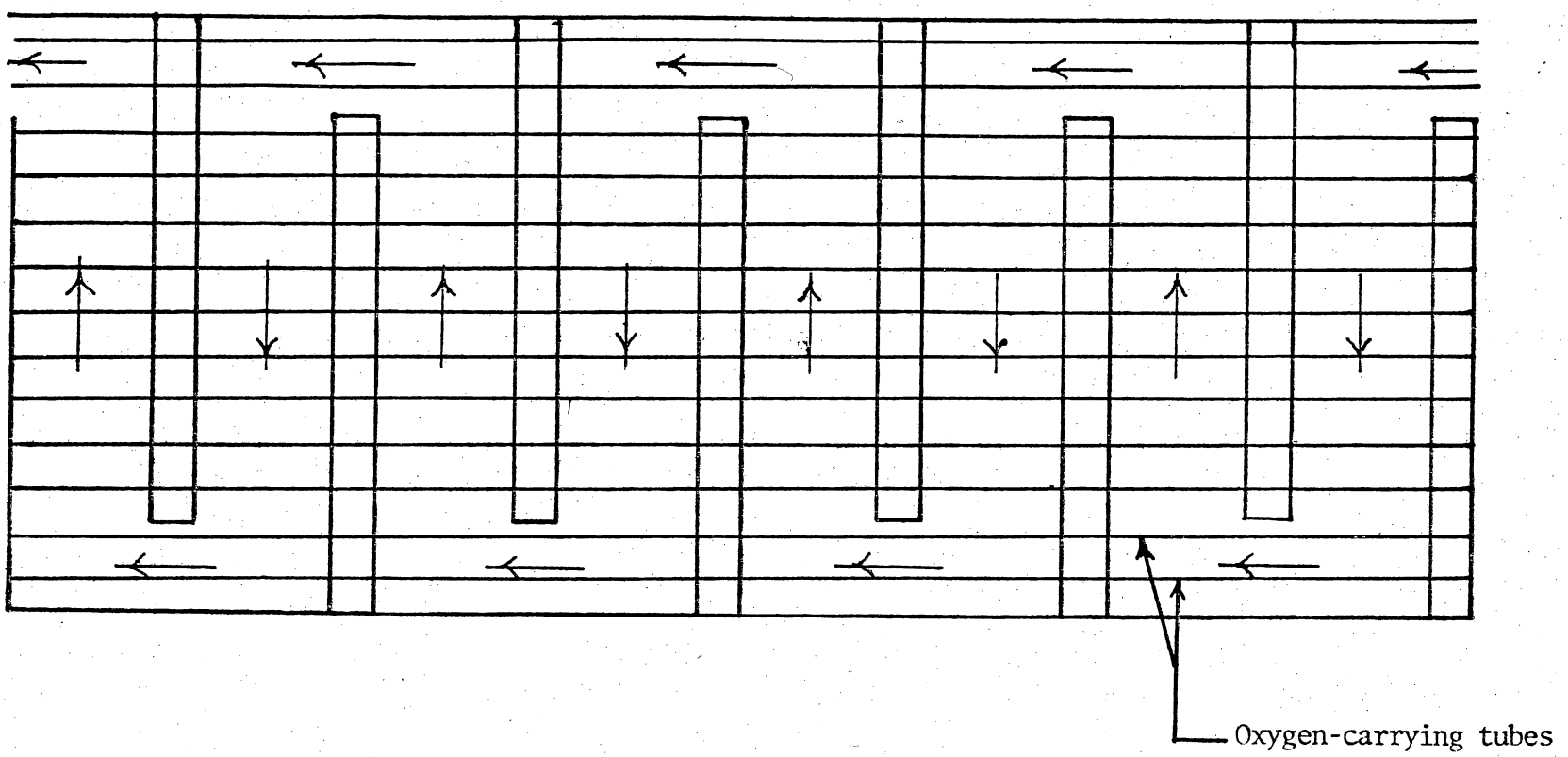


Fig. 6 Flow Augmentation Arrangement
( → Blood Flow)

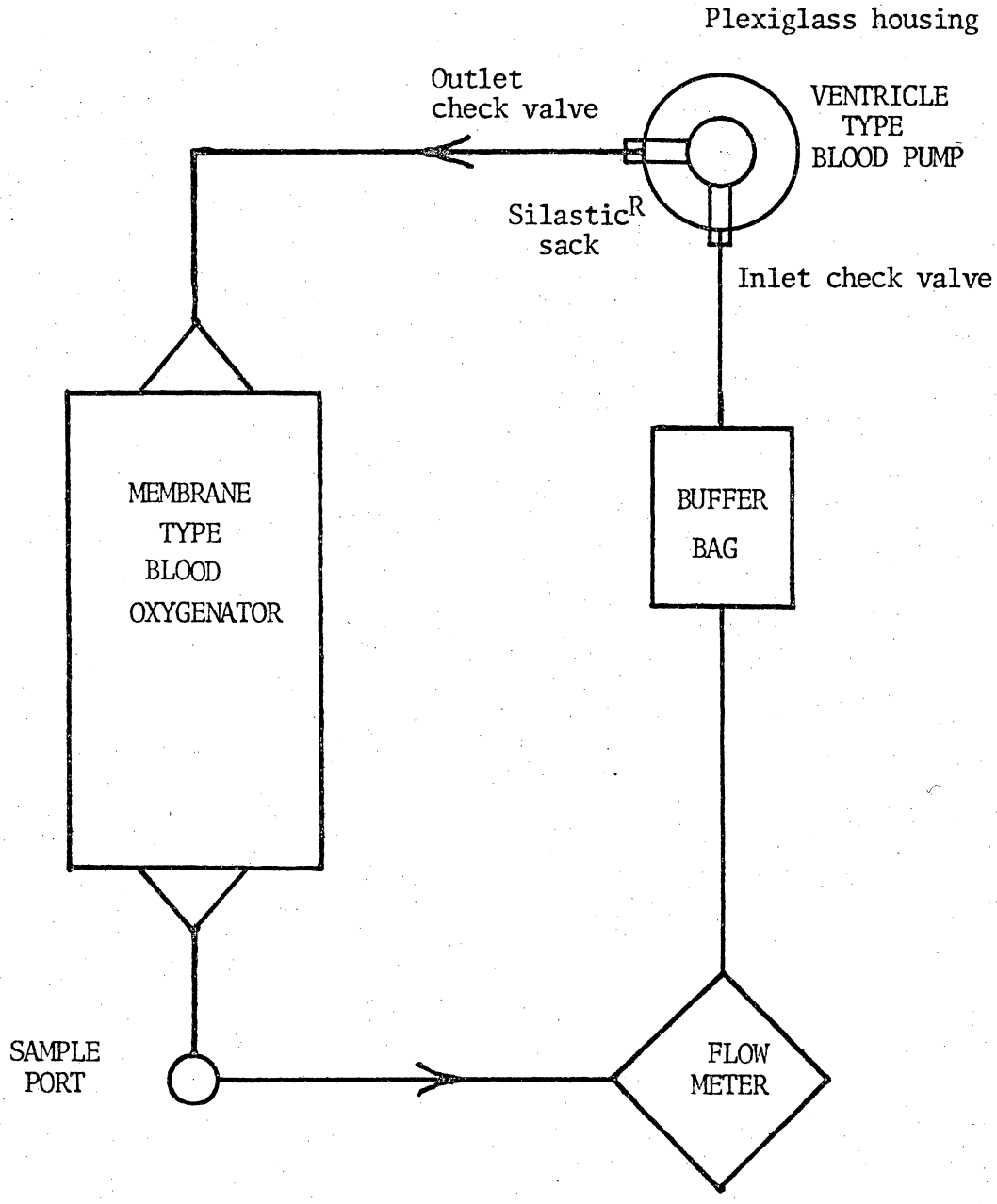


Fig. 7. Complete Extracorporeal Circuit
(⟶ Blood Flow)

order to insure uniformity. One sack served as the control while the other two sacks were used to prime the circuit. Great care was taken to prevent hemolysis while priming the circuit. The entire circuit was rinsed with 0.85% (normal) saline, followed by slow priming without violent agitation or exposure to the atmosphere. Also, all tests and storage of blood were conducted at temperatures ranging from 2-6$^{o}$C to retard bacterial or fungal growth.

