

DEVELOPMENT OF A PUMP-OXYGENATOR TO REPLACE THE HEART AND LUNGS; AN APPARATUS APPLICABLE TO HUMAN PATIENTS, AND APPLICATION TO ONE CASE*

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THE CONTRIBUTIONS OF ROBERT GROSS to the management of patent ductus arteriosus,¹ of Gross² and of Crafoord³ to the care of coarctation of the aorta, of Blalock to tetralogy of Fallot,⁴ of Brock⁵ to pure pulmonary stenosis and of Glover, Bailey and O'Neill⁶ to mitral stenosis have fired the imaginations of surgeons everywhere. The limiting factor in the surgical correction of most intracardiac congenital defects and of many acquired ones is the constant requirement of the patient for continued blood flow into the aorta and of the surgeon for a relatively bloodless field within the heart which will permit recognition and repair by direct visualization.

Many groups have undertaken to devise means of rendering the heart dry for such purposes. Sewell and Glenn,⁷ and Sanford

Leeds,⁸ have described pumps to circumvent the right heart, and Sirak⁹ one to circumvent the left. Stuart Welch and his associates¹⁰ have described a compound pump to do all the work of the heart. Another school of thought, to which we subscribe, feels that the heart and lungs both should be removed from the circulation, for any other method requires such complicated incannulation technics as to be prohibitive. Gibbon and his associates have been pioneers¹¹ here. The work of others has been reviewed elsewhere.¹² Our group has worked four years on the problem.

Having reached a stage that seemed to justify clinical application, Dr. R. L. Varco was consulted in search of the most suitable type of case for trial because of his familiarity with the problems of congenital cardiac surgery and the technics he has developed in dealing with them. Partial support of the circulation by our heart-lung apparatus seemed to us to be inconclusive at best as a demonstration of the efficacy of the apparatus. The selection was made of cases of interatrial septal defect with cardiac enlargement beginning before the age of two years, and recurrent failure. Here are cases doomed without repair. The method of Henry Swan has been reported to be of limiting success.^{13, 14} The method of Gordon Murray¹⁵ likewise has not been reported successful in producing complete

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The authors hereby express their most appreciative recognition of the contribution of our machinist, Mr. Hilbert Huso, without whom the present machine could not have been constructed. They also wish to express gratitude to Miss LaVonne Young and Miss Donna Nissen, technicians, and to Mr. Richard Kelly, a pre-medical student helper, who have volunteered uncounted extra hours to the prosecution of this work.

closure. Effecting closure by the method under study therefore has impressed us as offering something not hitherto available to these patients.

BACKGROUND OF WORK

During the past four years work has been in progress at the University of Minnesota in developing a combined pump and oxygenator capable of replacing the functions of the heart and lungs for periods sufficient to permit intracardiac surgery in a relatively dry field and under direct vision. As we reported recently, 64 perfusions in dogs have been performed with an apparatus consisting of a modification of the Gibbon oxygenator and of the Dale-Schuster pump.¹⁶ This machine permitted cardiomy with a fairly dry right ventricle. It caused no essential changes in prothrombin time, sedimentation rate or hemoglobin concentration, but in 30 minutes of perfusion, as much as one-half the serum protein was lost, the platelets fell one-third the original value, the W.B.C. was cut in half, and all too often marked metabolic acidosis developed, usually followed by fatal gastrointestinal hemorrhage in a few hours. The partial pressure of CO₂ in the blood remained normal or low. Finally, a distressing portion of these 64 perfusions showed inadequate oxygenation.

FURTHER BASIC STUDIES

During the year since completion of the 64 perfusions on the original machine, basic studies along varied lines have been conducted, and the combined information has been employed in the construction of a more adequate pump-oxygenator apparatus. These studies are presented in this paper in broad outline only, for the purpose of clarifying the changes in the apparatus.

R. M. Nelson found that the hemorrhagic state which complicated many perfusions can be consistently reproduced by

intravenous injections of suspensions of the paracolon bacillus, with fatal gastro-intestinal hemorrhages, mucosal congestion, petechiae along the coronary vessels, serosal exudations and death within as little as three hours.¹⁷ Nelson has continued these studies and will report them shortly. The apparatus was found to be contaminated, primarily with this organism, and sterilization proved best achievable by employment of 12 hours of circulating and standing 3 per cent formaldehyde solution. Prior to

TABLE I.—*Example of Relation of Uptake of Oxygen to pH of the Blood in the Eight Cylinder Oxygenator.**

Time After Start of Perfusion	pH	O ₂ Sat. %
0	7.33	
5'	7.31	87
15'	7.29	80.3
(Added 10G. NaHCO ₃)		
20'	7.72	99
30'	7.64	96.5

* 6¼% CO₂ in O₂ in chamber. 19 Kg. male dog. B. P. 60 mm. Hg at 15 min. 110 mm. Hg at 21 min. All other factors held constant.

the formaldehyde, we recirculate distilled water, and 1:1000 aqueous zephiran. The system is rinsed with 7 to 8 gallons of pyrogen-free 0.9 per cent sodium chloride solution. A test for formaldehyde, sensitive to 1 part in a million,¹⁸ serves to control the washing process.

