

AN INTRATHORACIC PUMP TO REPLACE THE HUMAN HEART: CURRENT DEVELOPMENTS AT THE CLEVELAND CLINIC

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THE number of deaths from cardiovascular disease each year in the United States is close to one million. If we eliminate patients who are old, those with peripheral vascular disease, those who have no further desire to live, and those who are seriously ill or crippled for other reasons, the victims of heart disease alone can still be counted in the hundreds of thousands per year. Some cardiac patients who do not meet death too suddenly or patients who die in the operating room during attempts to correct irreparably sick hearts might be subjects for total replacement of their hearts with a pump. The question of whether or not such a pump inside the chest would be acceptable, desirable, and economically justifiable must be considered in the light of the only alternative—death. These philosophic questions, however, may well be postponed until it will have been shown that a heart to function inside the chest is available, reasonably reliable, and can replace an animal's heart for some time.

The world literature on the subject can be easily summarized. Nearly all available information has been published in the *Transactions of the American Society for Artificial Internal Organs*, volumes 3 through 6.

In 1957, Dr. P. F. Salisbury outlined the possibilities for implantation of physiologic machines into the mammalian organism and identified the problems connected with artificial hearts and artificial kidneys. At the same meeting, Dr. Selwyn P. McCabe, then at the National Institutes of Health, demonstrated a heart built for implantation. It was made of polyvinyl chloride and brought to further perfection in a demonstration of the Mark Company at a meeting of the Federated Societies in 1959. Dr. Bert Kusserow was able to substitute partially the right side of the heart by a pump inside the abdomen in 1958. Later, he was able to substitute partially the left side of the heart. Hastings, Potter, and Holter reported implantation of a heart inside the dog's chest, driven by a reciprocating fluid column, as did Liotta and co-workers. Fry, Fry, and Eggleton, after removal of a dog's heart, have maintained the circulation by a double pump in close proximity to the chest. We know that Dr. N. M. Amosov, Kiev Institute for Advance Training of Physicians, U. S. S. R., is working on the replacement of the heart by a pump driven by compressed air. Kusserow suggested use of a magnetic field to power remotely an implantable blood pump, and demonstrated the possibility. Schuder and Stevenson indicated that energy transfer into the closed chest would be possible by means of stationary coupling coils and a portable high-power oscillator.

In our laboratory, as a preliminary study, we tested the mechanical actions of many gasoline and other small pumps commercially available. Some electrically driven gasoline pumps, such as those used in heavy trucks, approach the requirements of the human heart as a pump, but they do considerable damage to the blood cells.

In 1957 it was agreed with Mr. E. Thorn of Thompson Products (now Thompson Ramo Wooldridge) to start work on a joint problem: Thompson Products was to make the energy-providing parts, we were to make of plastic the blood-handling parts—the artificial ventricles, valves, atria, and blood vessels.

We conducted a preliminary experiment with an artificial heart made of Plastisol (polyvinyl chloride) on December 12, 1958. The dog's heart was removed, the Plastisol heart was placed inside and the chest was closed. The mechanical energy came from a reciprocating pump and an oscillating column of air via a plastic tube through the chest wall.

We abandoned Plastisol because it required a plasticizer, and substituted polyurethane VC,^{1,2} a new, virtually cross-linked polymer. It can be applied to a mold by dipping or painting from a solution to produce ventricles and valves.³ To make these parts completely free of bubbles—before manufacturers were able to do so—we dried the valves either by surrounding them with ice or placing them under increased air pressure. Later these methods were superseded by adding cyclohexanone to the tetrahydrofuran solvent; but before slower evaporating solvents became available, the use of special methods developed in our laboratory made the start of this work possible.

No less than 51 research groups in the United States are either working directly on valve prosthesis or doing closely related work. Two hundred and fifty participants and guests were brought together in a conference sponsored by the National Institutes of Health. The proceedings in book form⁴ may be consulted for references. It is already apparent that the application of valvular prosthesis in man is far less difficult than it is in the dog. No valve is as yet proved by time in either man or dog. At present, the ball valve developed by Starr and Edwards in Oregon is the most successful prosthesis for the mitral valve in man. A polyurethane foam valve with chordae tendineae was successfully applied by Braunwald in one patient.

For aortic prostheses, there is a choice of several designs: Three silastic monocusp valves with self-sealing rim and Dacron skeleton are used by Hufnagel. More or less simple, flat, Teflon leaflets painted over with polyurethane are used by Kay. The valves used by William H. Muller are also made of Teflon. Roe's valve is more intricate. Bahnson's valve seems to have the most followers. It consists of Teflon with an industrial selvage as the insertion rim. The problem of anchoring of aortic valves has not been sufficiently solved as many still depend upon sutures for permanent fixation. A ball valve, which has been used for several years in the descending aorta by Hufnagel, has led to occasional success in the ascending aorta as employed by Harken.