Blood samples for plasma hemoglobin determination were taken at the start and periodically during the test runs. Each test lasted five days. Each sample was drawn carefully from the circuit and the control sack. All syringes and test tubes used to collect the samples were thoroughly rinsed with normal saline to minimize hemolysis.

Plasma hemoglobins were determined by using a slight variation of the commonly used cyanmethoglobin method for serum hemoglobin determination in the serum (31). The concentrations of hemoglobin were very low. Therefore, instead of using .02 ml plasma samples in 5 ml of Drabkin's solution, 2 ml were used. This enabled the reading of the hemoglobin concentration on our spectrophotometer (Coleman Jr. II) at a wave length of 540 millimicrons. Each test was done in duplicate to reduce chances for gross errors not being detected.

5. Oxygenation Studies

This portion of the work was concerned with the oxygenation of the blood by the capillary oxygenator. These studies took place at 37$^{o}$C and at a pH of approximately 7.3 to simulate body conditions. The blood was freshly collected and deoxygenated by bubbling nitrogen through it. Hemoglobin saturation with oxygen was reduced to 30-40%.

The entire circuit was primed with the deoxygenated blood. The blood then flowed through the system under various flow rates of 200 ml/min, 225 ml/min, and 300 ml/min. Blood samples were taken immediately after the blood passed out of the oxygenator. The oxygen saturation of the hemoglobin was determined by using the IL 182 CO-Oximeter (serial number 1429). To calculate the cc's of oxygen transferred across one square meter of membrane per minute, the following calculations were used:

a. Available surface area for oxygenation (A)

$$A = \frac{(\pi d_o l)(n)(6.45\ cm^2/in^2)}{10{,}000\ cm^2}$$

where,

A = Available surface area for oxygenation ($m^2$).
$d_o$ = Outside diameter for each tube (inches).
l = Length of tube exposed to blood (inches).
n = Number of tubes.

b. Oxygen transfer ($O_T$)

$$O_T = \frac{(\Delta O_2)(V)(Hb)(HbO)}{A}$$

where,

$O_T$ = Oxygen transferred ($cc O_2/min/m^2$).
$\Delta O_2$ = Change in percent of oxygen saturation.
V = Flow rate (ml/min).
Hb = Hemoglobin concentration (gms/100ml).
HbO = Oxygen bound to hemoglobin (for bovine blood=1.36 $cc O_2/gm Hb$).
A = Surface area ($m^2$).

## Chapter IV

## RESULTS

### A. Oxygenation Studies

Tables 2 through 6 show the oxygenating capabilities of the oxygenator. Tables 2 and 3 show the oxygen transfer of the oxygenator with and without mechanical agitation. It is obvious that increasing the agitation of the oxygenator greatly increases the oxygen transfer of the unit. This agitation in all probability destroys the boundary layer created by laminar flow of the blood.

The effects of changing the flow rate and agitation rates are demonstrated in tables 2-6. At very fast agitation levels (180 rpm's) and a flow rate of 200 ml/min, 94 $cc O_2/min/m^2$ is transferred. However, as soon as the external agitation is terminated, the oxygen transfer immediately drops (to 65.7 $cc O_2/min/m^2$ in this case). If the flow rate is raised to 300 ml/min, the oxygen transfer is greatly increased to approximately 141 $cc O_2/min/m^2$. Note that no mechanical agitation is required to accomplish this increase.

Oxygen pressure in the tubes was varied from 20 pounds per square inch (psig) to 15 and 25 psig (tables 5 and 6). Oxygen transfer dropped with a corresponding drop in oxygen pressure in the tubes (table 5). The same trend is observed in table 6. Note that two samples contained free oxygen bubbles indicating a very rapid transfer of oxygen; so rapid, in fact, that the hemoglobin could not bind to the oxygen as fast as it was transferred across the membrane. There was no evidence of a rupture. Obviously, this pressure level would be of great danger

to a patient because of the large possibility of gas emboli. Again note that the increase in flow rate from 225 ml/min (table 5) to 300 ml/min (table 6) greatly enhanced oxygen transfer for each given increase in oxygen pressure.

It is important to note that all oxygen transfer values are very conservative, since it was assumed that all of the membrane surface area was available for oxygen transfer. However, this is not the case; since a rather large reduction in surface area occurred when flow augmentation was added to the oxygenator.

B. Hemolysis Studies

The results of this study can be seen in figures 8-12. Figures 8 and 9 show hemolysis levels caused by the extracorporeal blood pump. Note the net increase in plasma hemoglobin concentration (the difference between the final value of the circuit and that of the control) in each test. This difference was 54.5 mg% for test 1 and 54.0 mg% for test 2. This shows excellent repeatability for the system. Also, note the relatively constant hemolysis level of the control throughout the duration of each test.

The hemolysis test results for the complete system are shown in figures 10 and 11. In these, note that the pattern of hemolysis is identical to that of the system without the oxygenator. The net hemolysis was very near to that for the blood pump alone (61.0 mg% for test 1 and 62.5 mg% for test 2). This was much less than expected. Also, note that hemolysis was nearly the same for both groups of tests. These results lead to an interesting possibility. Even though no oxygen is being forced into the tubes, the blood can still receive

oxygen from the atmosphere surrounding the oxygenator, due to the fact that the blood chamber is constructed of a Silastic® membrane sheet. There is, therefore, a $pO_2$ gradient from the atmosphere into the blood. It is obvious that this is occurring, because the blood circulating through the oxygenator is much brighter red in color than that of the nearly black control blood. Therefore, because of the low hemolysis rates observed with the oxygenator in the circuit, the red blood cells may be protected from hemolysis by the fact that oxygen can be transferred into the blood.

Fig. 12 gives even more dramatic evidence to support the last statement. This test was conducted without any flow augmentation whatsoever in the oxygenator. After 5 days of continuous running, the net increase in plasma hemoglobin concentration was only 19 mg%. This test showed that the oxygenator appeared to actually retard the red blood cell damage caused by the pump. This test was repeated, but a power failure after approximately 60 hours invalidated the results after that time. However, a 48-hour check showed no increase in plasma hemoglobin concentration over the control.

A close examination of the curves for the extracorporeal systems in figs. 8-12 shows another unexpected occurrence. Note that at approximately the 70 hour mark of the run, a change in the slope of the curve can be seen. After this point, the hemolysis rate seems to increase slightly.