The frequent inadequacy of oxygenation with the rotating vertical cylinder pattern of Gibbon led to further evaluation of oxygenator technics. The Bjork-Crafoord¹⁹ machine, more varieties of smooth, corrugated, and stepped cylinders, and the screen cylinder of Flick and Stokes²⁰ all proved disappointing, whether by virtue of inadequacy of oxygenation in relation to volume content of blood, foaming, or ungainliness for practical purposes. Evaluation of slowly rotating screen discs on which the blood is laid by jets led to adoption of such a principle. A 38 cm. disc of 18 by 18 mesh stainless steel screen of 0.009

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inch wire rotated 54 times a minute can consistently raise the oxygen saturation of 550 cc. of blood per minute from 45 per cent saturation to over 95 per cent saturation. Employment of multiple discs on a shaft, as Bjork mounted his smooth discs,

has provided us an oxygenator capable of handling a human adult.

Adequate oxygenation is impaired by the fall in pH which Bjork noted during perfusion and which we have studied in considerable detail. Addition of sodium bi-

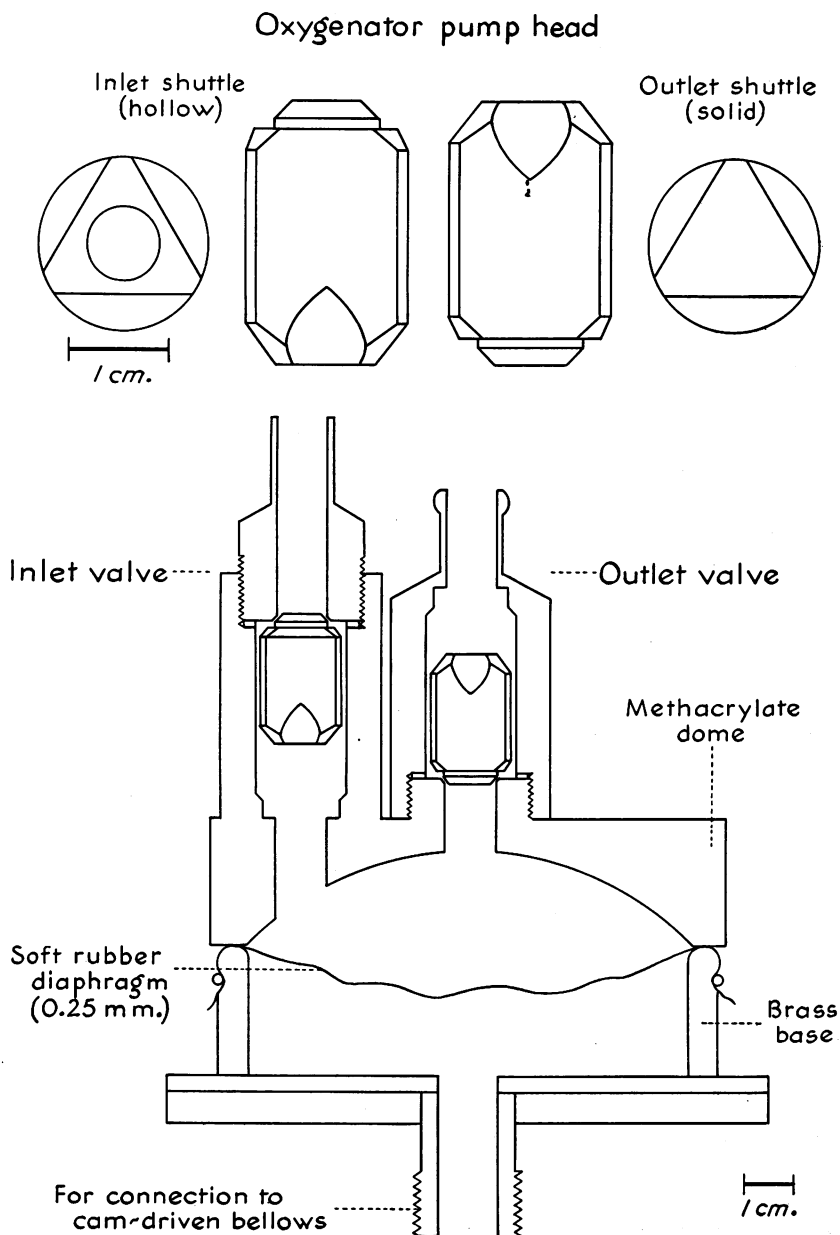


FIG. 1.—Section of oxygenator pump head.

