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DISPOSABLE MEMBRANE OXYGENATOR (HEART-LUNG MACHINE) AND ITS USE IN EXPERIMENTAL SURGERY

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PROLONGED OPERATIONS in the open heart at normal body temperature require heart-lung machines as a substitute for cardiopulmonary function. The principle of all these is the same: they withdraw blood from the venae cavae, oxygenate it, and return it into the aorta. Thus the patient's heart is completely bypassed (Fig. 1). It was believed for a long time that the machine would have to pump and oxygenate blood in amounts equal to the normal resting cardiac output—at least 100 ml. per kg. of body weight per minute. Accordingly, several elaborate machines have been devised to pump and oxygenate 5 liters of blood per minute, for example by Dennis,[1] Jongbloed,[2] and Kolff and Dubbelman.[3,4] The most successful design was that of Miller, Gibbon, and Gibbon.[5] A similar machine is in use at the Mayo Clinic[6,7] with outstanding success; its complexity and cost have prevented its wider use.

* *Fellow.*

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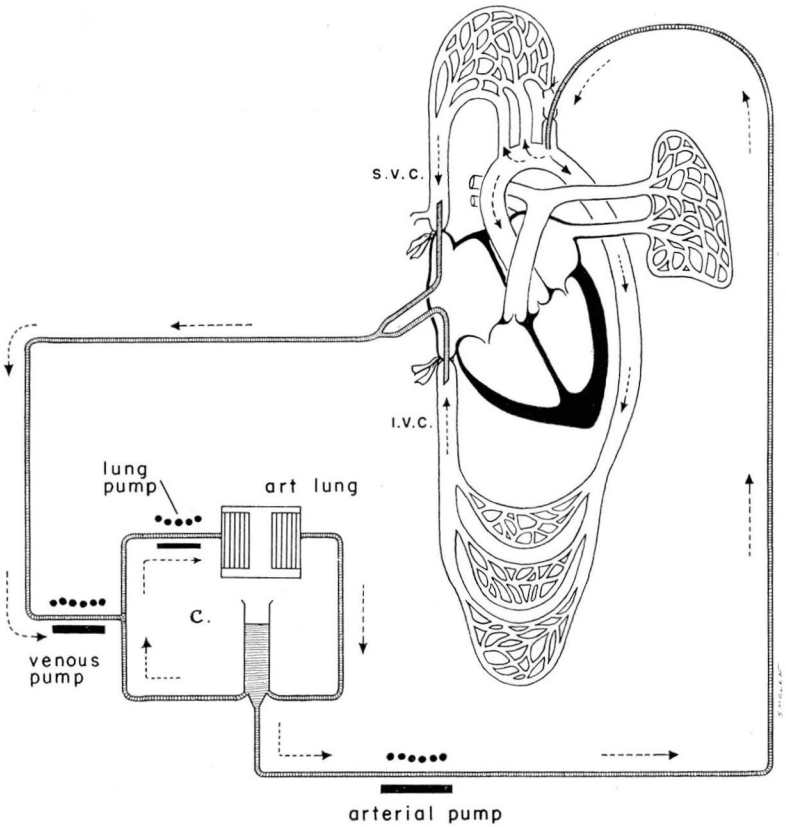

Fig. 1. Diagram showing general principles of artificial maintenance of circulation. The blood is sucked out through two cannulae from the venae cavae. It is oxygenated and is pumped back into a branch of the aorta, in this case the left subclavian artery. The flow in the proximal part of the aorta is reversed and the coronary arteries having their openings above the aortic valve are provided with blood by the machine. When ligatures are tied around the roots of the venae cavae and the azygos vein, no blood will enter the heart, except that coming from the coronary sinus and the thebesian veins.

Andreason and Watson [8,9] in England have shown that dogs survived at least 35 minutes of occlusion of both venae cavae when only the azygos vein was left open and cardiac output was reduced to 10 to 18 milliliters per kilogram of body weight per minute. Lillehei, Varco, and co-workers [10-14] have greatly advanced cardiac surgery in this country by using this principle. In dogs, they found that flow rates of 30 to 45 milliliters, as provided by cross circulation or some type of artificial heart-lung apparatus, were more suitable than the '*azygos flow*' rates of 10 to 18 milliliters per kilogram per minute. Their successful experience with 110 patients has established the principle and the procedure as being clinically valid.

The possibility of using a small flow rate revived the old idea of oxygenating blood in an apparatus using membranes. The advantages are obvious: There are no air bubbles, the possibility of air embolism is excluded; blood is not exposed to foam or screens or metal, so that potential sources of fibrin formation are eliminated.

During the earliest experience with the rotating type of artificial kidney in human beings,[15] it was observed that blue blood which entered the machine would become red during its course through the dialyzing tubing. Dubbelman[3] calculated the amount of blood that could be oxygenated in this apparatus and found that the process was impractical when high rates of blood flow were necessary. Brubaker and Kammermeyer[16] compared the gas permeabilities of various membranes and found that polyethylene is permeable to both oxygen and CO_2. Clowes[17] showed that the oxygenation of blood through a membrane of polyethylene of 1-mill thickness is much better than that through a membrane of 1.5-mill thickness. Kolff and Balzer[18] demonstrated the disposable artificial lung, here described in detail, at the first meeting of the American Society for Artificial Internal Organs in 1955. It is based on the principle of oxygenation through a polyethylene membrane. One lung unit will oxygenate 75 ml. of blood per minute; this, at a flow rate of 35 milliliters per kilogram of body weight per minute, corresponds to the requirements of a 2-kg. dog. By placing more than one unit in parallel, we can adapt the apparatus to dogs (or to children) weighing from 2 to 21 kg. (4 to 47 pounds). During use, each lung unit holds 500 ml. of blood.

This paper will describe the disposable oxygenators, the pump, the additional equipment used, and the experimental results obtained in a study of more than 130 perfusions in dogs.

Description of Apparatus

The artificial lungs. After trying out various sizes, we selected the following type of

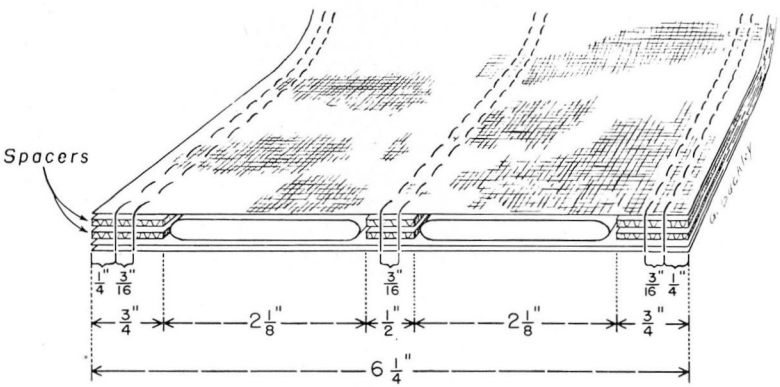

Fig. 2. Cross section of membrane arrangement of the artificial lung. There are three layers of Fiberglas window screen, two tubes of polyethylene, and three pairs of spacers (to allow space for the tubes to become distended with blood).

polyethylene lung: 7-meter long strips of plastic-coated Fiberglas screen envelope two polyethylene tubes (Fig. 2). The polyethylene tubing has a lay-flat diameter of 2 inches and its wall-thickness is 1/1000 of an inch (1 mill).* The two tubes have an oxygenating area of 14,000 sq. cm. On each side of the tubing are spacers to allow some distention of the tubing when the blood flows through it. The 7-meter long strips are specially stitched, as described for the disposable coil kidney.[19] The strips are wound around a can (10 cm. in diameter) and are provided with inlet and outlet tubing, also identical to those used in the coil kidney. The completed coil (Fig. 3) is placed in an ordinary transparent plastic bag, such as that used for vegetables. Oxygen is blown into the bottom part of the artificial lungs at a rate of 30 liters per minute (for eight lungs). It is heated to approximately 40 degrees C. in a copper coil immersed in a constant-temperature water-bath. A string is tied around the top of the bag, just tightly enough so that oxygen flow will distend the bag, but loosely enough so that CO_2 and excess oxygen may escape through the top. The lungs are prefabricated and sterilized with ethylene oxide by Baxter Laboratories,** and can be kept sterile until needed. Since the lung units are contained in transparent plastic bags, a blood leak can be seen. A small pinhole leak does not interfere with use of the lung, but if a large leak develops, that particular unit must be replaced. The lungs are pretested at the factory, and in our experience only one in approximately 80 units had to be replaced because of leaks.

The pumps. We use the same type of commercially available finger pump as that used by Lillehei and co-workers. For the arterial and venous pumps we use a dual Model

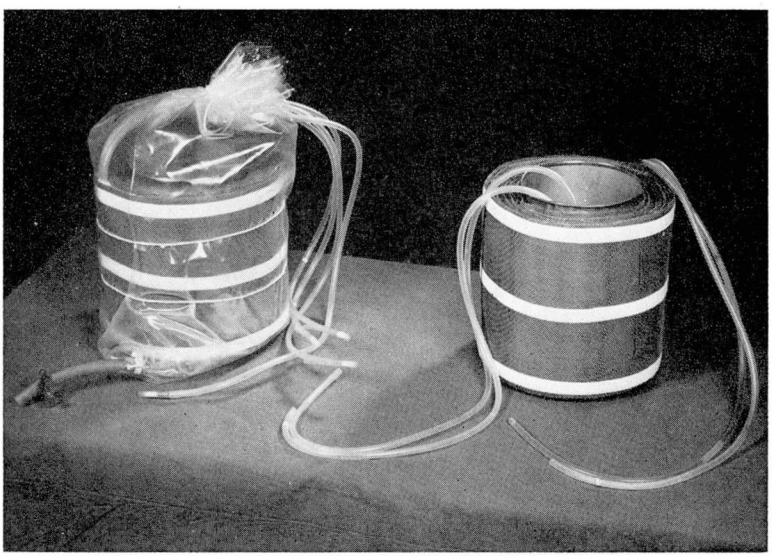

Fig. 3. Artificial lung (right) and artificial lung in a plastic bag with tube for oxygen inlet at the bottom.