TABLE 2: OXYGENATION with and without MECHANICAL AGITATION

(TEST 1)

Temperature.....37°C
pH.....7.34
Tube Pressure.....20 psig
Hemoglobin.....12.3

| SAMPLE DESCRIPTION | FLOW RATE (ml/min) | % HEMOGLOBIN SATURATED WITH OXYGEN | OXYGEN TRANSFER ($cc O_2/min/m^2$) |
|---|---|---|---|
| INLET SUPPLY | — | 39.2 | — |
| FLOW WITH NO MECHANICAL AGITATION | 200 | 46.6 | 11.7 |
| FLOW WITH SLOW MECHANICAL AGITATION (60 rpm's) | 200 | 76.0 | 54.8 |
| FLOW WITH FAST MECHANICAL AGITATION (180 rpm's) | 200 | 92.8 | 79.4 |

TABLE 3: OXYGENATION with and without MECHANICAL AGITATION

(TEST 2)

Temperature.....37°C
pH.....7.34
Tube Pressure.....20 psig
Hemoglobin.....12.3

| SAMPLE DESCRIPTION | FLOW RATE (ml/min) | % HEMOGLOBIN SATURATED WITH OXYGEN | OXYGEN TRANSFER ($cc O_2/min/m^2$) |
|---|---|---|---|
| INLET SUPPLY | — | 24.2 | — |
| FLOW WITH NO MECHANICAL AGITATION | 200 | 49.8 | 17.2 |
| FLOW WITH SLOW MECHANICAL AGITATION (60 rpm's) | 200 | 78.6 | 76.6 |
| FLOW WITH FAST MECHANICAL AGITATION (180 rpm's) | 200 | 91.8 | 96.0 |

TABLE 4: OXYGENATION with and without MECHANICAL AGITATION

(TEST 3)

Temperature.....37°C
pH.....7.34
Tube Pressure.....20 psig
Hemoglobin.....12.3

| SAMPLE DESCRIPTION | FLOW RATE (ml/min) | % HEMOGLOBIN SATURATED WITH OXYGEN | OXYGEN TRANSFER ($cc O_2/min/m^2$) |
|---|---|---|---|
| INLET SUPPLY | ——— | 32.0 | ——— |
| FLOW WITH FAST MECHANICAL AGITATION (180 rpm's) | 200 | 97.7 | 94.0 |
| FLOW WITH NO MECHANICAL AGITATION | 200 | 78.6 | 65.7 |
| FLOW WITH NO MECHANICAL AGITATION | 300 | 97.9 | 140.5 |
| FLOW WITH NO MECHANICAL AGITATION | 300 | 98.2 | 142.0 |

TABLE 5:

OXYGENATION
with
FLOW AUGMENTATION
without
MECHANICAL AGITATION

Temperature.....37°C
pH.....7.32
Tube Pressure.....Varied
Hemoglobin.....12.3

| SAMPLE DESCRIPTION | FLOW RATE (ml/min) | TUBE PRESSURE (psig) | % HEMOGLOBIN SATURATED WITH OXYGEN | OXYGEN TRANSFER ($cc O_2/min/m^2$) |
|---|---|---|---|---|
| INLET SUPPLY | — | — | 34.0 | — |
| FLOW AUGMENTATION ONLY | 225 | 25 | 93.0 | 96.3 |
| FLOW AUGMENTATION ONLY | 225 | 25 | 92.4 | 95.0 |
| FLOW AUGMENTATION ONLY | 225 | 15 | 83.7 | 81.4 |
| FLOW AUGMENTATION ONLY | 225 | 15 | 84.4 | 82.5 |

TABLE 6: OXYGENATION with INCREASED FLOW AUGMENTATION and without MECHANICAL AGITATION

Temperature.....37°C
pH.....7.34
Tube Pressure.....Varied
Hemoglobin.....12.3

| SAMPLE DESCRIPTION | FLOW RATE (ml/min) | TUBE PRESSURE (psig) | % HEMOGLOBIN SATURATED WITH OXYGEN | OXYGEN TRANSFER ($cc O_2/min/m^2$) |
|---|---|---|---|---|
| INLET SUPPLY | — | — | 33.0 | — |
| FLOW AUGMENTATION ONLY | 300 | 20 | 85.5 | 115.5 |
| FLOW AUGMENTATION ONLY | 300 | 20 | 86.2 | 117.0 |
| FLOW AUGMENTATION ONLY | 300 | 25 | 97.2* | 141.5 |
| FLOW AUGMENTATION ONLY | 300 | 25 | 96.8* | 140.0 |
| FLOW AUGMENTATION ONLY | 300 | 15 | 76.6 | 96.0 |
| FLOW AUGMENTATION ONLY | 300 | 15 | 77.8 | 98.5 |

*Bubbles in sample due to high oxygen content.

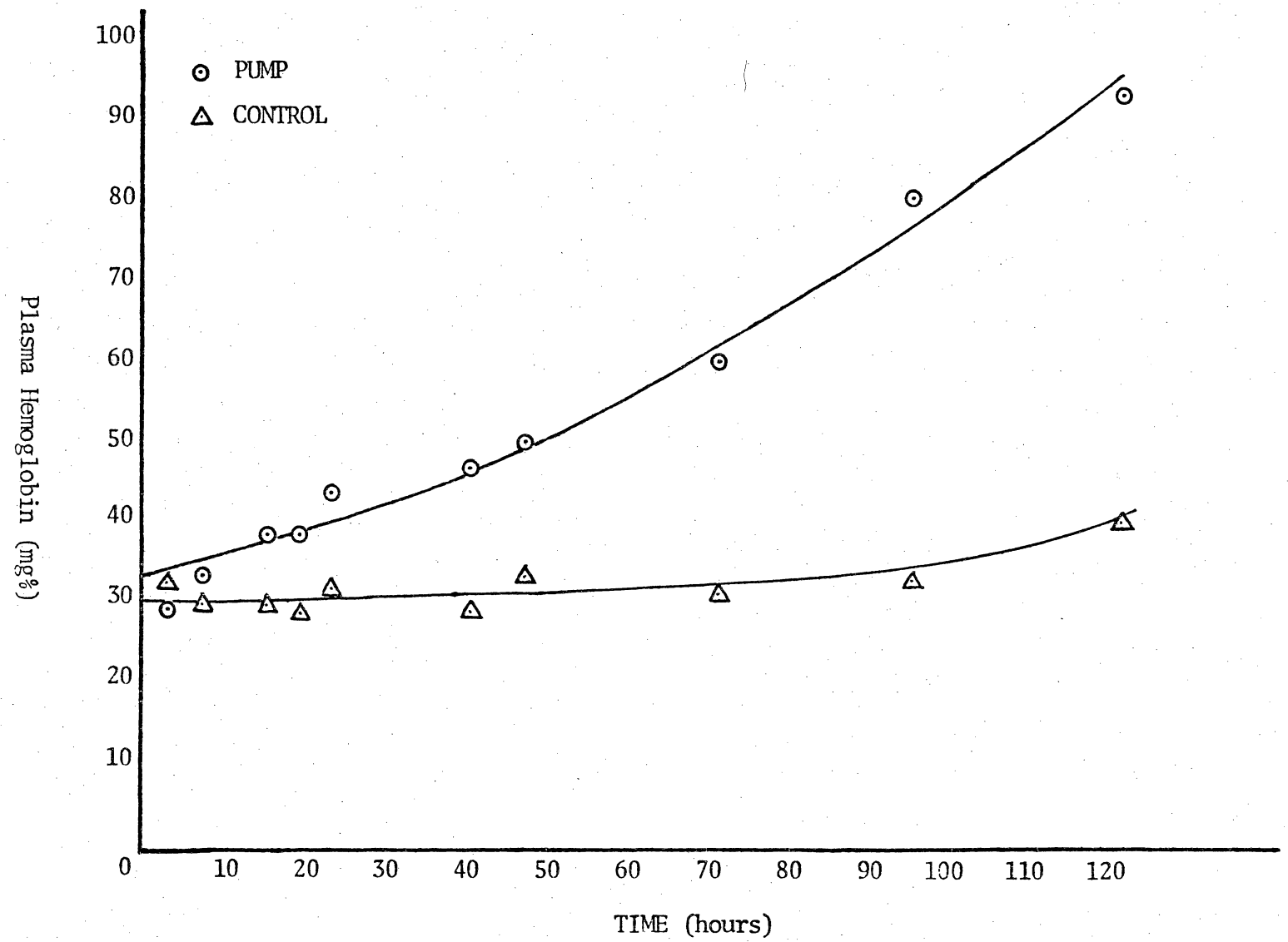


Fig. 8. Hemolysis with a Ventricle Type Blood Pump (Test 1)