carbonate solution to the blood in amounts adequate to correct the pH in the old, marginal oxygenator was noted rather consistently to produce a striking improvement in oxygenation and also in blood pressure (Table I). It is apparent, therefore, that a drop in the pH under the circumstances of these perfusions produces not only a fall in oxygen carrying capacity at equilibrium, but also a fall in the rate of oxygenation.

blood pressure drop during perfusion has concentrated attention on the initial fall to 60 or 70 mm. Hg mean pressure formerly commonly seen immediately after the start of perfusion. Interference with vasopressor reflexes, especially the Bainbridge reflex, seemed inescapable. We have tried to compensate for such interference by initiating perfusion, (1) with intra-arterial transfusion from the machine of 10 per cent of the

TABLE II.—Changes During Complete Perfusion of a Human Patient.

	Hg Gm. %	Hema- tocrit %	W.B.C./ mm ³	PMN %	Eosin./ mm ³	Platelets/ mm ³	Arterial O ₂ Saturation %	Venous Saturation %
Patient control	12.2	43	4,600	56	55	155,000		
Donor reservoir	10.3	46	6,300	51	100	88,000	97	
Immediate pre-perfusion	8.9	40	13,400	81	77	194,000	90	
3 minutes		40					96	62
15 minutes		43					93	57
30 minutes		44					96	85
End perfusion 38 min.	11.4	45	5,750	62	44	92,000	98	
Suction blood						96,000		

Further studies on the development of metabolic acidosis during perfusion have suggested that adequate dietary preparation of animals prior to serving either as subjects or donors is most important. In addition, any profound blood pressure drop during perfusion is followed by marked metabolic acidosis. For this reason it is essential that no interruption in operation of the machine occur during perfusion, for, under such circumstances, with the heart open and the cavae occluded, the blood pressure falls abruptly to zero. Prolonged blood pressure drops to less than 80 mm. Hg. mean pressure during perfusions are followed regularly in the postoperative period by progressive decline in blood pressure which is refractory except temporarily to employment of massive transfusion whether by artery or vein, or of such vasopressor drugs as Neosynephrine.*

Observation of the dire effects of any

* Neosynephrine hydrochloride is the brand of phenylephrine hydrochloride manufactured by Winthrop-Stearns, Inc., New York 13, N. Y.

estimated blood volume of the subject, (2) with administration in that blood of 0.5 mg. of Neosynephrine, and a slow continuous addition of no more than a total of 5 mg. during perfusion and afterward, and (3) with careful governing of the flow from the vena cava to the machine, based on the arterial blood pressure, for four to five minutes before complete diversion to the machine of the venous blood returning toward the heart from the body.

Extensive studies during this period of re-orientation have taught us a great deal about the avoidance of hemolysis. The pumps have again been revised in order to minimize turbulence, crushing of cells, and unessential abrupt changes in pressure. Re-circulation of blood in pumps or the pump-oxygenator apparatus results in higher plasma hemoglobin levels than are seen in whole body perfusions. The present apparatus during 30 to 40-minute exclusions of the heart and lungs of dogs has shown an average increase of plasma hemoglobin concentration of 19 mg. per 100 cc. of

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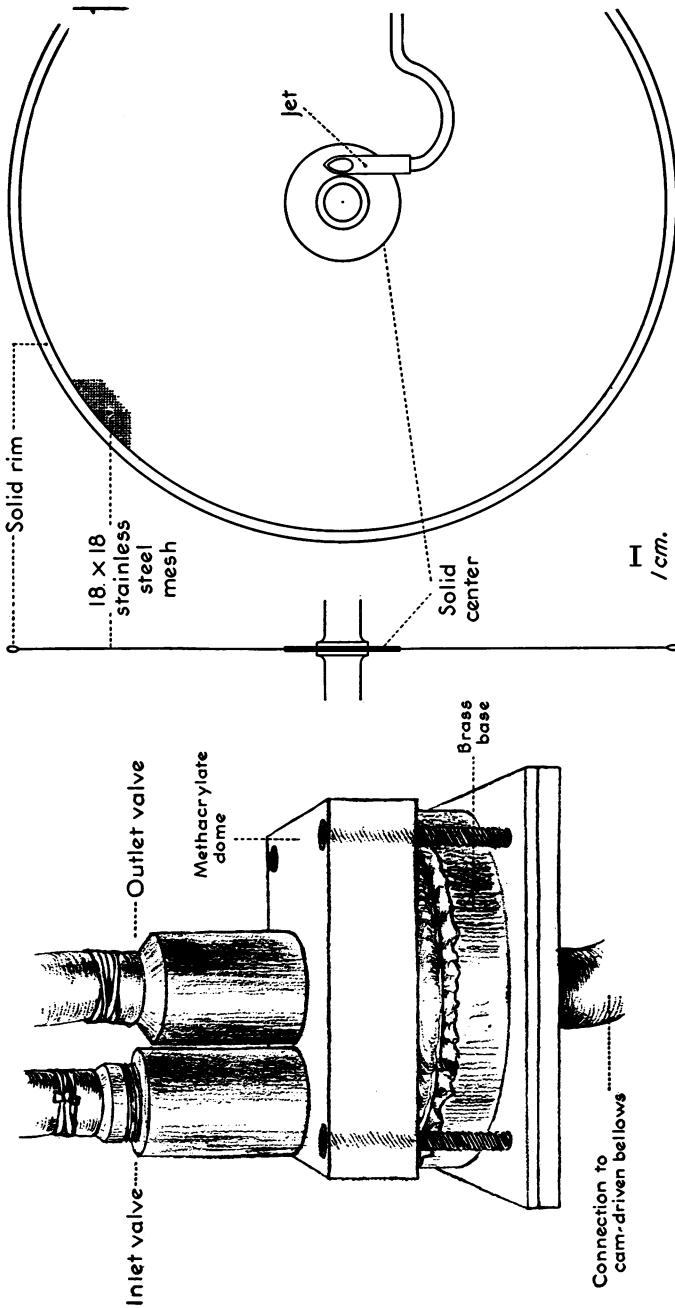