* *Polyethylene tubing was provided by Visking Corp., 6733 West 65 Street, Chicago 38, Illinois, through the courtesy of Mr. W. E. Henderson, Assistant Manager of the Plastic Film Development Department.*

** *Baxter Laboratories, Morton Grove, Illinois.*

T 6 F Sigmamotor Pump.* The variable-reduction transmission in this pump has been provided with dials for calibration (Fig. 4) by Mr. Frederick Olmsted of the Research Division. A third pump or "lung pump" is used for the lung circuit. This pump is a single Model T 6 F Sigmamotor Pump.*

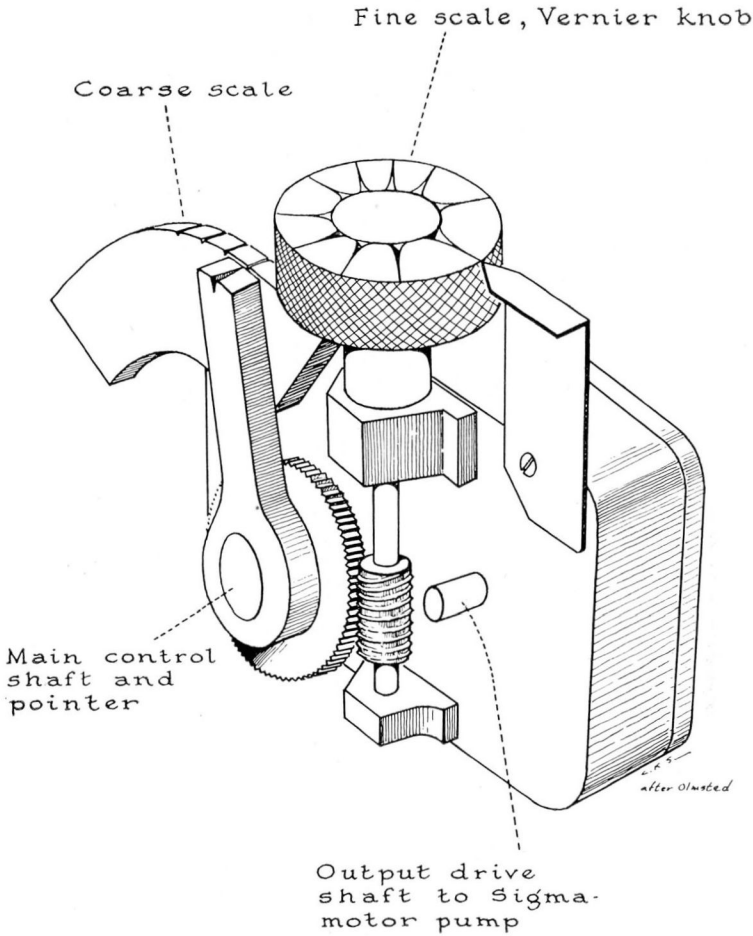

Fig. 4. Calibration adjustor made by Mr. Frederick Olmsted for the variable-speed reduction transmission of the blood pumps.

The blood circuit. In order to maintain a constant volume of blood in the oxygenator system we have adopted the third pump, as did Miller, Gibbon, and Gibbon.[5]

The center section of Figure 5 outlines the lung circuit. The first step is to recirculate blood through this circuit at a constant rate. The lung pump is set to provide a flow slightly in excess of the maximal flow planned for the experiment. Blood travels through the lungs and is collected in a manifold made from a plastic bag similar to a blood-trans-

* *Sigmamotor, Inc., Middleport, New York.*

fusion bag. Since flow through the lungs, resistance in them, and the volume of blood that accumulates in them are stable, the blood in the collecting manifold assumes a constant level. This level can be adjusted by raising or lowering the attached burette. Polyethylene is permeable to oxygen and CO_2 but is almost impermeable to water, so that there is no appreciable loss through evaporation. Although changes in volume of as little as 20 ml. can be detected, we have found that the blood level in the manifold remains stable over several hours.

To establish an artificial circulation, the arterial pump is set at a predetermined rate (usually 35 ml. per kg. of body weight per minute) and the venous pump is adjusted so that rates of inflow and outflow are identical, as judged from the level in the collecting manifold. Since the volume of blood in the manifold and burette is large, accidental sudden reduction of inflow does not immediately deplete blood from the machine or

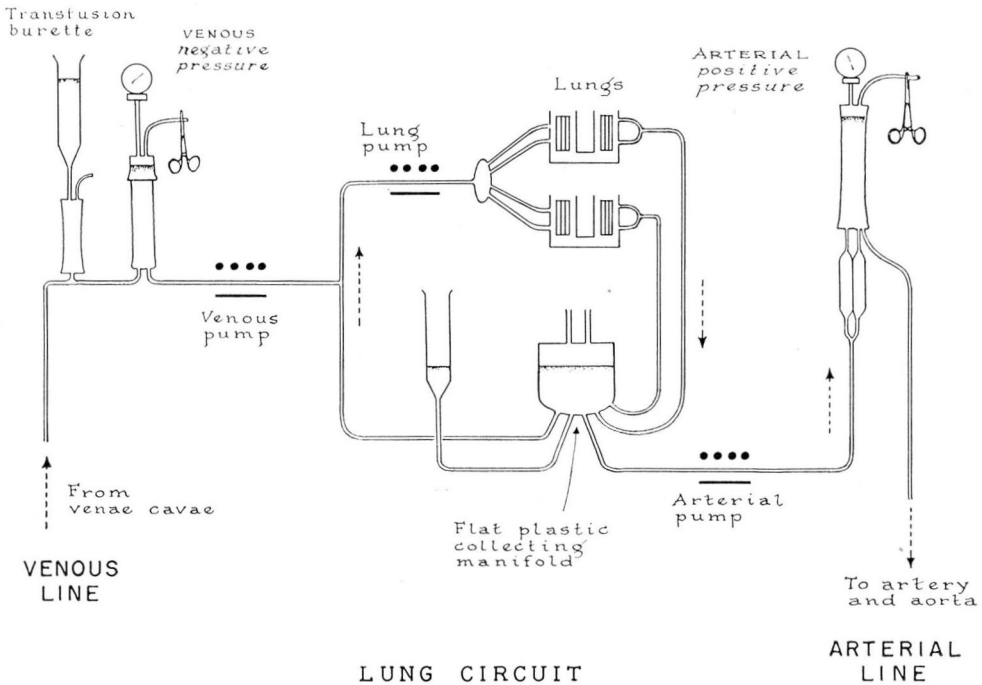

Fig. 5. Artificial heart-lung circuit. Blood coming from the venae cavae passes a bubble catcher with a negative-pressure manometer that indicates the degree of suction. The venous pump delivers the blood into the lung circuit. The arterial pump at right, pumps the oxygenated blood out of the circuit through two filters, and a bubble catcher with a positive-pressure manometer. This manometer indicates the animal's blood pressure when the pump is not running. It will indicate the sum of the animal's blood pressure, plus the pressure necessary to overcome the resistance in the arterial lines and cannulae while the pump is running. In the center of the figure is the lung circuit. The lung pump is set at a rate slightly higher than the highest rate at which the arterial pump will work in the particular experiment. The speed of the lung pump is not changed; with both venous and arterial pumps not running, an equilibrium is established and the blood in the collecting manifold stays at the same level. When the venous and arterial pumps are started and the level is maintained, input and output of the machine are exactly alike.

result in air embolism. When reduction of inflow does occur, it usually indicates that the dog has lost too much blood, so that caval flow is inadequate. When this is the case, the dog is transfused from the transfusion burette. Inadequate caval flow or obstruction of venous catheters may be recognized from an excessive negative pressure in the manometer attached to the bubble-catcher in the venous line.

Details of the arterial line, the venous line, and the manifold that distributes the blood over several lungs are shown in Figures 6, 7, and 8. The only parts of the heart-lung machine that are not yet provided by the Baxter Laboratories at this time are two silicone-coated burettes and the rubber tubing that fits in the pumps.

Blood used. Blood is drawn into siliconized blood-transfusion bottles* containing 12 mg. of heparin in 30 ml. of a diluent consisting of glucose 2½ per cent, and sodium chloride 0.45 per cent in water. Each bottle received 500 ml. of blood. Usually the blood is collected by puncture of the femoral artery. If the artery has to be prepared under local anesthesia, succinylcholine, 10 to 20 mg. is used,† rather than a barbiturate which might pass via the blood into the 'patient' dog.