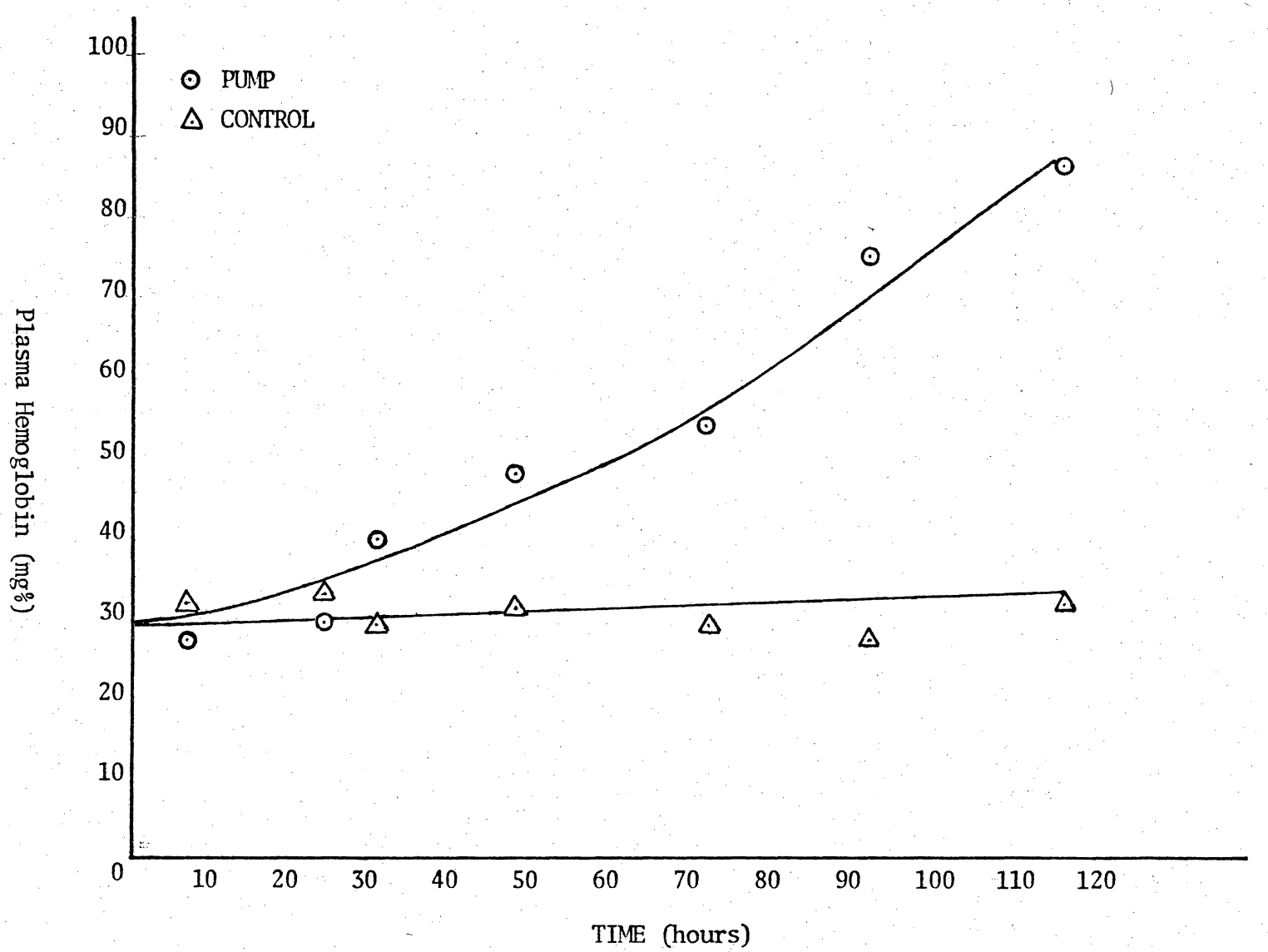


Fig. 9. Hemolysis with a Ventricle Type Blood Pump (Test 2)

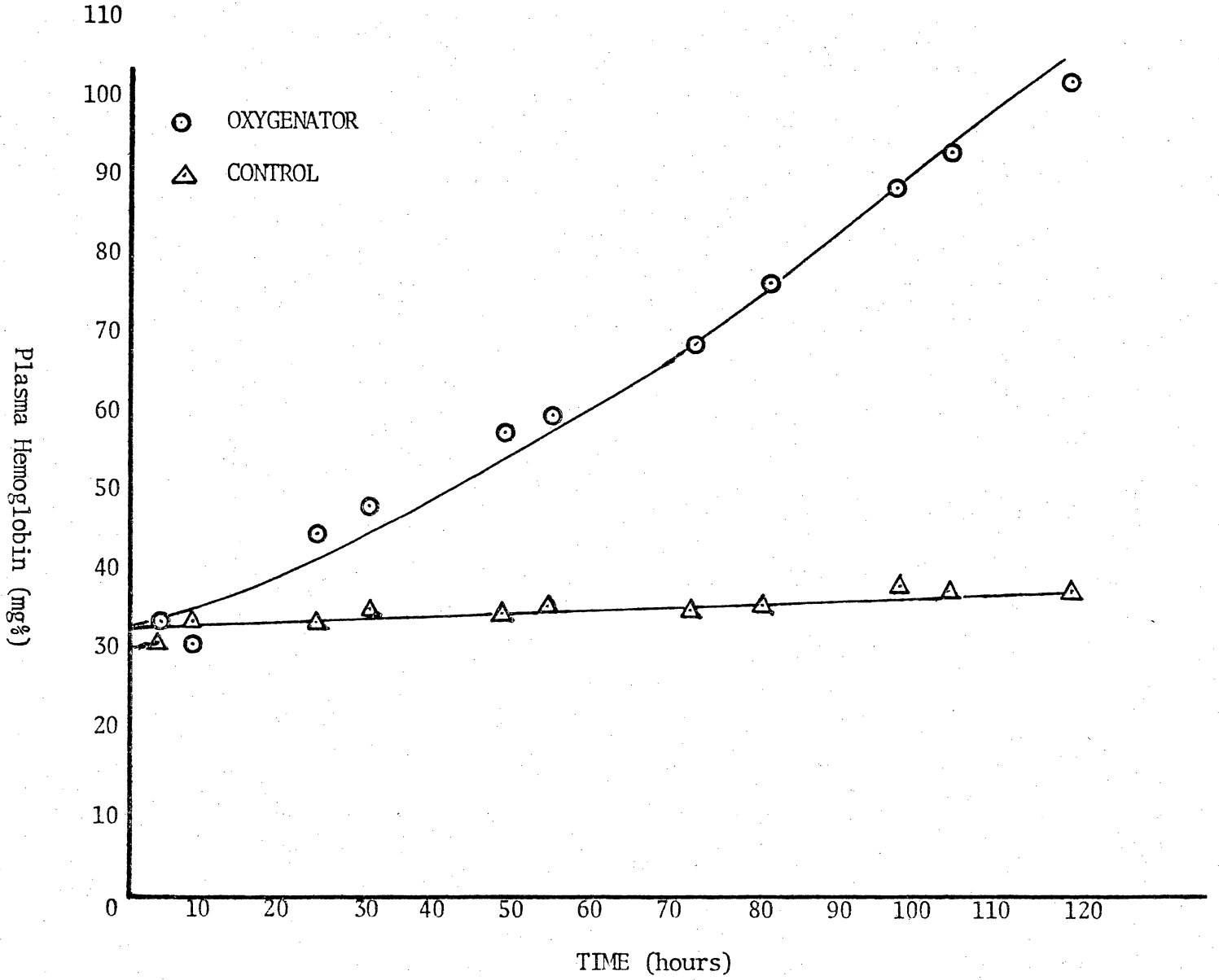


Fig. 10. Hemolysis with a Membrane Type Blood Oxygenator and a Ventricle Type Blood Pump (Test 1) (Flow Augmentation without Mechanical Agitation)