FIG. 2

FIG. 3

FIG. 2.—Perspective sketch of oxygenator pump head. Blood is laid on a 38 cm. disc of 18 by 18 mesh stainless steel which rotates 54 times a minute. The present apparatus contains 11 such units, and can oxygenate satisfactorily approximately 6000 cc. of blood per minute.

blood.²¹ In two perfusions the concentrations dropped during the half-hour occlusion of the vena cava. The urine was not found to contain hemoglobin.

Success frequently has been destroyed by inadequate pulmonary ventilation before and after perfusion. Our respirator²² has been altered to maintain 17 cm. of water pressure in the trachea during about 30 per cent of the respiratory cycle. A flexible bag in an adjustable wire mesh cage is immersed 17 cm. under water in a large beaker. Connection of this bag by tubing to the respiratory circuit provides the shape of respiratory pressure curve desired. Areas of atelectasis secondary to retraction and manipulation now disappear spontaneously.

THE APPARATUS

Blood is pumped by modified Dale-Schuster pumps from the vena cava, through a flow meter, and to a system of jets which films it on several 38 cm. screen discs as they rotate slowly on a horizontal axis for exchange with a mixture of O₂ and CO₂. On dripping from the screen discs, the blood is pumped back to the femoral artery. Flow of blood from the vena cava to the heart is arrested by ligature during perfusions.

The pump consists of a methacrylate dome over a rubber diaphragm (Figs. 1 and 2). The rubber diaphragm is made to oscillate by water pressure from a rubber bellows and motor-driven camshaft arrangement below. Valves in the dome give directional flow. The pattern of the valves was suggested by Carl Walter.²³ A rotameter flow meter is employed.

The oxygenating discs are enclosed in a sealed chamber of vitreous enameled steel and methacrylate (Fig. 3). Three and one-half per cent CO₂ in O₂ is the gas mixture which keeps the partial pressure of CO₂ in the blood closest to normal levels. The oxygenating unit is thermostatically main-

tained at the temperature of the blood in order that the gas mixture may be precisely fully saturated with water vapor. Maintenance of a fixed level of blood in a small cup at the bottom of the oxygenator has proved of extreme importance, for variations of 100 to 200 cc. have caused marked blood pressure changes. Such a level maintenance also is essential to prevent aspiration of gas into the arterial pumps. It is accomplished by an arrangement of tambour, mercury switches and solenoids which limits the diastolic filling of the two parallel arterial pumps. The general pattern of the machine is indicated in Figure 4.

We use neither bubble traps nor filters in the circuit.

In performing perfusions, of which 80 have now been done in dogs, a careful routine has proved necessary. In experiments in which survival is sought, the dog freshly received from the pound or dealer must be well fed for 2 weeks, checked for distemper, and de-wormed. We are limited as to space and have not been able to proceed often in this manner. Penicillin and streptomycin are started the night preceding perfusion. One hundred mg. thiamine prior to operation, 0.5 mg. atropine, and 4 mg. morphine have been added serially, for reasons which will be described elsewhere.