It is unnecessary to fill the machine with saline prior to use. The equipment is assembled dry and it is directly primed with blood. This avoids undesirable dilution of the donor blood with saline. We need approximately 500 ml. of blood for each lung unit that

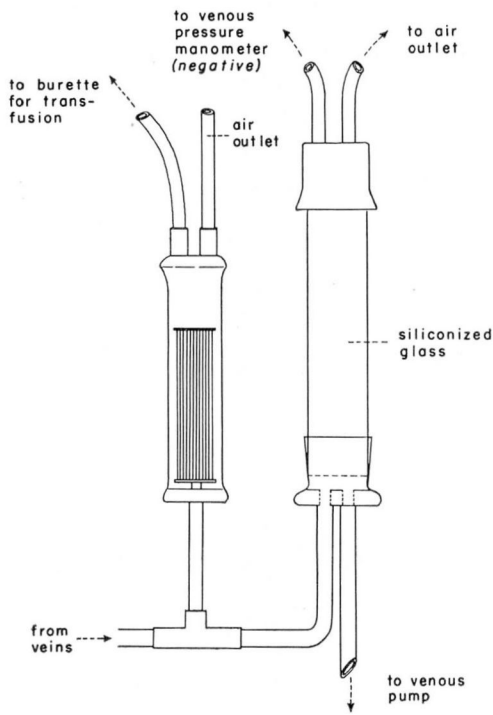

Fig. 6. Venous inflow line, with a filter for blood that enters from the transfusion burette (made by Baxter Laboratories).

* *Provided through the courtesy of Baxter Laboratories.*

† *Respiration is maintained with a respirator.*

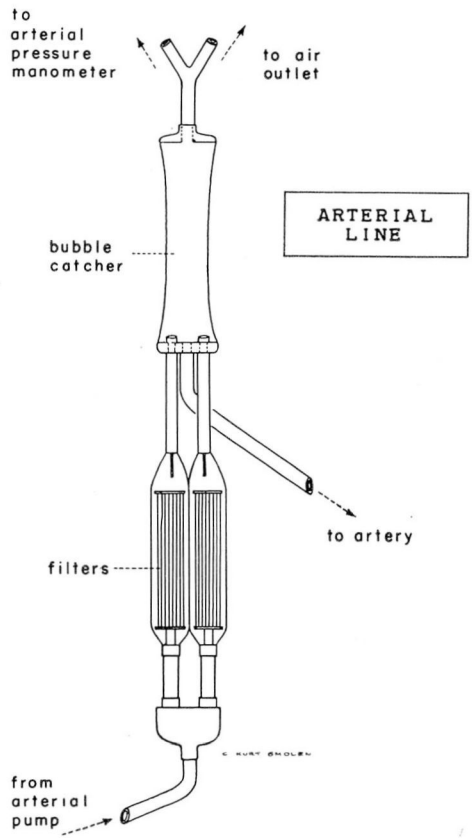

Fig. 7. Arterial outflow lines have two filters and a bubble catcher (made by Baxter Laboratories).

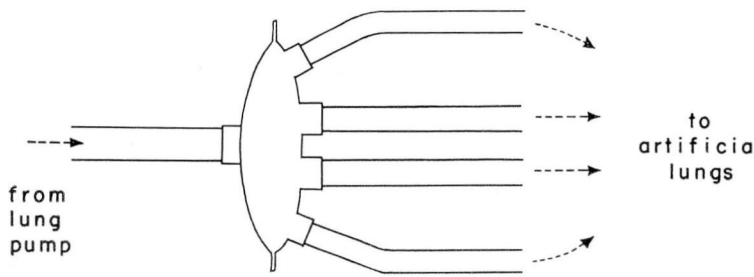

Fig. 8. A lung manifold. We have other manifolds for eight lung units (made by Baxter Laboratories).

is used, plus 500 ml. to fill lines, circuits, and burettes.

The blood lost during operation is collected in a measuring cylinder that is coated with silicone so that the volume can be measured accurately without being obscured by foam. An equivalent volume of blood is replaced and an additional 15 ml. per kilogram of body weight is transfused during each run.

Technic

Anesthesia. Preoperative medication: Procaine penicillin, 400,000 units, and streptomycin, ½ gm., are administered on the day before and on the day of the experiment. Morphine, 5 to 15 mg. depending on the weight of the dog, is administered one or two hours before operation.

Induction: One per cent thiopental (Sodium Pentothal) is administered intravenously in small interrupted doses, for endotracheal intubation, in an average total dose of 10 mg. per kg. of body weight. This anesthesia is supplemented with succinylcholine, diluted 1 mg. per ml., given intravenously in intermittent doses (total 0.5 to 1 mg. per kg. of body weight) to maintain diaphragmatic relaxation. Controlled respiration with 100 per cent oxygen is maintained throughout the procedure except while the cavae are occluded. Immediately prior to connection with the machine, the dog is hyperventilated; but during the actual run, the lungs are permitted to remain 50 per cent collapsed. Since anesthetic agents given to the dog intravenously during the run would be sucked into the machine, they are injected as needed into the arterial outflow line from the machine. Ninety per cent of the animals require no more anesthesia during or after the run. Light anesthesia is preferred so that the dog is moving at the end of the procedure, permitting adequate and immediate evaluation.

Operative technic. In the early experiments, testing of the oxygenator was the main purpose, and cannulation was performed from the neck. A long plastic cannula with side openings was inserted from the external jugular vein through the right atrium into the vena cava caudalis. Ligatures were tied around the venae cavae where they enter the atrium, and around the azygos vein. Thus, all venous flow into the heart was closed off before the heart was opened. (There were side holes in the catheter where it lay in the cranial and caudal venae cavae.) The blood was returned to the arch of the aorta through a cannula inserted through a carotid artery. The chest was opened in the fourth or the fifth intercostal space on the right side.

To train the surgical team for the intrathoracic cannulation and to simulate the procedure that later would be used in human infants, transverse thoracotomies were performed. The venae cavae were cannulated from the right auricle, and the aorta from the left subclavian artery. The technic has been described by Lillehei and co-workers, and the cannulae that we used are like theirs.* After the technic of cannulation had been mastered, we returned to inserting the arterial cannula through the cervical portion of the carotid, in order to avoid

**Pharmaseal K-60 expendable, plastic suction catheter Size 14 French.*
Pharmaseal K-21 expendable, plastic oxygen catheter Size 10 French.
Pharmaseal Laboratories, Glendale 1, California.

the transverse thoracotomy. Healing of a transverse thoracotomy, especially in large dogs, is difficult.

Postoperative care. All dogs were observed for at least six hours postoperatively. The administration of meperidine hydrochloride sometimes was necessary to keep the dogs quiet during the postoperative hours when they were kept on the table to facilitate recording of blood pressure, aspiration from the chest tube, and transfusion of blood if necessary. The tip of the chest tube should be in the dorsal part of the chest cavity, just above the diaphragm, and the dog should lie on the side in which the catheter is inserted. During the first three or four hours after operation, the dogs received a continuous infusion with protamine sulfate and sodium bicarbonate, as will be described later.

Table 1.—*Results of experiments with artificial heart-lung machine*

Lig. of V.C.	Rt. aur. opened	Rt. vent. opened	I.A.S.D. made and closed	I.V.S.D. made and closed
+	—	+	—	—
—*	—	—	—	+
+	+	—	—	+
+	+	—	—	+
+	+	—	+	+
+	+	+	—	—
	+	—*	—	+
	+	+	—	
	+	+	+	
			+	
			+	
			—	

Each + or — represents one dog.
+ Dog survived and recovered completely.
— Dog died within two days after the operation.
*—*Dog died more than one week after the operation.*

Results

Mortality. Table 1 pertains to the work done before the first of November 1955 and presents results with 43 dogs consecutively treated with various operative procedures. It is evident that each new procedure in the beginning took its toll. Later, when we began to perform transverse thoracotomies, and when we practiced on very small pups (the smallest weighed 1.2 kg.), we again had a high mortality.

The late mortality in dogs for the most part was caused by pleural effusion or wound infection with empyema. Some late deaths were due to atelectasis of one lung, caused by an air leak or mucus in the bronchus.

Before attempting elective potassium arrest, which will be discussed in the following article, we had performed seven consecutive experiments, in all of which the right ventricle was opened and in all of which the dogs recovered.

Hemolysis. Dog blood hemolyzes readily, and the extent of hemolysis largely depends on the method of drawing the blood. A survey of the influence of hemolysis on survival, on the occurrence of hemoglobinuria, and on the increase of plasma hemoglobin was made during the early experiments of this series. It was found that the plasma hemoglobin contents of 23 dogs that survived, ranged from 84 to 360 mg. per hundred milliliters (average 195 mg.); those of four dogs that died, ranged from 144 to 306 mg. per hundred milliliters (average 222 mg.). There were no indications that a high plasma hemoglobin had any ill effects, although we consider it undesirable. Often four dogs were treated on the same day with the same blood in the machine. The plasma hemoglobin in the machine was determined at the beginning and at the end of the day. The increase was less than 20 mg. per hundred milliliters after a whole day on six of nine occasions. Hemoglobinuria never was observed, although all dogs were placed on white cellucotton sheets after the experiments. In the more recent experiments of this series, good control over hemolysis was achieved by drawing the blood into siliconized bottles* and by avoiding the formation of foam (Table 2).

In the early experiments the oxygen content of the blood was determined by the Van Slyke method† (Table 3). It was established that one lung unit could oxygenate 75 ml. of blood per minute. In the more recent experiments the percentage of oxygenation was determined with the reflex oxymeter of Brinkman.[20]** When the small-flow principle is used, the oxygen saturation of venous blood is extremely low, which puts high demands on the capacity of the oxygenator. However, the oxygen saturation of the arterial blood still was more than 90 per cent. Some determinations are presented in Table 4.