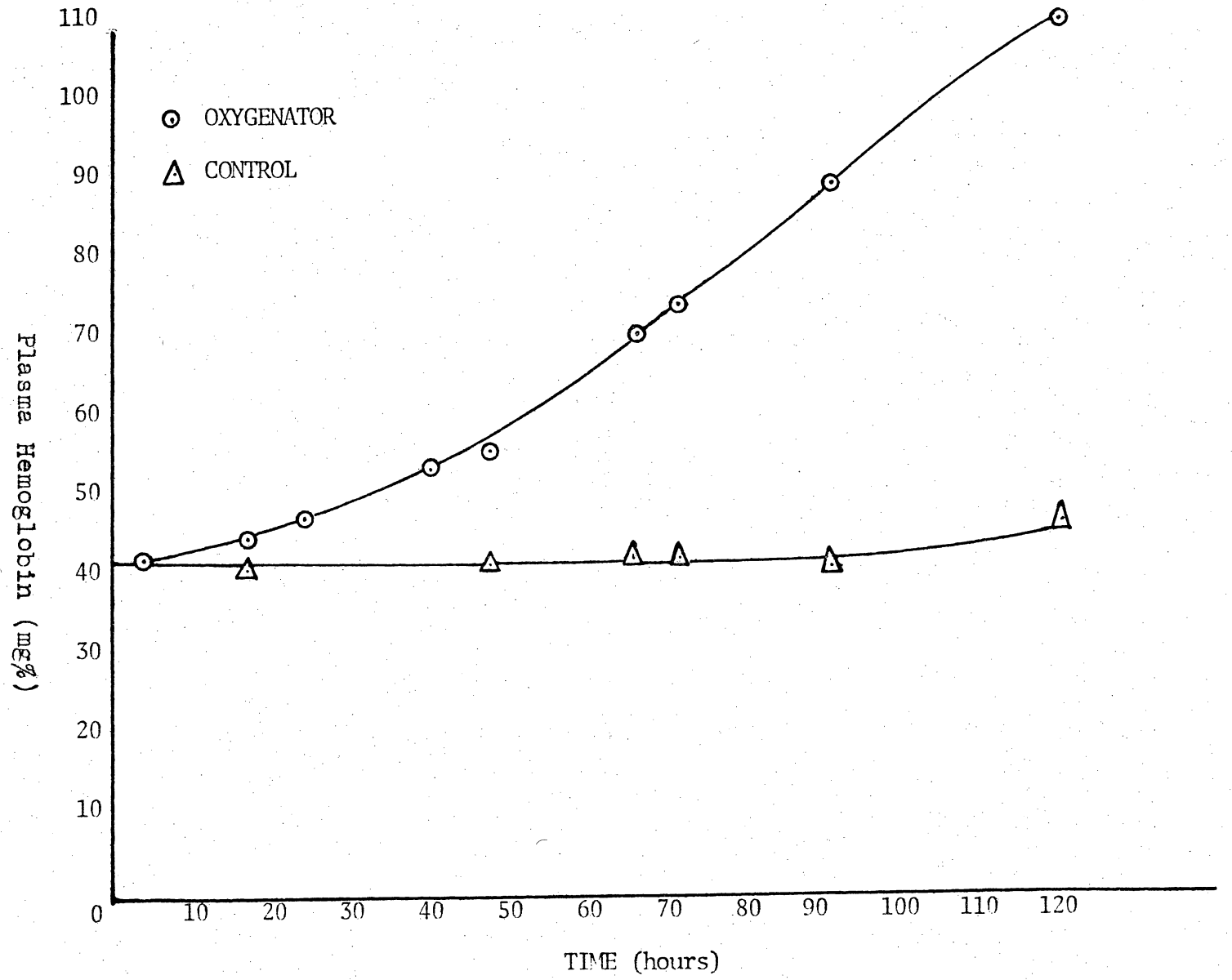


Fig. 11. Hemolysis with a Membrane Type Blood Oxygenator and a Ventricle Type Blood Pump. (Test 2) (Flow Augmentation without Mechanical Agitation)