A tracheal tube with inflatable balloon is placed. Cannulas of stainless steel as large as possible are placed in the left femoral artery for return from the machine and in the femoral vein for support before and after perfusion. The chest is opened from side-to-side in the fourth interspace, with extreme care in hemostasis, using the coagulating current. Superior and inferior vena cava, azygos vein, right internal mammary artery, and right atrium are freed for incannulation. Heparin is given intravenously in the amount of 1.5 mg. per kilogram of body weight. A cannula is placed in the internal mammary artery for blood pressure tracings during perfusion,

and cannulas are placed through the azygos vein into the superior vena cava and through the auricle into the inferior vena cava.*

During placement of cannulas, the machine is flushed with freshly drawn blood to each liter of which 35 mg. heparin has been added. Having first been wetted with

0.9 per cent sodium chloride solution to facilitate filming on the screens, 1500 cc. of blood is required to flush out virtually all the excess sodium chloride and leave the system filled. (Volume content 800 cc.) Connections are made at once, for cannulas cannot long be left in the cavae without blood pressure drop.

In starting a perfusion, 10 per cent of the estimated blood volume and 0.5 mg. of Neosynephrine are added to the system. More blood is added as samples are drawn or blood is otherwise lost during perfusion. A very slow drip of Neosynephrine and sodium bicarbonate is maintained into the

* Incannulation for caval return could be more easily accomplished by the Sanford Leeds technic, by which all blood is retrieved through a cannula with open angle inserted via the azygos vein into both cavae, but the patent foramen ovale lies behind it and is therefore rendered inaccessible.

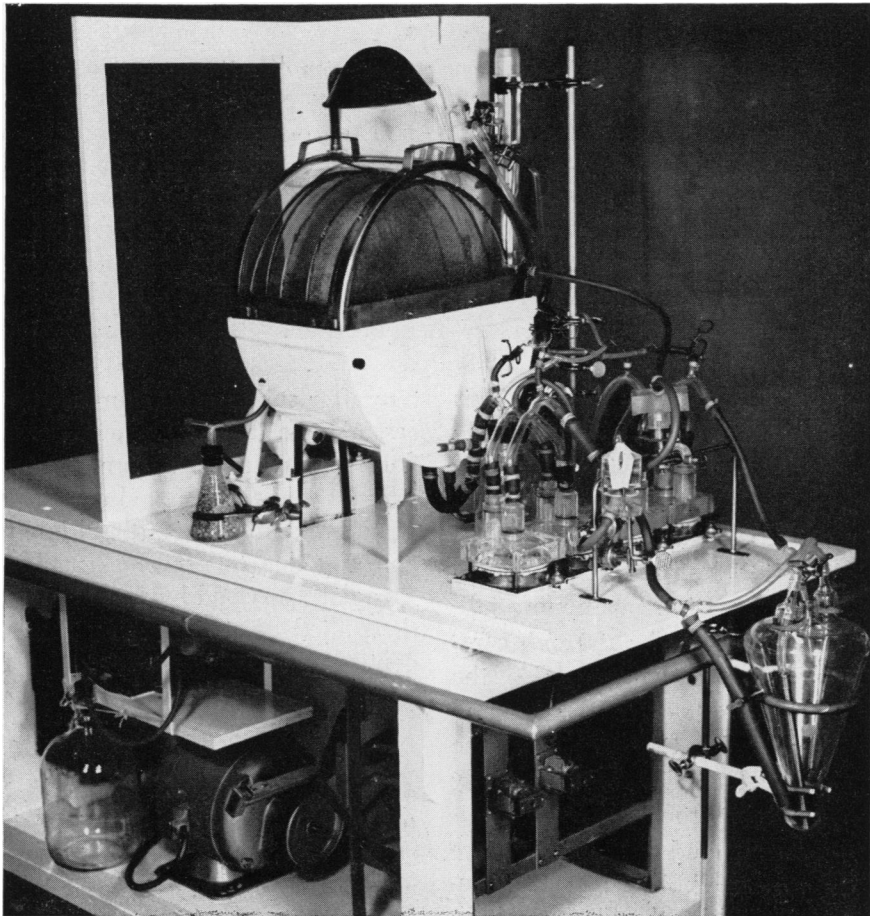


FIG. 4.—General pattern of pump-oxygenator apparatus. A cover of wood and transparent plastic aids in temperature maintenance, but is not shown here. All motors, machinery, and trap bottle are below the table top. The pump heads and connections are in the foreground. The oxygenator tank behind contained but five screen discs; it has been replaced by an 11-disc unit.

oxygenator. The cavae are prevented from returning blood to the heart by ligatures binding them to the respective cannulae.

A second special cannula is now introduced through a preplaced purse string into the right atrium and into the coronary sinus, a procedure which is surprisingly easy of accomplishment. Blood from this cannula, about 10 per cent of that from the cavae, also goes to the machine. The respective cannulae may be secured in appropriate position by use of Roger Anderson external fixation apparatus, and the atrium may be widely opened. A suction tip placed near the inferior caval cannula keeps the field fairly dry, and usually retrieves about 20 cc.

sample to determine the total dose (usually about 60 mg.).