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* *Baxter Laboratories, Morton Grove, Ill.*

† *Determinations were made in the laboratory of F. Mason Sones, Jr., M.D., in the Department of Cardiovascular Disease.*

** *Manufactured by Kipp in Delft, Holland.*

Table 2. — *Plasma and blood hemoglobin in gm./100 ml. (Free plasma hemoglobin as indicator of hemolysis during treatment with heart-lung machine)*

Experiment No.	Total duration of functioning of artificial heart-lung	Surgical intervention	Dog before	Machine before	Dog end	Machine end	Dog 1 hour later	Comment
125	15 min. connection. Recirculation time before 30 min.	Interventricular septal defect made and closed	Plasma Hb. . . . 0.018 Blood Hb. 12.5	0.030 12.8	0.018 8.3	0.024 9.2	0.018 8.1	Recovered
127	22 min. connected. Recirculation time before 20 min.	Elective K arrest; interventricular septal defect made and closed	Plasma Hb. . . . Blood Hb. 14.4	0.042 14.7	0.036 13.0	0.42 12.1	0.066* 12.3	Recovered
132	31 min. connected. Recirculation time before 15 min.	Elective K arrest; ventriculotomy and auriculotomy	Plasma Hb. . . . 0.036 Blood Hb. 13.7	0.024 12.7	0.054 14.0	0.042 13.2	0.054 12.3	Recovered
135	46 min. connected. Recirculation time before 15 min.	Elective K arrest; ventriculotomy	Plasma Hb. . . . 0.054 Blood Hb. 18.3	0.042 12.5	— 12.2	0.054 11.3	0.066 10.3	Recovered

* *Higher plasma hemoglobin 1 hour postoperatively probably was caused by difficulty of drawing samples from cannula. Anemia in first dog was caused by dilution of blood in the machine with saline.*

Table 3.—*Oxygen uptake of blood during oxygenation in artificial heart-lung machine, determined at the end of the experiment*

Experiment No.	Flow rate, ml./min.	Number of lungs	O_2 venous blood	O_2 arterial blood	O_2 capacity
48	300	4	6.2 vol. %	14.4 vol. %	15.9 vol. %
51	280	4	6.9 vol. %	12.9 vol. %	13.3 vol. %
59	300	4	—	14.5 vol. %	15.5 vol. %

Table 4.—*Oxygen saturation in blood coming from the artificial heart-lung machine, determined at the end of the experiment*

Experiment No.	Flow rate, ml./min.	Number of lungs	O_2 saturation
112	300	4	96%
113	300	4	98%
114	300	4	94%
120	150	2	95.5%
133	350	4	92%

Acidosis (pH and CO_2).* (Table 5) Acidosis may be expected in anesthetized dogs.[21] Following the method of Swan and associates[22] and Osborn,[23] we hyperventilated the dogs prior to connecting them to the heart-lung machine. This lowered the carbon dioxide content and often overcorrected blood pH so that alkalosis resulted. A further metabolic acidosis must be expected during extracorporeal maintenance of circulation, especially when the small-flow principle is followed.[24]

CO_2 is effectively removed from circulating blood in the heart-lung machine; this is most evident in the donor blood that has been recirculated through the heart-lung machine for some time. It loses about one half of its CO_2; however, the pH of this blood is only slightly altered. We have also shown the changes of CO_2 and pH during the experiments in dogs treated or untreated with $NaHCO_3$. Before we administered $NaHCO_3$, the metabolic acidosis was evident. With $NaHCO_3$ this acidosis could be corrected or overcorrected as in experiments 128, 129, 130 (Table 5).

* *Most of the chemical determinations were made under the personal supervision of A. Hainline, Jr., Ph.D., and by Miss Victoria Asadorian, of the Department of Clinical Pathology.*

Table 5.—*Changes in pH and in CO_2 during experiments with heart-lung machine. (In the later experiments pH was corrected with $NaHCO_3$.)*

Experiment No.	Duration of arterial circ. with venae cavae occluded	pH, CO_2 Venous blood from dog		Blood recircul. in machine before connect.	$NaHCO_3$ into machine during run, mEq./kg.	pH, CO_2 Venous blood from dog, end	pH, CO_2 Blood from machine at end	$NaHCO_3$, mEq./kg., postop. infusion	pH, CO_2 Venous blood from dog 1 hr. postop.	More than 1 hr. postop.	Next morning	Comment
		Onset anesth.	Before connect.									
123	20 min.	7.32 20.6 m.mol.	7.58 7.4 m.mol.	7.39 5.7 m.mol.	None		7.20 10.0 m.mol.	None	7.26 15.5 m.mol.	7.37 15.5 m.mol.	7 40 16.3 m.mol.	Recovered
124	10 min.	7.22 18.2 m.mol.	7.55 12.7 m.mol.	7.35 7.4 m.mol.	None	7.33 10.8 m.mol.	7.31 9.1 m.mol.	2 mEq./kg.	7.28 21.0 m.mol.	7.31 24.0 m.mol.	7.33 21.4 m.mol.	Recovered
125	10 min.		7.46 12.5 m.mol.		None	7.24 10.4 m.mol.	7.25 11.6 m.mol.	2.5 mEq./kg.	7.12 18.2 m.mol.			Recovered
127	19 min.		7.34 17.2 m.mol.	7.41 12.5 m.mol.	None	7.37 15.5 m.mol.	7.24 15.5 m.mol.	11 mEq./kg.	7.34 30.3 m.mol.			Elective K arrest; recovered
128	14 min.		7.49 12.9 m.mol.	7.33 9.1 m.mol.	7.5 mEq./kg.	7.34 20.6 m.mol.	7.35 17.2 m.mol.	7.5 mEq./kg.	7.42 30.3 m.mol.			Elective K arrest; recovered
129	14 min.		7.64 11.2 m.mol.	7.42 11.2 m.mol.	4 mEq./kg.	7.39 19.3 m.mol.	7.38 14.6 m.mol.					Elective K arrest; accidental death
130	19 min.		7.51 10.0 m.mol.	7.46 13.0 m.mol.	7 mEq./kg.	7.32 24.1 m.mol.	7.32 23.2 m.mol.	7 mEq./kg.	7.56			Elective K arrest; died from empyema after 8 days
132	26 min.			15.0 m.mol.	4.5 mEq./kg.	7.4	7.38 24.6 m.mol.	4.5 mEq./kg.	7.48 20.8 m.mol.			Elective K arrest; recovered
135	42 min.		12.5 m.mol.	15.5 m.mol.	5 mEq./kg.	18 m.mol.	17.5 m.mol.	5 mEq./kg.	29 m.mol.			Elective K arrest; recovered

We now routinely administer a continuous drip of sodium bicarbonate during the run, 4.5 mEq. per kg. of body weight. It is made up to 100 ml. with 5 per cent fructose in water and is administered into the collecting manifold during the run. This seems to bring both pH and CO_2 to normal levels. A second dose of 4.5 mEq. of sodium bicarbonate per kg. is administered in the course of three hours postoperatively. It is made up to 100 to 300 ml. with 5 per cent fructose in water to which 25 or 50 mg. of protamine sulfate is added. Thus, pH and CO_2 levels are maintained at the expense of a slight increase of serum sodium.

Changes in serum sodium and serum potassium (Table 6). The slightly elevated serum sodium of blood in the machine is caused by the 40 ml. saline solution used as diluent for the heparin in the blood-collecting bottles. An alternative would be to put 30 or 40 ml. of 5 per cent glucose in the bottles, but this would lead to blood sugar levels of at least 380 or 480 mg. per hundred milliliters in the machine and almost the same instantaneously in the dog. As this may be undesirable we recently used 0.45 per cent saline solution and 2½ per cent glucose as diluent for the heparin.

The $NaHCO_3$ injected during the run seemed to have little effect on serum sodium; however, postoperatively the same dose tended to increase serum sodium, although still within the range of normal variations. The serum potassium posed no problem, not even in dogs that underwent elective cardiac arrest with potassium citrate.

Temperature. The oxygen going into the artificial lungs was heated to 40 degrees C., but no other heating for the blood in the machine is provided. Consequently, the dogs showed a fall in body temperature often to 34 degrees C. during the run, which was counteracted with a heating pad (care was taken to avoid burns).

Disturbances in clotting mechanism. The tendency of the animal to bleed has created difficulties for numerous investigators in this field. We also have lost a number of dogs from oozing or diffuse hemorrhage. In our recent experiments this complication has become rare. Heparin has been given: 0.8 mg. per kg. of body weight to the dogs and 12 mg. per 500 ml. of blood. The blood was collected in siliconized bottles (Baxter) with 30 or 40 ml. of saline solution or 5 per cent glucose as diluent. Heparin was neutralized with protamine sulfate (Upjohn), 25 mg. for small and 50 mg. for large dogs. This was followed by a continuous intravenous infusion of the same amount of protamine sulfate to prevent 'heparin rebound.'

Heparin rebound. This is a treacherous hemorrhagic phenomenon. When heparin is neutralized by protamine sulfate, the clotting time becomes normal in a matter of minutes. However, protamine sulfate seems to be eliminated from the blood stream before heparin is, thus leaving the heparin uncovered, as demonstrated by protamine titration. The following is an example of heparin rebound.