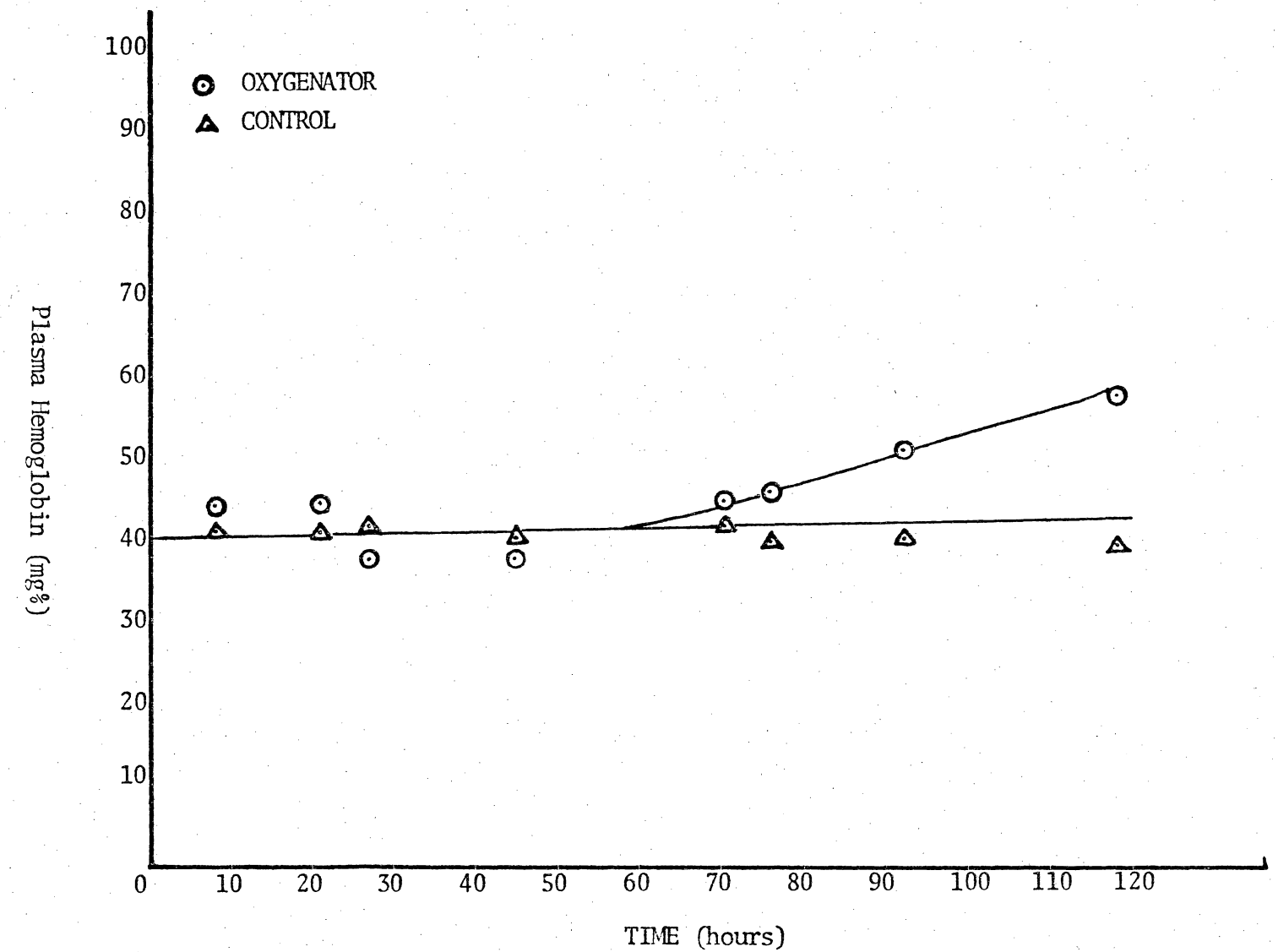


Fig. 12. Hemolysis with a Membrane Type Blood Oxygenator and a Ventricle Type Blood Pump (Test 1) (Without Flow Augmentation or Mechanical Agitation)

# Chapter V

# DISCUSSION

## A. Oxygenation Studies

The oxygenation studies gave insight into the oxygenating capabilities of the oxygenator. The discussion involves first, the general theory, problems, and possible solutions involved in blood oxygenation by membrane oxygenators, and second, specific areas pertaining to the Arp oxygenator.

When membrane oxygenators were first introduced, their most significant advantage over the direct contact units was the alleviation of much of the associated trauma to the formed elements of the blood. However, effective oxygenation of the blood was much less in the membrane oxygenator. It is well documented in the literature that the major hinderance to the transport of oxygen lies not in the membrane itself, but in the blood film geometry (4,15,22,46,56). In most membrane oxygenators, the blood flow is laminar; i.e. not turbulent. As with any flowing fluid, blood follows the rules of fluid mechanics. At any given longitudinal section of an oxygenator perpendicular to the blood flow, the velocity distribution usually follows a parabolic flow pattern (37); this is because blood in a steady state, laminar flow behaves like a homogenous, non-Newtonian fluid (15). The maximum velocity is at the center of the flow and is approximately twice the average velocity (37). This flow pattern results from frictional effects of the membrane surface and the blood. In essence, there is a slower moving layer of blood of finite thickness, the boundary layer, next to the

membrane surface (69). There is near zero flow in the region of the membrane, and this results in a diffusion controlled mass transfer which is definitely more significant in dictating the physical dimensions of an oxygenator than any other factor (4,15,29). Therefore, greater membrane surface areas are required resulting in large, cumbersome units. This in turn requires larger priming volumes (15,69) and may cause an increase in blood trauma (33). In fig. 13 we can see this boundary layer phenomenon in a simplified form.

Now let us see why this boundary layer is of concern in the development of membrane oxygenators. The effective diffusion of oxygen through the blood depends on an oxygen partial pressure ($pO_2$) gradient (15,69); this is, of course, the operative method of the lungs. This diffusion process can be seen in fig. 14. Diffusion is from an area of high partial pressure (oxygen side of the membrane) to an area of low partial pressure (the blood). If any area in this process becomes oxygen saturated, the $pO_2$ gradient slows down or completely stops. This, then, is what happens when we have boundary layer formation. The plasma and red blood cells adjacent to the membrane are rapidly saturated with oxygen (4). Also, the diffusability of oxygen through the plasma itself is slow compared to its diffusability through the membrane (56). The combination of these two events destroys the $pO_2$ gradient, thus slowing down or stopping the flow of oxygen into the center of the blood flow. Any additional oxygen moving into the boundary layer serves only to increase the saturation of the hemoglobin in this region (30) and may cause the formation of free gas bubbles in the blood. This is especially true for oxygenators that operate with a

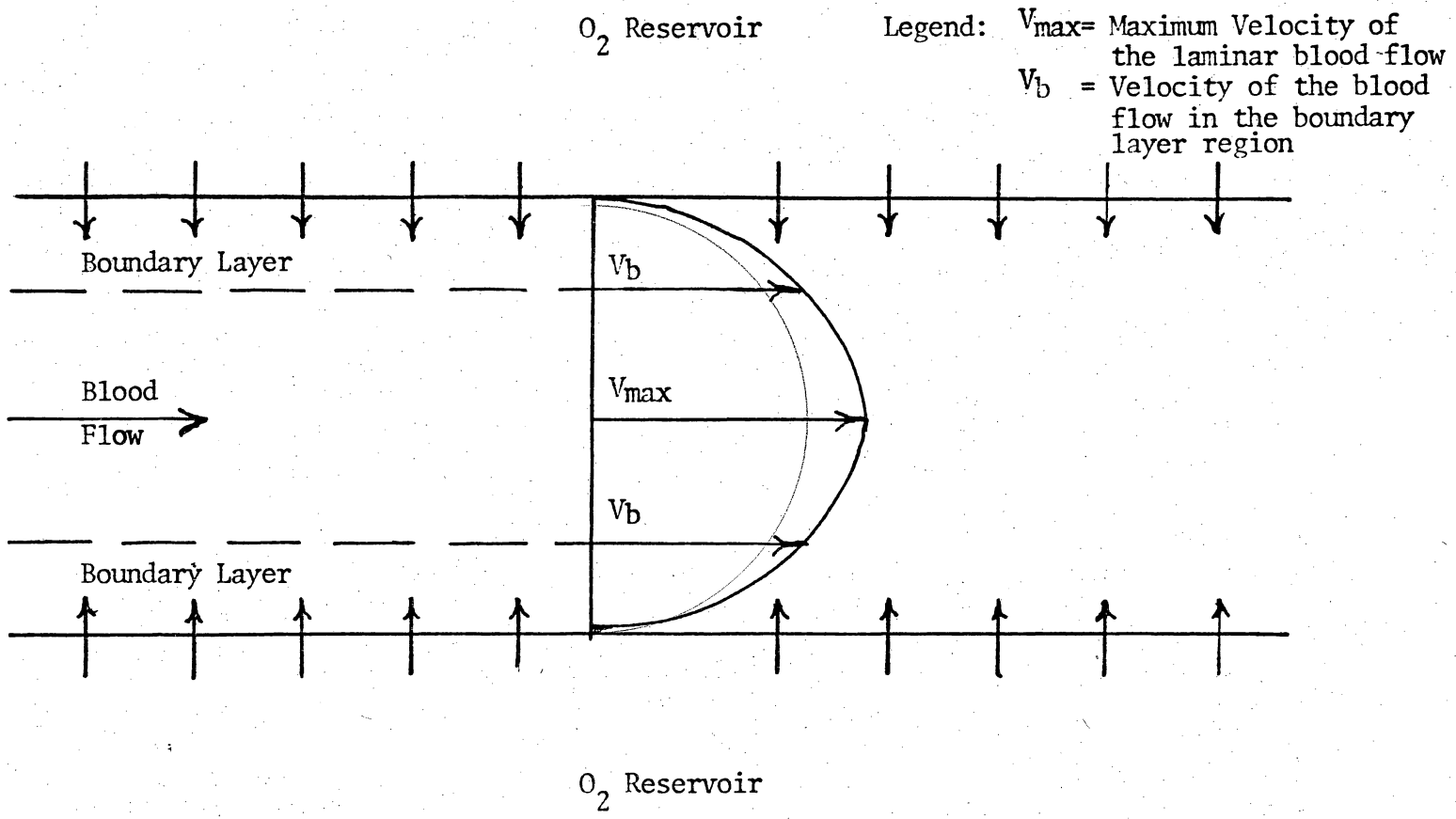


Fig. 13. Simplified View of Blood Flow in a Membrane Type Blood Oxygenator Illustrating Boundary Layer Phenomenon (Note: $V_b < V_{max}$)