Our performance since construction of the new machine has been impaired by developmental problems. Of nine dogs in which the above procedure was undertaken, three died after apparently successful perfusion because of failure to maintain pulmonary exchange; this appears to have been corrected by changing the shape of the tracheal pressure curve. One died of air embolism arising from faulty rubber tubing to the caval cannulae. One died of surgical error in not recognizing the septum; a large opening was made in the posterior atrial wall, which sealed temporarily and broke

TABLE III.—Changes During Complete Perfusion of a Human Patient.

	CO ₂ mm/l	Plasma HCO ₃ mEq./l	Part. Press. CO ₂ mm. Hg	Pl. Hgb. mg. %	Pyruvic Acid mg. %
Patient control.....	24.7	27	57	196	1.40
Donor reservoir.....	10.3	12	16		.60
Immediate pre-perfusion.....	15.2	18	24	0	2.70
3 minutes.....	12.3	15	25		1.53
15 minutes.....	14.8	17	27	48	1.72
30 minutes.....	11	13	21		2.80
End perfusion 38 min.....	9.4	10.5	19	118	3.22
Suction blood.....				232	2.52

of Thebesian vein blood per minute. This is returned to the circuit only if badly needed, for blood mixed with air under these conditions suffers excessive hemolysis. The septum now is in the field and may be sutured with arterial silk. In the congenital defects at autopsy it is much more substantial than in the dog. The atrium is carefully sutured about the two cannulae, the coronary sinus cannula is withdrawn and the hole closed, the ties occluding the cavae are removed, the lungs are carefully re-inflated, the flow through the machine is stopped cautiously; and the cannulas are appropriately removed. Blood pressure recording is continued by the femoral artery after ligation of the internal mammary.

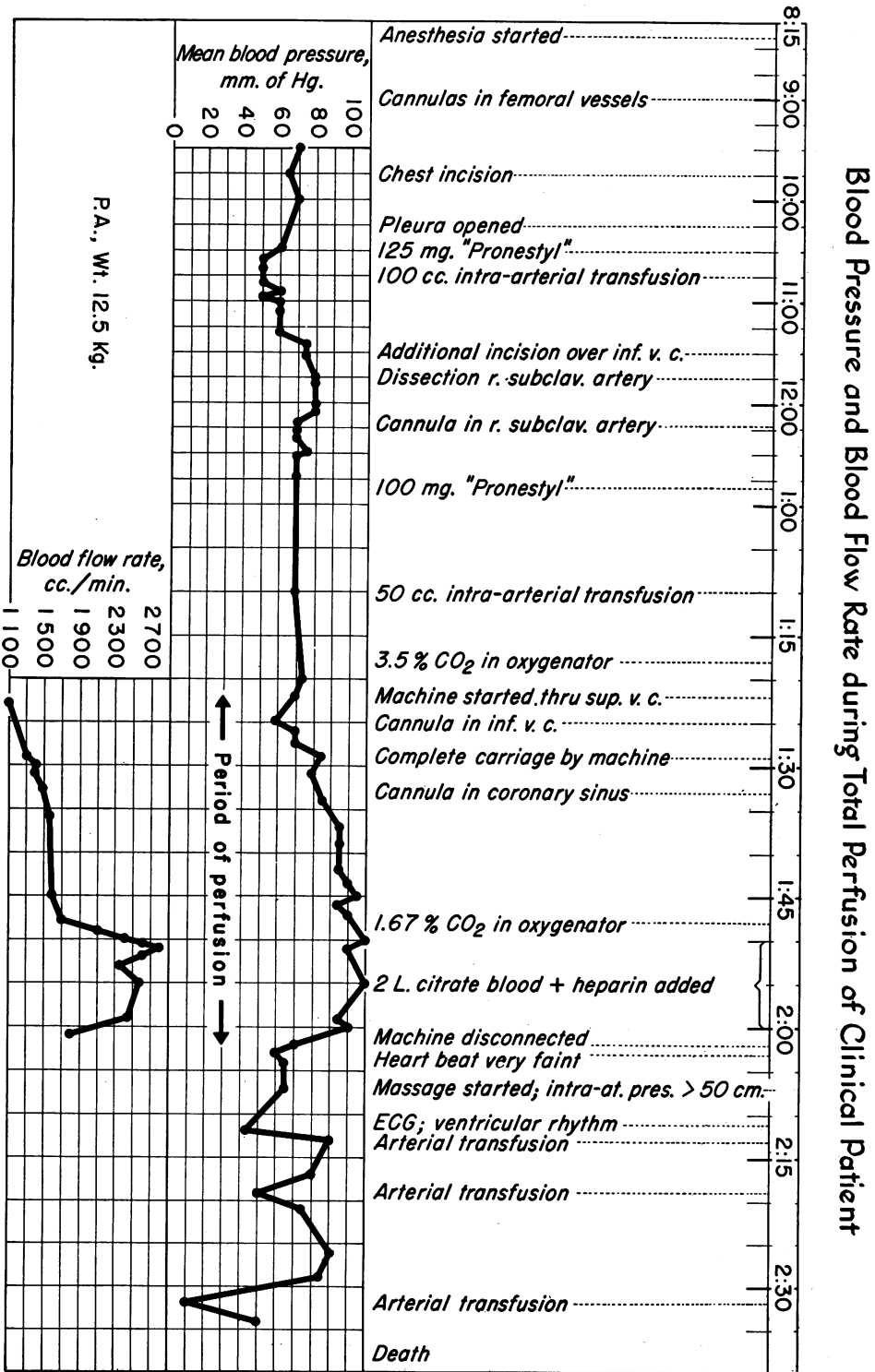
Protamine infusion is begun at once, with the protamine titration on a terminal