Table 6.—*Serum Na and K changes (in mEq./l.) in dogs during and after treatment with the heart-lung machine (in the later experiments pH was corrected with $NaHCO_3$ as indicated, and in the last five there also was elective cardiac arrest; serum Ca and P (in mg.%) in one dog).*

Experiment No.	Duration of artificial circulation with venae cavae occluded	Venous blood from dog, before	Blood circulating in machine just before connection	Elective K arrest	$NaHCO_3$ into machine	Venous blood from dog, end of run	Blood from machine	$NaHCO_3$ given as postoperative infusion	Venous blood from dog 1 hour later	Venous blood from dog next morning	Comment
123	20 min.	Na 145 K 3.3 Cl 118 Ca 9.6 mg.% P 3.5 mg.%	Na 131 K 3.9 Cl 106 Ca 7.0 mg.% P 3.3 mg.%	No	None	—	Na 131 K 3.7 Cl 106	None	Na 139 K 3.4 Cl 110	Na 133 K 4.3 Cl 110 Ca 8.7 P 4.1	Recovered. Blood collected in transfusion bottles with glucose
124	10 min.	Na 145 K 3.5	Na 150 K 3.2	No	None	Na 155 K 3.4	Na 150 K 3.5	2 mEq./kg.	Na 160 K 3.9	Na 143 K 4.0	Recovered
128	14 min.	Na 148 K 4.3	Na 153 K 3.7	Yes ± 0.5 gm.	7.5 mEq./kg.	Na 162 K 3.2	Na 162 K 3.9	7.5 mEq./kg.	Na 168 K 2.9		Recovered
129	14 min.	Na 145 K 3.7	Na 148 K 4.0	Yes 0.25 gm.	4 mEq./kg.	Na 140 K 3.4	Na 135 K 3.5				Accidental death
130	19 min.	Na 155 K 4.0	Na 147 K 3.1	Yes 0.375 gm.	7 mEq./kg.	Na 157 K 2.9	Na 156 K 3.1	7 mEq./kg.			Died from empyema 8 days postoperatively
132	26 min.	Na 148 K 3.7	Na 150 K 4.2	Yes ± 0.25 gm.	4 mEq./kg.	Na 143 K 3.5	Na 147 K 3.4	4 mEq./kg.	Na 153 K 3.3		Recovered
135	46 min.	Na 143 K 3.8	Na 150 K 4.0	Yes 0.2 gm.	4.5 mEq./kg.	Na 148 K 3.9	Na 153 K 3.2	4.5 mEq./kg.	Na 158 K 4.4		Recovered; second dose of K required for ventricular fibrillation

The average of 73 determinations of serum Na in normal dogs in our laboratories was 144 (138—164) mEq./l.
The average of 69 determinations of serum K in normal dogs in our laboratories was 3.7 (3—4.6) mEq./l.

Experiment 101. The dog weighed 8.3 kg. Surgical procedure: interventricular septal defect made and closed. Thrombocytes before the experiment were 260,000 and afterward were 230,000 per cu. mm. Heparin dosage was as usual, 12 mg. for each bottle of blood to fill the machine and 0.8 mg. per kg. into the dog at onset. It was estimated that for a blood volume of 800 ml. there was not more than 20 mg. of heparin in the dog at the end of the experiment. Twenty-five milligrams of protamine sulfate was given at the end of the surgical procedure. Clotting time 15 minutes later was nine minutes. However, when protamine sulfate was added for a protamine titration test, all tubes clotted within five minutes. During the next hour, loss of blood necessitated transfusion of 280 ml. citrated (nonheparinized) blood. An additional amount of 10 mg. of protamine sulfate was given; however, one hour later the blood would not clot at all. Protamine titration indicated no clotting except in the two last tubes with the highest concentrations of protamine sulfate. Twenty milligrams of protamine sulfate given intravenously was of no avail; there was no clotting. Seventy milligrams of protamine sulfate given intravenously thereafter reduced the clotting time to 10 minutes (the clot was solid). The clotting time remained 9 or 10 minutes for the next eight hours. The dog was able to walk through the laboratory, but it continued to bleed into the chest and finally died. The cause of the hemorrhage could not be determined. We know from experience with patients who have been treated with the artificial kidney that oozing may continue long after the clotting time has returned to normal.

Thrombocytes. Orienting experiments with our oxygenator, performed during a visit to Doctor Lillehei's laboratories, showed that it caused transient falls in white blood cell and platelet counts of peripheral blood. The transient fall in platelet counts was confirmed in later experiments (Table 7) but did not

Table 7. *—Platelet count per cubic millimeter of blood before and after treatment with the artificial heart-lung*

Experiment No.	Duration of perfusion	Type of operation	Dog blood before	Machine before	Dog after	Machine after	Dog after 1 hour	Comment
103	15 min.	I.V.S.D.	—	180,000	250,000	240,000	300,000	3 hr. later, 290,000. Died 10 days p.o. of wound infection
132	31 min.	Elective cardiac arrest; ventriculotomy and auriculotomy	290,000	—	180,000	160,000	300,000	Recovered

always occur. Within one hour the platelet counts were back to normal. The excellent clot retraction after administration of protamine sulfate also indicated normal platelet function. When the heparin was neutralized with an estimated dose of protamine sulfate* the adherence of the blood clot to an applicator stick could be studied (Fig. 9). It may be seen that during the one run, at least in one experiment, adherence was poor, although it was back to normal within 15 minutes.

* *This work was done by Cecil M. Couves, M.D., who was working as a guest in our laboratory.*

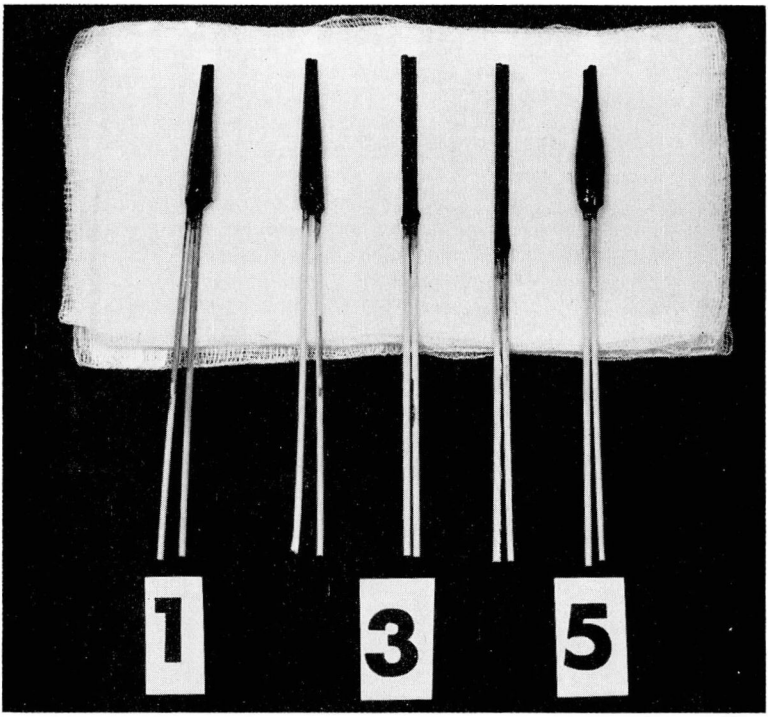

Fig. 9. Demonstration of clot formation before, during, and after an experiment. Applicator sticks have been placed in blood samples and have been removed after the blood was clotted (*Cecil M. Couves, M.D.*). No. 1—Clot before the dog had been heparinized. No. 2—Clot after the dog had been heparinized, but heparin was neutralized with protamine sulfate in the sample. No. 3—Blood from the machine, showing only a very minute clot adherent to the sticks, despite the fact that heparin in the sample had been neutralized with protamine sulfate. No. 4—Blood from the dog toward the end of the experiment, while the dog still was connected to the machine; heparin in the sample also had been neutralized. No. 5—Clot from the dog's blood 15 minutes after the experiment and after the administration of protamine sulfate to the dog. The clot is normal.

Prothrombin times. During treatment with the artificial heart-lung, prothrombin times changed no more than might be expected from hemodilution (Table 8). This excludes damage to the early phases of the clotting mechanism in the two experiments studied.

Bleeding time. Stabbing with a hemolet into the undersurface of the dog's tongue at the end of the experiment and after administration of protamine sulfate did not reveal a prolongation of the bleeding time in any of the dogs in which it was tested.