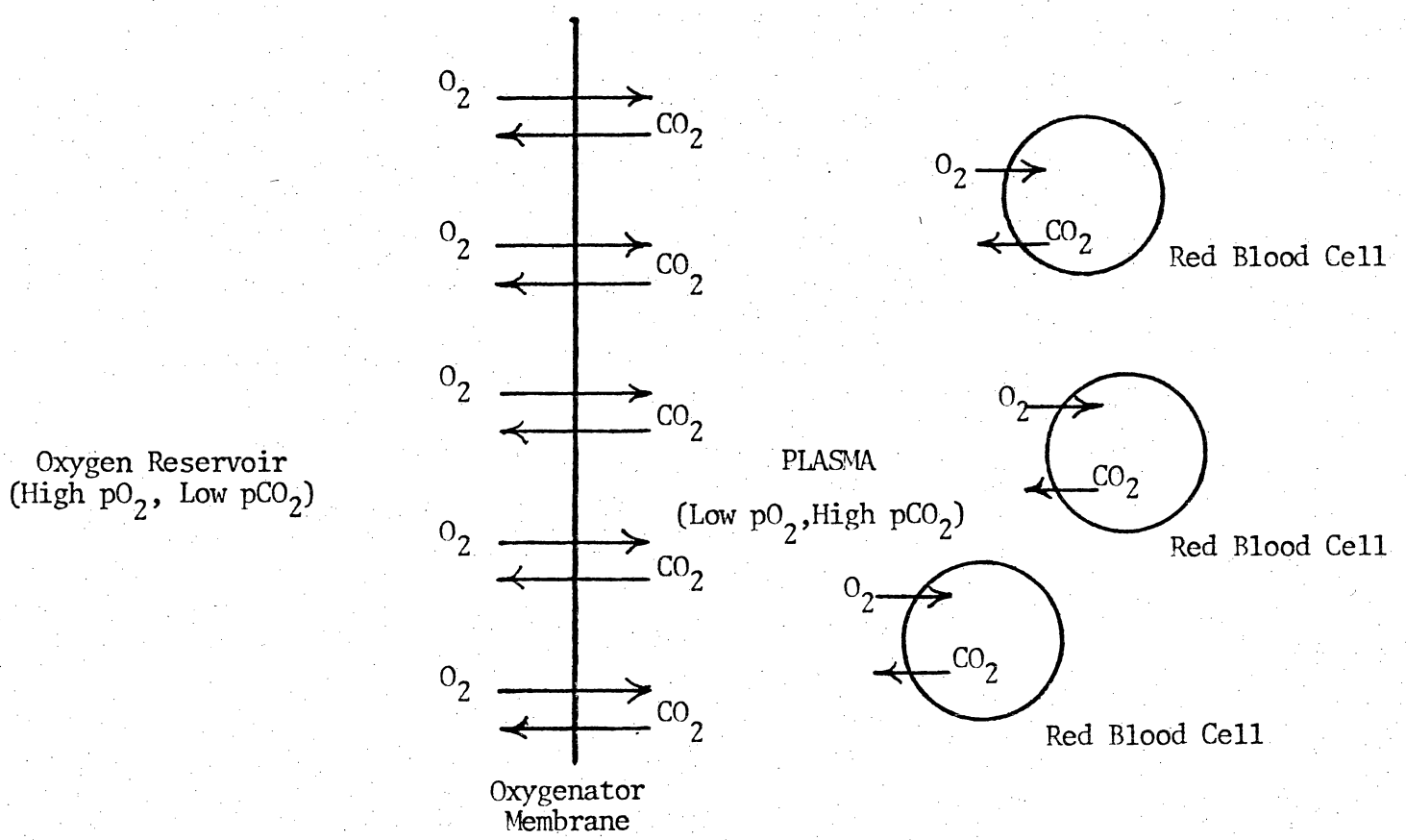


Fig. 14. Diffusion of Gases in a Membrane Type Blood Oxygenator

high $pO_2$ on the gas side of the membrane (such as ours).

Therefore, to achieve maximum oxygen transfer, the boundary layer must be removed. It has been shown that oxygen transfer gradually increased as the boundary layer was destroyed (4). Oxygen diffusion actually approached a transfer rate that was membrane limited rather than boundary layer limited. There have been two major approaches to this problem of boundary layer destruction. The first involves the production of the thinnest possible blood film by passage of blood through closely spaced, flat membranes (4,15,22,27). This presented problems such as maintenance of adequate flow rates, stabilization of membrane leakage, and maintenance of constant distances between the membranes (4). Also, there was a limit to the thinness of the blood film.

The second and most successful method of destroying the boundary layer is the induction of convective mixing of the blood (32). This mixing destroyed the blood boundary layer by creating secondary flows usually perpendicular to the blood flow. This caused a rapid turn over of the highly oxygenated boundary layer into the bulk of the blood (4, 47,74). Agitation of the blood was accomplished by two major methods: blood flow obstacles and external forces such as shaking (27). It was shown that elements placed in the blood stream promoting circulation of blood from the center of the flow to the walls reduced the size requirements of flat plate oxygenators (15). Periodic remixing of the blood at input and output junctions was also shown to significantly enhance oxygen absorption (15).

It must be noted, however, that trauma to the blood accompanies almost any improvement of oxygen transfer (27). Therefore, a balance between the transfer augmentation method and the associated increase in trauma must be determined.

Now let us see how the preceeding discussion applies to the oxygenator being studied. The boundary layer problem obviously exists in all oxygenators. In preliminary studies, poorly oxygenated blood (20-30% saturation) with a laminar flow pattern through the oxygenator changed from almost black to slight maroon in color. However, if the unit was agitated, the blood became bright red, indicative of almost 100% saturation of the blood with oxygen. (This was verified by measurements made with the CO-Oximeter.)

With the first design of the oxygenator, it was intended that blood would flow through the unit without any hindrance or agitation. (The flow was parallel to the oxygen tubes.) It was thought that many oxygenating surfaces in the flow instead of one would cause more blood oxygenation. Apparently, though, each tube was surrounded by its own boundary layer since poor oxygenation results were obtained. It was then decided that wave augmentation perpendicular to the blood flow would suffice. Next, the agitating unit was designed and built; tables 2-4 illustrate the destruction of the boundary layer and almost 100% saturation of the hemoglobin with oxygen.

Before proceeding with the testing, it was necessary to determine the level of the blood trauma caused by the agitator. If the mechanical agitation which produced the increased oxygenating capabilities of the system caused excess blood damage, then it was useless to proceed;

this, unfortunately, proved to be the case. With each agitator arm 90 degrees out of phase with its neighbor and a shaft speed of sixty rpms, extreme hemolysis, indicated by a bright red plasma, was observed after only four hours of continuous running. Next, using the most gentle setting of the agitator, (each arm was just slightly out of phase with its neighbor and a shaft speed of forty rpms to give a wave motion to the blood) intense hemolysis was again observed after only five hours of continuous running. This setting also gave unsatisfactory oxygenation results since this agitation level was not adequate to disrupt the boundary layer.