free after conclusion of an apparently successful procedure. Another also died from faulty closure of the atrium. One died after a faulty connection failed during perfusion. (The pressure in the arterial line was 1200 mm. Hg due to use of a small cannula.) Two dogs survived by several days. One of these died of strangulating ileac intussusception due to tape worms; the chest appeared intact. The other was sacrificed at 12 days because of shortage of cage space.*

We have been gratified in achieving orientation in the surgery involved by perfusing a dead dog to simulate the hemostatic problems of real life. Under such circumstances we have acquired some real confidence in our ability to cope with the clinical problems.

* One of the first total perfusion survivors has been kept 15 months. She is apparently normal.

Fig. 5.—Graph of mean blood pressure and flow rate changes during total body perfusion of a human patient.



PERFUSION IN A CLINICAL PATIENT

We are apologetic in reporting a single case of perfusion with this machine, but do so nevertheless because the ultimate loss of the patient does not negate the fact that the apparatus proved adequate for the purpose, because it provides promise of a useful tool in further cases, and because much valuable information has been gleaned. The patient was a girl of six who suffered crippling dyspnea and some cyanosis on exertion. After two cardiac catheterization studies, a diagnosis of Lutembacher's syn-

of medications and fluids. The right subclavian artery was dissected free for incannulation, and served admirably. The azygos vein was but 2 mm. in diameter, and cannulas of thin-walled stainless steel were therefore placed through the wall of the atrium into the venae cavae for withdrawal of venous blood. Ties of twill tape were placed about both cavae to insure complete removal of blood. The atrium was opened widely, and a suitably shaped glass cannula was easily placed in the coronary sinus. A suitable steel suction tip was placed at the

TABLE IV.—Changes During Complete Perfusion of a Human Patient.

	Serum Proteins			Sodium mm./l	Potassium mm./l	Chloride mm./l
	Total G/L	Alb. G/L	Glob. G/L			
Patient control.....	6.8			147	5.1	102
Immediate pre-perfusion.....	5.5	2.3	3.2	139	4.7	94
3 minutes.....	5.1	2.3	2.8	160	5.1	88
15 minutes.....	5.9	2.6	3.3	155	5.2	88
30 minutes.....	5.9	2.6	3.3	162	5.4	89.6
End perfusion 38 min.....	5.7	2.1	3.6	156	5.6	85

drome had been made. The patient had been explored in December, 1950, by R. L. Varco, at which time insertion of a finger through the left auricular appendage had failed to reveal the mitral stenosis which it had been planned to alleviate. A huge interatrial defect had however been found, and attempted repair had been deferred in anticipation of availability of the heart-lung machine.

The apparatus having reached the present state of development, and the patient failing rapidly, she was re-admitted for re-exploration on April 1, 1951. After suitable studies, surgery was undertaken on April 5, in spite of pulmonary edema and such cardiac enlargement as completely to collapse the left lung.

The technics of employment of the oxygenator were altered somewhat from those employed for the dog. Cannulas were placed in the left superficial femoral artery for intra-arterial transfusion if needed and for blood pressure observation throughout, and in the femoral vein for administration

side of the inferior caval cannula. It seemed to us that stabilization of the four tubes in the right atrium could be better managed manually than by use of the Roger Anderson apparatus, an opinion we reversed on review after death. In spite of return of all caval and coronary sinus blood to the oxygenator, an amazing amount of blood from the Thebesian veins, had to be returned via the aspirator tip. It was estimated to be 250 cc. per minute, roughly 15 times that seen in normal hearts of dogs of equal weight.

The control of coagulation was accomplished by drawing blood into Fenwal ion exchange column donor sets. All donors were matched with all other donors as well as with the patient. As blood was placed in the apparatus, 35 mg. of heparin was added first to each liter, and then the calcium ion was replaced, 60 mg. of calcium ion per liter.