The general conclusion in regard to clotting mechanisms with this type of artificial heart-lung is that when heparin is adequately neutralized with protamine sulfate, only transient changes in the clotting mechanism occur. Within 15 minutes the changes revert to normal. However, the use of old blood,

Table 8.—*Prothrombin times before, during and after treatment with the artificial heart-lung*

Experiment No.	Duration of perfusion	Type of operation	Prothrombin times in sec., and hemoglobin in gm./100 ml.					Comment
			Before	After heparinization*	Blood from machine at end*	Blood from dog at end*	Blood from dog **after 15 min.	
125	15 min.	I.V.S.D.	6 sec. Hb.12.5gm.	9 sec. Hb.12.8gm.	11 sec. Hb. 9.2 gm.	—	8 sec. Hb. 8.3 gm.	Recovered
127	22 min.	Elective cardiac arrest; I.V.S.D.	8 sec. Hb.14.4gm.	9 sec. Hb.14.7gm.	10 sec. Hb. 13 gm.	10 sec. Hb. 12 gm.	8 sec. Hb.12.3gm.	Recovered

* *Protamine sulfate added to sample.*
** *Dog had received usual amount of protamine sulfate.*

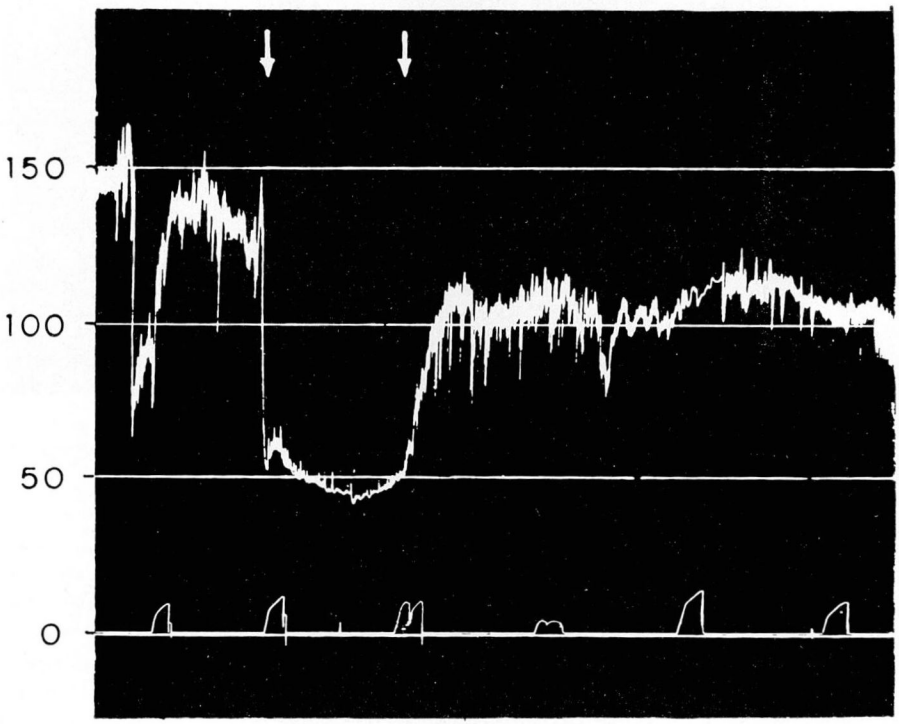

Fig. 10. Experiment 55. Arterial blood pressure is indicated in mm. Hg. Time is indicated at the bottom in 10-minute intervals. At the first arrow, the artificial heart-lung is started and ties are put around the venae cavae. There is a sharp drop in arterial pressure and during the following minutes the right ventricle is opened. It is closed, and at the second arrow the ligatures are removed from the venae cavae. Blood pressure rises to about 100 mm. Hg within a few minutes.

large amounts of dextran, or failure to clean parts of the machine affect the clotting mechanism disastrously.

Arterial blood pressure. During the extracorporeal circulation at low flows, the blood pressure falls more or less sharply when the venae cavae are occluded (Fig. 10) and in successful experiments rises again after release of the ligatures. Sometimes it takes 15 minutes for the blood pressure to be restored (Fig. 11).

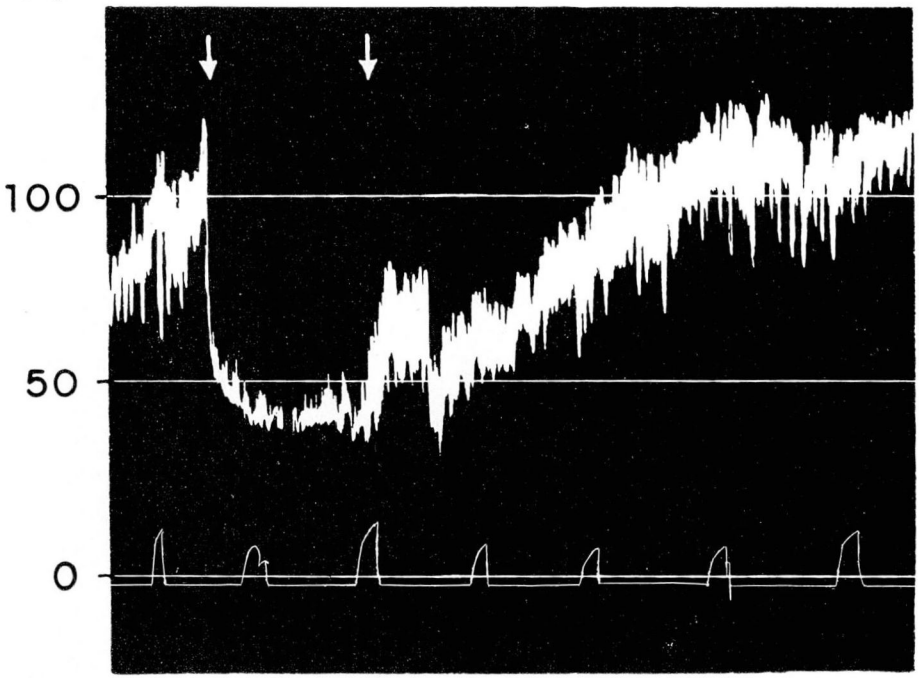

Fig. 11. Experiment 72. An interventricular septal defect is made and closed. At the second arrow the ligatures around the venae cavae are released, but it takes the blood pressure about 15 minutes to rise to 100 mm. Hg.

In some dogs we have observed a late fall in blood pressure which could not be explained on the basis of loss of blood. It is akin to the fall in blood pressure that Olmsted and Kolff observed several years ago after replacement transfusion in dogs. It usually responds well to additional transfusion (Fig. 12). When it is not corrected it leads to respiratory arrest. Some dogs have required the administration of mephentermine sulfate (7½ mg. in a 10-kg. dog) or a continued infusion of norepinephrine to help them over a period of low blood pressure that could not be explained on the basis of loss of blood, and could not be corrected by blood transfusion alone.

Venous blood pressure. The continuous observation of the venous blood pressure during the postoperative course has been very helpful in some cases when trouble arose. Prior to anesthesia and under local anesthesia, a plastic cannula is inserted in the femoral vein and is moved up until its tip almost

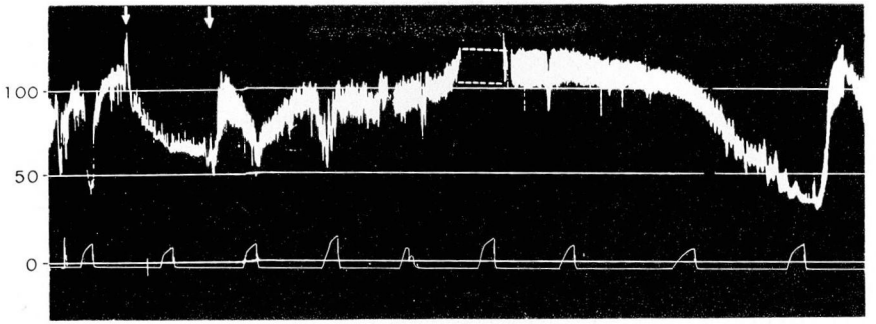

Fig. 12. Experiment 64. An auricular septal defect is made and closed. After release of the venae cavae at the second arrow, the blood pressure starts to rise. There is a temporary fall that possibly is due to protamine sulfate. The blood pressure rises again, but about one hour after termination of the experiment it falls again. When it was detected it could easily be corrected with infusion of blood, although the fall could not be explained on the basis of loss of blood.

reaches into the chest. This catheter later is used for the administration of intravenous anesthetics, draining of blood samples, the administration of a continuous drip in the immediately postoperative stage, and occasionally it has been used as the venous cannula if the dogs were reconnected to the machine for a second run. When both the venous pressure and the arterial pressure are low, the dogs should most likely be transfused. When the venous pressure is high while the arterial pressure is low, the cause of trouble should be other than loss of blood. It may be that the closure of the pericardium over the distended heart is too tight or it may be failure of the right ventricle.

"Second run." Thirteen dogs had low arterial blood pressure after the experiments, which evidently was due to cardiac failure. Extensive cutting into the interventricular septum probably was the cause. It has been possible to bring them into better condition by reconnecting them to the artificial heart-lung, leaving caval flow intact and using either the original cannulae or peripheral cannulation. In some dogs the artificial heart-lung was restarted two or three times. One dog was reconnected to the machine five hours after completion of the first experiment. A detailed history of this dog follows.

Experiment 125. The dog weighed 8.5 kg. The venae cavae were cannulated from the auricle; the aorta was cannulated from the right carotid artery. After the artificial heart-lung had been started and the venae cavae had been occluded, the right ventricle was opened and a large interventricular defect was made and closed. The right ventricle was closed. The superior vena cava was opened and two minutes later the inferior vena cava was opened. After 15 minutes the artificial heart-lung was stopped; blood balance was made and proved to be 200 ml. in favor of the dog. Blood pressure was 130 mm. Hg, protamine sulfate, 25 mg., was given, the heart was not distended, clotting time was 11 minutes. Infusion of $NaHCO_3$ was started. After about one hour, the electrocardiogram revealed complete atrioventricular block (Fig. 13). The dog's condition gradually deteriorated. The ventricular rate was 60, blood pressure was 55 mm. Hg, although 45 ml. of blood aspirated from the chest had been replaced by transfusion. The venous pressure ranged from 6 to 9 cm. of water. The clotting time was four minutes. Blood

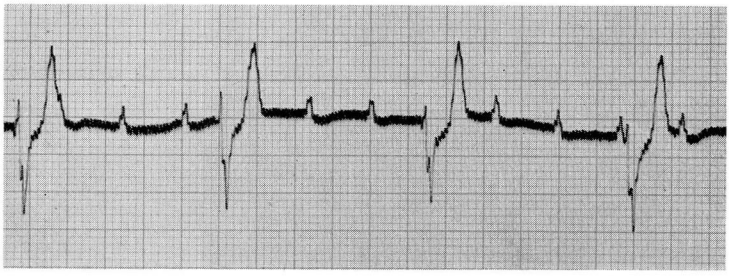

Fig. 13. Experiment 125. Electrocardiogram of the dog taken in the interval between the first and second treatments with the artificial heart-lung. There is a complete A.V. block showing Q waves and abnormal QRS complexes. The ventricular rate is 57, the auricular rate is 180 per minute.

pressure continued to go down, and four hours after the operation it was 44 mm. Hg. The dog that had been alert and awake before, gradually was becoming unconscious. Since in our experience dogs will not do well if they are allowed to have a low blood pressure for a long time, an infusion of norepinephrine, 4 ml. (1 mg.) in 750 ml. 5 per cent fructose was started. This brought the blood pressure up to 60 to 85 mm. Hg.