The decision was then made to attempt to find some way of channeling the blood through the oxygenator without mechanical agitation while still being able to disrupt the boundary layer. This mechanism was previously discussed in detail in the methods and materials.

The channeling mechanism proved to be the answer. No mechanical agitation was necessary to achieve good oxygenation results. The new approach produced the necessary flow augmentation without mechanical agitation and produced almost no blood damage. Instead of the blood flow being parallel to the tubes, most of it was perpendicular to the tubes (fig. 6). This pattern caused a gentle mixing of the blood destroying much of the boundary layer. The hemolysis results indicated no significant blood damage excluding, of course, sublethal damage which was not determined.

Another important factor was an increase in flow rate from 200 ml/min to 300 ml/min seemed to enhance oxygenation (tables 3 and 5). This probably caused further internal agitation. Hemolysis tests were not

done, however, at this rate.

If one refers to the oxygen transfer formula in the "Methods and Materials", it is apparent that a critical relationship exists between oxygen saturation and flow rate. One must not too quickly assume that if flow rate is increased, the overall transfer is increased. This is only true up to a point, since higher flow rates can cause a lower percent saturation of the blood with oxygen.

At this point, other important parameters of the oxygenating system should be discussed. A factor considered was the pressure of the oxygen in the tubes. Pressures of 15 psig, 20 psig, and 25 psig were tested. At 25 psig, the $pO_2$ gradient was high; the hemoglobin was rapidly saturated, and bubbles of free gas were formed. The $pO_2$ gradient provided by the 15 psig appeared too low to effectively saturate the blood. The 20 psig seemed to give the best results at any flow rate, and there was no problem with free gas bubbles.

A further very significant factor in the research was the input oxygen saturation of the inflowing blood. The vast majority of testing of membrane oxygenators described in the literature used input saturations usually no lower than 60%; the normal venous return to the heart is 68-70% (74). It is reiterated that we used saturations of 30-35% giving us a tremendous advantage over any existing system. If blood can be oxygenated to a clinically acceptable saturation (95%) quickly and without significant blood damage, as we have done, then certainly, it can be accomplished at the higher levels of saturation encountered in pathological situations.

B. Blood Damage Studies

Any serious effort at extended support of the circulation must include the biological tolerance of the blood to the constant damage caused by the extracorporeal circuit (6). There are two major areas of damage that involve the red blood cell. First is the area of immediate and complete disruption of the red cell membrane resulting in the release of large amounts of hemoglobin and the remaining cellular constituents into the plasma. Second, and perhaps more significant over long-term by-pass, are the more subtle forms of damage which may impair the ability of the red cell to survive or function over a normal life span (6). This type of damage has been termed sublethal damage.

The primary area of cell membrane destruction is at the oxygenator membrane/blood interface. It is common knowledge that maximum shear stress occurs at this interface. The proposed model for both laminar and turbulent flows involves cells flowing in the proximity of the membrane walls of the oxygenator and at the surfaces of the other elements of the extracorporeal circuit; the cells become anchored to the wall and draw out long processes of cell membranes (9). It appears that hemolysis is directly proportional to the number of red cell/wall encounters (8). This certainly explains the desirability of laminar flow over turbulent flow. In laminar flow, the boundary layer tends to reduce the cell/wall encounters (9). However, a turbulent flow has a greater velocity gradient than a laminar flow. Therefore, the turbulence destroying the boundary layer should enhance cell/wall encounters and, in turn, wall lysis (9). This emphasizes the critical balance that must be maintained between blood damage and oxygen transfer

across the membrane. These problems were obvious in our present studies. Violent agitation gave good oxygenation results (tables 1 and 2) but intense hemolysis after only four hours; no agitation gave the reverse. A gentle mode of internal agitation (with the oxygenator) resulted in an acceptable level of oxygen transfer and slight gain in hemolysis resulted (figs. 10 and 11).

Secondary hemolysis is inherent because of the nature of the fluid itself. This involves shear stresses exerted on the cells by the blood flow. However, little concrete information is available; there is mainly speculation. The problem of studying shear stresses effects on red cells (e.g. increased hemolysis) lies in the difficulty of separating them from cell/wall interaction effects. In the present study, shear stresses probably were more significant than in other studies. For example, increased viscosity resulted from a temperature decrease from the normal $37^{o}C$ to $2\text{-}6^{o}C$. If the velocity of the blood is unchanged, the red blood cell will be exposed to increased shear stress. Furthermore, it has been revealed that mechanical fragility increases with temperature decrease from $37^{o}C$ to $4^{o}C$ (9).

The five day hemolysis studies of the oxygenator present another possible effect of cell/wall interaction and shear stresses. At between sixty and ninety hours the rate of hemolysis increases. This may be an example of the "wearing down" effect by the oxygenator. In other words, the red blood cell membrane becomes fatigued and, therefore, is weakened. This is not documented in the literature, since no one has tested for this length of time. Blackshear (9) does state, however, that red cells exposed to prolonged intermediate shear stresses become

distorted so that their membranes collapse.

While discussing cell membranes, it is worthwhile to point out that with the oxygenator in the circuit there was no appreciable increase in blood damage than that caused by the circuit without the oxygenator. This opposes the original assumption, since the addition of the oxygenator meant a relatively large increase in surface area. One test (fig. 12) even showed a large decrease in hemolysis (before beginning flow augmentation). Even after the addition of the flow augmentation, there was not much increase in the hemolysis levels. This seemed to imply that oxygen had a stabilizing effect on the red cell membrane. Again, this is an area of limited, though much needed, research. Blackshear (7) noted a protective effect of an extracorporeal circuit with an operating oxygenator. Also, Blackshear (9) showed that mechanical fragility was reduced in blood saturated with oxygen. In searching for further information, it was discovered that periods of both anoxia (54) and hyperoxia (54) tended to disrupt red cell membranes. This implies a possible correct level of oxygenation whereby the membrane is stabilized. However, this problem was beyond the scope of this research.

A final area of blood trauma must be discussed: sublethal damage. (Only recently has this important area been explored.) When a red blood cell membrane stretches, it behaves as if pores were ruptured, thus allowing cytoplasmic substances to pass through (43). These pores are similar to those appearing in a woven fabric such that the pore diameter is large even though the fabric stretches only 10-20% (9). This filamentous protein mesh structure on the surface of the red blood cell

membrane is supported by the fact that actin and myosin - like proteins - were extracted from the membrane (58). Other workers have also demonstrated this pore-like structure with a monomolecular protein film (5, 63).

When the membrane stretches sufficiently, the cell contents may be altered by the "leaking out" of certain cytoplasmic substances (9). The important point is that this effect may occur even though no noticeable hemolysis is taking place. Therefore, smaller substances are able to escape before the hemoglobin. Potassium ions, ATP, and 2-3 diphosphoglycerate (DPG) were found to escape before hemoglobin. The latter two - ATP and 2-3 DPG - are particularly vital to membrane stability. This may increase the susceptability of the cell to further stress caused by the extracorporeal circuit (9). Additional hemolysis, therefore, may also occur after the patient has been disconnected from the unit.

# Chapter VI

# CONCLUSIONS

From this study it was concluded that the Arp Membrane Type Blood Oxygenator can effectively transfer oxygen to the blood with very little hemolysis over a period of at least five days.

It appears that boundary layer phenomenon is the single largest obstacle to oxygen transfer. It must, therefore, be destroyed; but in such a way as to cause the least possible damage to the blood. For the oxygenator in this study, flow augmentation proved to be far superior to mechanical agitation in accomplishing this.

It was also concluded that the ventricle type blood pump was very gentle to the blood and provided adequate flow rate.

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