One of our first concerns was to make valves that might be used in this artificial heart. Polyurethane tricuspid semilunar valves developed in our laboratory function well.⁵ We make them by dipping or painting on a single open mold.³ High-pressure molding and casting (using low pressure) of these valves is still under study.⁶ These valves can be used to replace the mitral valves in dogs⁵ and one cusp of the artificial valve may replace one cusp of the aortic valve.⁷ However, the problem of thrombosis has not been solved.^{3,8,9}

While our laboratory team was working on plastic valves and heart chambers, Mr. S. H. Norton of Thompson Ramo Wooldridge designed and made an artificial heart driven by five solenoids. In January 1959, it was placed inside a dog after the dog's heart had been removed.¹⁰

During the following months additional experiments were performed to determine the performance and the limitations of this artificial heart. Production of heat by the solenoids was deemed more than acceptable. It was found that this mechanical heart produced about 800 calories a day. Whether or not the carrier of such a heart would have to reduce his culinary caloric intake to preserve a desirable

figure, I cannot tell. The design of this artificial heart permits heat dissipation via the large bloodstream through the ventricles. After having proved that this heart would sustain the circulation of the dog, it was decided to make the device more efficient, and we took up the problem of efficiency of the solenoids. Many companies in the United States make thousands of solenoids every year for use in household washers, driers, and refrigerators. Therefore one would expect the art of building solenoids to be highly developed—but it is not.

Visits to the Westinghouse research laboratories in Pittsburgh, and to the General Electric research laboratories in Schenectady disclosed the fact that the ideal solenoid for our application, a small, light, efficient solenoid with a large stroke, did not yet exist. Thus, experiments were set up to activate solenoids with a pulsed current rather than with continuous direct current (DC) or alternating current (AC). When a fully charged condenser is discharged through a commercially available AC solenoid, forces ten times greater than those specified by the manufacturer for normal operation are obtained. Consequently we can use solenoids of about one fifth the weight of those previously needed.¹¹ The force produced by the solenoid may be stored in a spring and may be delivered by it to the pump. Liquid springs,* although not yet available for the small forces we need, seem to be the most promising future development.

Direct determinations of the performance of a pulsed solenoid are difficult to make either by calculation or by experiment. If one were to substitute a number of springs in a solenoid-spring combination and then experimentally to determine which spring stores the highest energy, one would need a great number of experiments—and one never would achieve the optimum. A fortunate breakthrough came here when the springs were discarded and instead quartz-force transducers were put under the solenoid.¹¹ In this setup the plunger moves so slightly that inertial forces need not be considered. Now a method is available for calculating both the optimal solenoid and the optimal spring to be used in an artificial heart.¹¹

Diastolic pumping or diastolic counterpumping to support the circulation in a patient with a failing heart presented an opportunity to experiment with the pulsed solenoid. Considerable work has been done lately in other laboratories to show that it may be useful to remove blood from the aorta during systole, thus lowering the load on the patient's heart, and to reinject that blood during diastole. During diastole this blood cannot flow back into the ventricle because the aortic valves are closed, but it may increase the perfusion of the coronary arteries.

The principle of assisted circulation, which means bypassing the heart and lungs and relieving the load on both of them, is not new. The blood has been provided with oxygen with a Clark and Gollan oxygenator for a patient with emphysema. Dennis and co-workers have applied assisted circulation in patients with impending death from coronary heart disease. Salisbury and co-workers have found that an elevated left atrial pressure is consistently lowered when the extracorporeal circuit carries more than 25 per cent of the circulation. Counterpumping has been applied by Dr. Kantrowitz in a special way. He wrapped the diaphragm of a dog around its

**Tayco Developments Inc., North Tonawanda, New York.*

aorta and stimulated the diaphragmatic muscle to contract during the dog's heart diastole. A definite second pressure wave could be demonstrated. Claus, Harken, and co-workers have pursued counterpumping by letting blood out of the femoral artery during systole and pumping it back in during diastole. At a recent meeting they reported successful application in three patients who might otherwise have died. Dogs with induced coronary thrombosis could be saved from certain death by application of this pump during a few hours after the injection of plastic globules in coronary arteries. Dr. Watkins calls it "postsystolic myocardial augmentation."

It is possible to withdraw blood continuously from the vena cava via the femoral vein, to oxygenate it,¹² and then to pump it back into the aorta during diastole.¹³

We gave a development contract to the Cordis Corporation of Miami, Florida, to build the equipment. It is now in clinical use. Dependent upon the delay from the R wave, an extra pressure wave produced by the pulsed solenoid is superimposed during diastole upon the pressure curve in the aorta as was demonstrated in dogs.¹³ This extra wave is supposed to increase coronary circulation in a failing heart.