It had been hoped the procedure could be performed without return of suction tube blood, but the huge losses by The-

besian veins forced us to do so, after less than 15 minutes of perfusion. As Table III indicates, plasma hemoglobin values were not inordinately high at 15 minutes in spite of suction blood already having been added. Further data on the perfusion are presented in the graph of Figure 5.

After opening the atrium widely, a common atrium (persistent ostium primum) was found. In the absence of adequate time to close the defect completely (Thebesian loss), adjacent tissue anteriorly was employed to attempt closure in spite of the recognition of a good deal of encroachment on the tricuspid orifice. Some 11 interrupted sutures were placed in the 40 minutes the patient was depending on the machine.

During this time the loss of blood by suction tip to an accessory suction apparatus was such that the 2.5 liters of blood reserved for replacement were lost, and the status of the procedure required substitution of citrated blood. Late in the repair it was appreciated that the force of the heart beats was extremely weak, and no vigorous beats occurred after removal of the cannulas. Belatedly this was recognized as a citrate effect; addition of calcium gluconate by vein improved the force greatly, but not enough to compensate for the stenosis produced at surgery.*

Observations on the cytology of the blood, on salt and acid-base balance, and on protein levels were made and are presented in Tables II, III, and IV. The virtual absence of metabolic acidotic tendency is in striking contrast to the difficulties seen in the dog.†

* Failure of the heart to return to a normal strong rhythm had been seen only once in the 80 dog perfusions, in which only heparin was used as an anticoagulant. In that dog, fibrillation occurred midway in the perfusion.

† Protein studies in dogs suggest an explanation for the acidosis which occurs in them in the miserable nutritional background as they come to us.

COMMENT

In spite of the tragic loss of the patient in question, we are inclined to feel encouraged with the performance of this apparatus. The teamwork required is great, and every move must be carefully planned and rehearsed in the laboratory during dog perfusions ahead of time, as was exhaustively done here. At this procedure there were two physician anesthetists, four surgeons, four men to run the oxygenator and pumps and to switch over the suction apparatus, one man to run the intra-arterial transfusion apparatus, one man to draw and manage samples, two technicians, and two nurses. With further development of the technics and apparatus, these numbers and the human element can certainly be reduced.

From the experience here reported, certain lessons may be drawn. Some of these are:

1. The pump-oxygenator as it now stands is a practicable apparatus for the purpose of offering a chance of survival to cardiac patients who now have no such chance.

2. A wide open chest with broad retraction is essential. A wide opening of the atrium is essential to recognition of the defect as well. The flow of Thebesian blood renders visibility in dependent areas very difficult, but elevation of the right side of the patient should aid. A useful maneuver under the circumstances is simultaneous insertion of two fingers into the atrium in an effort to place one in the mitral and the other in the tricuspid orifice. Ready recognition of the inferior margin of the defect is thus possible, and it may be grasped by a forceps and brought into view for repair.

3. Coronary sinus flow is about 10 per cent of total cardiac output. Thebesian flow in the normal dog is about 1 per cent of the total cardiac output, but in the case of septal defect whom we perfused, it was 10 per cent of a cardiac output which was nearly three times normal. In these cases,

the Thesbesian flow can be feasibly removed only by suction tip, which produces hemolysis. Therefore enough reserve citrate-free heparinized blood must be on hand to replace 250 cc. per minute while the heart is open. Failure of prior availability of this information is responsible for the loss of our patient.

4. Simply to permit the heart to fill with Thebesian and coronary sinus blood at the end of the cardiectomy served to avoid air embolism.

5. Previous experience in the laboratory has indicated that the right ventricle can be rendered almost dry by an adequate cannula in the right atrium. The experience gathered from dogs and this case suggests that the right atrium is technically apparently the most difficult chamber of the heart to enter surgically.

CONCLUSIONS

1. A pump-oxygenator apparatus is described which appears superior to any we have studied in terms of high oxygenating and pumping capacity and low trauma to blood constituents.

2. This apparatus has behaved admirably in one human trial, although extraneous factors led to the loss of the patient.

3. This apparatus appears to have a place in further development of the surgery of cardiac abnormalities.

4. The metabolic acidosis seen in dogs during total body perfusion did not occur in this patient.

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Gibbon, Jr., who provided the first orientation to us and who has been ever ready to provide counsel and friendship.

The apparatus described requires the attention of two persons for flushing and priming with blood. After connections to the subject have been established, it requires the attention of one person to see that good filming is maintained and for the replacement of blood lost in the surgical field. The volume of blood in the apparatus during established perfusion is constant within limits of 10 to 12 cc., this is accomplished by automatic control of arterial stroke volume, dependent on the level of blood in a small reservoir below the oxygenator.

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