In the meantime a second dog had been treated with the heart-lung machine. Five hours after the original experiment, while the first dog's condition obviously was steadily deteriorating and it still had the atrioventricular block, it was reconnected to the artificial heart-lung. The venous cannula that previously had been inserted through the femoral vein into the vena cava caudalis and the arterial cannula in the right carotid artery were used. The flow was approximately 220 ml. per minute. No further anesthesia was used, and perfusion was continued for 32 minutes. After that the blood pressure was constant at about 75 mm. Hg without medication. A half hour later, the pulse rate suddenly rose to 84 beats per minute, and the blood pressure rose to 100 mm. Hg. Later the pulse rate rose to 176 beats and the blood pressure to 120 mm. Hg. Two hours after the second perfusion the dog was walking about in the laboratory. The following day the dog appeared to be weak, but he had an uneventful, uncomplicated recovery.

Electrocardiographic changes. Electrocardiographic recordings have been made of only a small number of dogs. As a rule the electrocardiogram changed little when the venae cavae were occluded and the animal was dependent upon the machine with its relatively small blood flow (Figs. 14A and 15A). However, intraventricular block or ventricular tachycardia occurred when stay sutures were placed in the ventricle, and especially when the interventricular septum was cut. The duration of the QRS complex decreased before the end of the procedure. In the two dogs that had electrocardiograms after one week, there was a striking return toward normal (Figs. 14B, 15B).

Ventricular fibrillation. Ventricular fibrillation has occurred only three times in 125 experiments. Cardiac massage is not necessary during artificial circulation. The heart of one dog (no. 61) fibrillated after it had been closed and the machine had been stopped. The machine was started again for eight minutes before a defibrillator was available. The heart of a second dog (no. 106) began to fibrillate 30 minutes after completion of the cardiac operation. The cannulae still were in place and he was reconnected to the machine. The heart of the

third dog (no. 113) started to fibrillate when the chest was opened. The dog quickly was connected to the artificial heart-lung. Ventriculotomy was performed and the heart was defibrillated. All three hearts could be difibrillated, and normal cardiac action and blood pressure were restored, although later we lost the dogs. The last dog died two days after the operation from atelectasis. Fibrillation also has occurred, as will be discussed later, in dogs treated with elective potassium arrest; they recovered.

Summary

Artificial heart-lung machines operate on the principle of taking blood from the venae cavae, oxygenating it and returning it to the aorta so that the heart is bypassed. The artificial lungs described here oxygenate blood while it flows through polyethylene tubing. Each unit has an oxygenating area of 14,000 sq. cm., holds 500 ml. of blood, and will oxygenate 75 ml. of blood per minute. This is enough to maintain a 2-kg. dog or patient, using the "low-flow" principle (35 ml. per kg. per minute). The lung units are cheap, disposable, and simple enough to be mass-produced.* As many as ten units can be used in parallel.

The artificial heart-lung circuit uses a third pump (Miller, Gibbon, and Gibbon[5]) so that it has a constant blood volume. The pumps are commercially available Sigmamotors. The tubing, filters, and manifold are disposable.* The apparatus is such that the subjects require only 0.8 mg. of heparin per kg. of body weight; each 500 ml. of priming (donor) blood is taken into a siliconized bottle containing 12 mg. of heparin in 30 ml. of diluent.*

Experience in about 140 experiments in dogs is reviewed. Anesthesia was light and blood loss was fully replaced. Oxygenation was more than 90 per cent, even when the venous inflow was highly unsaturated. Hemolysis was negligible. Metabolic acidosis was countered, first by hyperventilation and secondly by operative and postoperative infusions of sodium bicarbonate (4.5 mEq. per kg. of body weight each). Serum sodium increased within the normal range and serum potassium was not changed.

Bleeding problems were largely overcome. Transient disturbances of clotting mechanisms during the run, quickly reverted to normal. 'Heparin rebound' was recognized by protamine titration. It was corrected, and later prevented by repeated doses or infusions of protamine sulfate.

Arterial pressure ranged from 25 to 50 mm. Hg during occlusion of the venae cavae and extracorporeal circulation, at 35 ml. per kg. per minute; it returned to 100 mm. Hg within 5 minutes after release of the venae cavae in most successful experiments. Postoperative myocardial failure was best treated by reconnecting the subject to the artificial heart-lung, without tying of the venae cavae. This was done in 13 dogs.

Artificial circulation at small flow rates elicited only minor electrocardiographic changes, although severe changes ensued on cutting into the myocar-

* *Baxter Laboratories, Morton Grove, Illinois.*

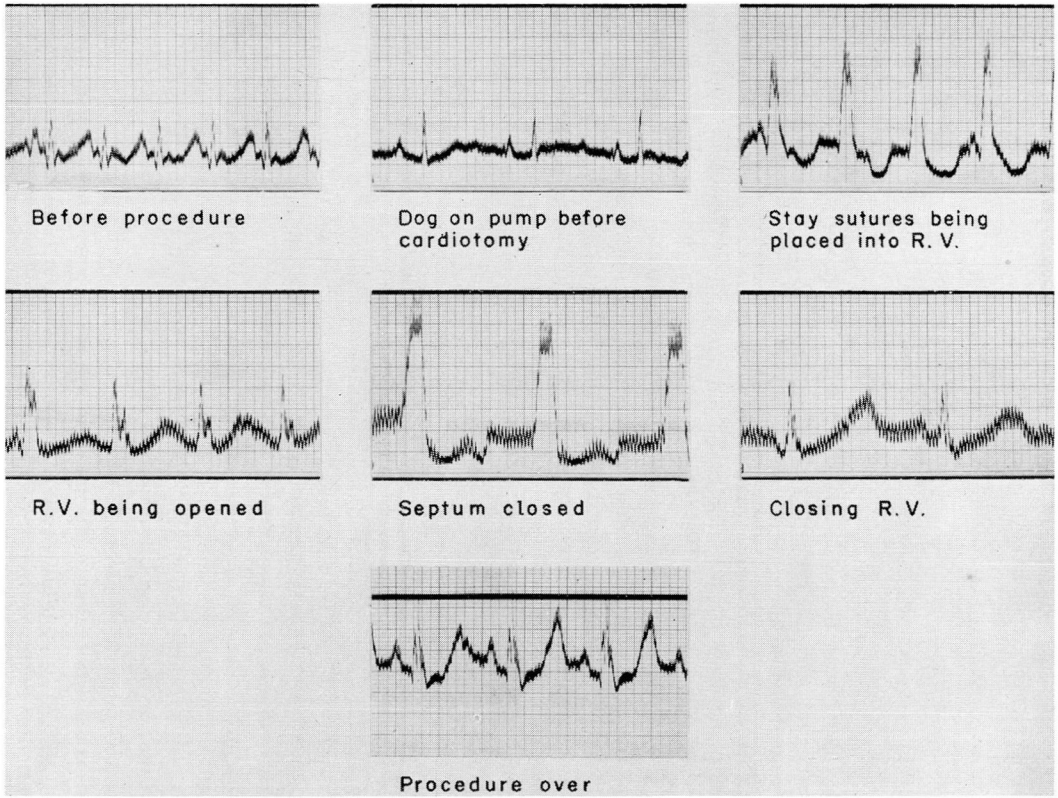

Fig. 14A. Recording at 50 mm./sec. *Before procedure. Dog on pump before cardiotomy.* P-R has increased from 0.09 sec. to 0.14 sec. and the T wave has become upright. *Stay sutures being placed into right ventricle.* Ventricular tachycardia: auricular rate *125*, ventricular rate *187*. *Right ventricle being opened.* Ventricular tachycardia. *Septum closed.* Decrease in ventricular rate to 100/min. *Closing right ventricle.* Sinus rhythm with QRS duration of 0.12 sec. *Procedure over.* Sinus rhythm with QRS of 0.10 sec.

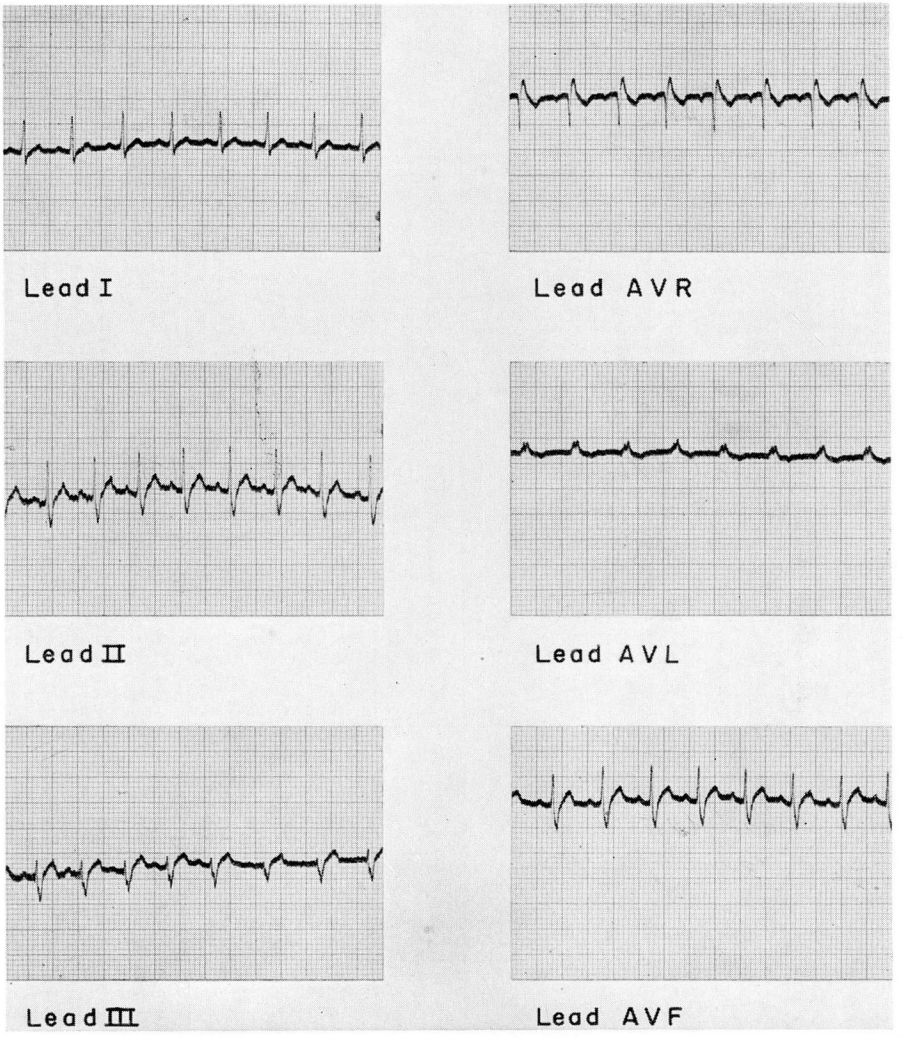

Fig. 14B. Recording at 25 mm./sec. P-R interval is the same as that preoperatively. The QRS duration is 0.08 sec. and the configuration is consistent with incomplete right bundle branch block. (*J. Mignault, M.D.*, and *W. L. Proudfit, M.D.*)

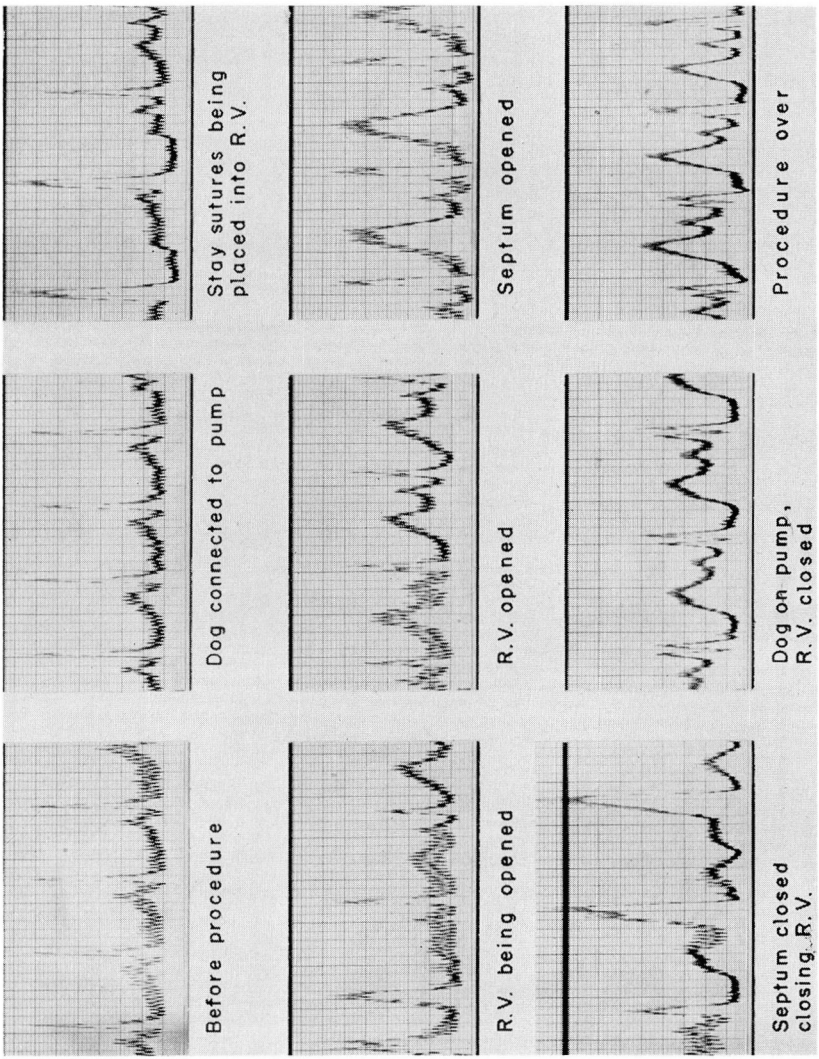

Fig. 15A. Recording at 50 mm./sec. *Before procedure.* QRS duration 0.06 sec. *Dog connected to pump.* No change from before procedure. *Stay sutures being placed into right ventricle.* QRS duration 0.08 sec. *Right ventricle being opened.* Ventricular premature contractions. T wave much higher in the normal beat. *Right ventricle opened.* Similar to previous ECG. *Septum opened.* QRS duration increased to 0.10 sec. and T waves still higher. *Septum closed, closing right ventricle.* Sagging of S-T segment and two ventricular premature contractions. *Dog on pump, right ventricle closed.* Similar to previous ECG, but T waves higher and rhythm regular. *Procedure over.* Similar to second ECG (made when dog was on pump). QRS duration is still 0.10 sec.

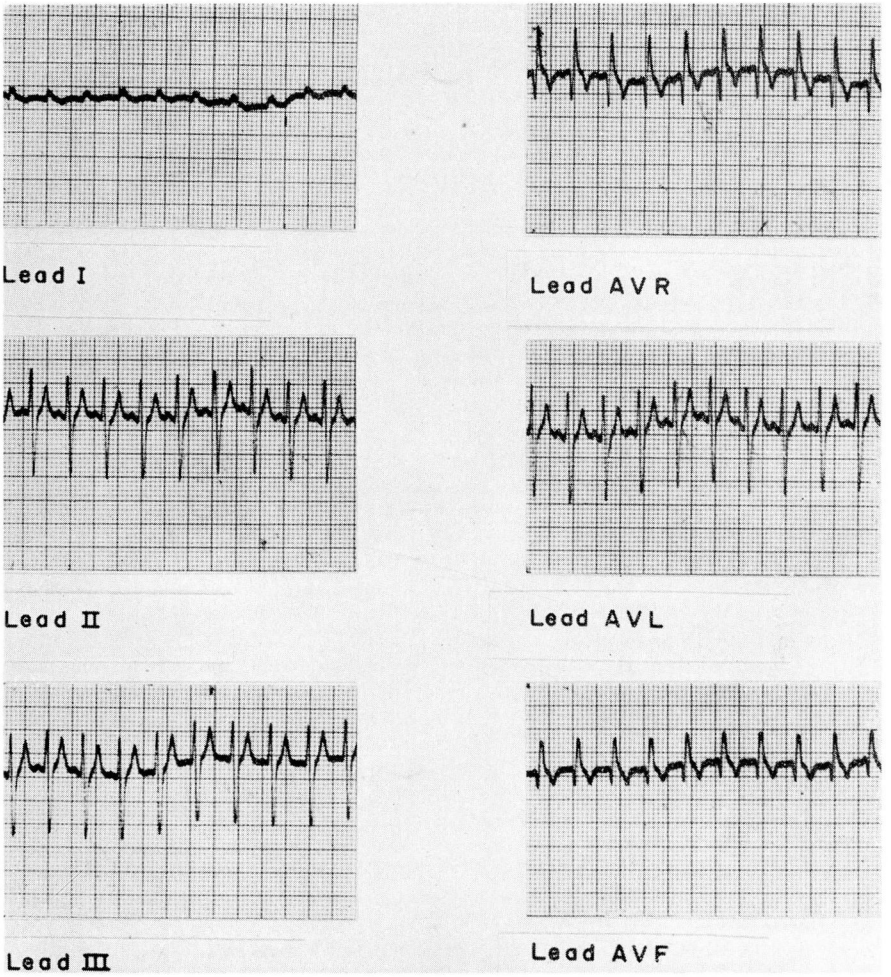

Fig. 15B. Recording at 25 mm./sec. QRS duration 0.08 sec. The configuration is consistent with incomplete right bundle branch block. T wave is inverted in lead 1.

dium. Most of these had disappeared at the end of a week. Ventricular fibrillation occurred only three times in 125 experiments. Defibrillation during the artificial circulation was easy.

Acknowledgment

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