Before we learned about pulsing solenoids, and at a time when magnet- or solenoid-driven hearts were still inefficient, we began to investigate small electromotors as a possible source of energy to drive a pump inside the chest. When airplanes and rockets required them, manufacturers became seriously interested in making small electromotors of sufficient durability for our project.

To drive the artificial heart, commercially available Globe motors* were selected. Today DC motors are not practical for the purpose, because their longevity is limited by the durability of the brushes. Alternating current motors have no brushes, but they are heavier and less efficient. We have seriously pursued two designs: one was a rotating pump;¹⁴ the other was termed a "pendulum" pump.^{15,16} Each has been developed far enough to allow substitution for a dog's heart as was actually done.

A novelty of the pendulum-pump heart is that the right and left hearts compress alternately rather than simultaneously. The ventricles are situated immediately against the electromotor so that the heat produced in it is transferred to the blood, and is dissipated by the blood flowing through each ventricle.¹⁶

Thus far we tried to use electrically driven devices inside the chest. Then suddenly the approach to our problem was changed. Two National Aeronautics and Space Administration (NASA) engineers suggested that if we would use a pump driven by air or gas, all our difficulties would be eliminated in regard to insufficient power, too much heat production, and too much weight. For power transmission a tube 6 feet long with an inner diameter of only 1/8 inch would suffice; and if helium replaced air, it might be possible to use tubing with an inner diameter of only 1/32 inch.

In December, 1960, the first experiments in dogs were performed with air-driven pumps. Simple solenoid valves interrupted the air pressure (*Fig. 1*) and were activated with the timing mechanism previously used for the Norton heart.¹⁰ A new type of piston pump was built using the Bellofram or rolling diaphragm

*Globe Industries, Dayton, Ohio.

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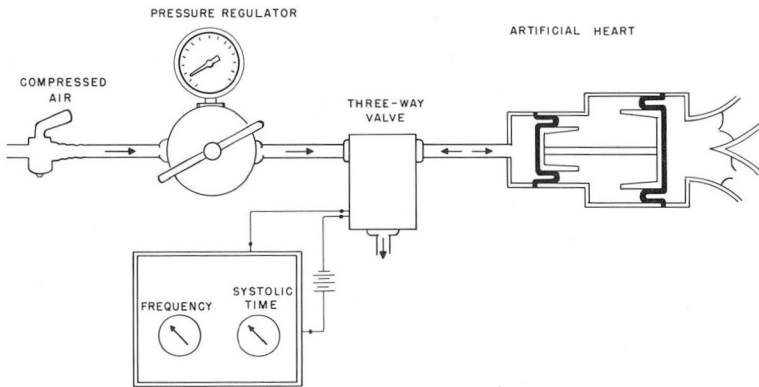


Fig. 1. Diagram of the systems using air-driven pumps. Compressed air is regulated by a pressure-regulating valve, and is interrupted by a three-way solenoid valve. This solenoid valve is opened and is closed by a timer on which frequency and duration of systole can be set. The compressed air operates a small driving Bellofram pump in the artificial heart. The small piston of the driving Bellofram is connected to the large piston of the blood chamber (at far right in the picture).

(Fig. 2).¹⁷ Since the right heart and the left heart are now activated by a power source outside the chest, there is no need to combine them in one unit; and to make them separately facilitates their insertion.

There is some encouragement in the fact that a number of dogs awoke after anesthesia and appeared to be normal for 5, 6, or 10 hours,¹⁷ but it is not clear why they deteriorated after 6 or 10 to 12 hours. The difficulties in most cases can be explained on the basis of simple failure of the hardware employed. But in other dogs no such explanation could be found. In one dog that survived a relatively long time there was evidence of small emboli in the kidneys leading to hemorrhagic infarctions. Undoubtedly, the formation of small clots and thrombi may have been a cause of deterioration. During the past three years we had been preparing for these difficulties with a long-range study of thrombosis on plastics placed inside of otherwise normal dogs' hearts.^{3,8,9} Based on these experiments certain rules could be set up to minimize the chances of thrombosis: the plastic should be smooth; there should be no areas where blood can stagnate; plastic should be exposed only to high-velocity flow; and insertion lines should be screened off with smooth material.

The problem of clotting on plastics is discussed in the book *Prosthetic Valves for Cardiac Surgery*, mentioned before. Litwak placed numerous Teflon leaflets into the pulmonary arteries in dogs and found that in the majority the Teflon became infiltrated and lost its flexibility. The chemical structure, the surface properties of certain synthetic polymers, and the relationship to thrombosis were discussed by Ross, Lazar, Greenfield, Bowman, and Morrow. Earlier work by Sawyer and others indicated that the electric surface potential of blood vessel walls can be related to the occurrence of thrombosis, and that a negative surface potential, at least statistically, has a preventive action.

The study of thrombosis on plastics is not complete. The most promising

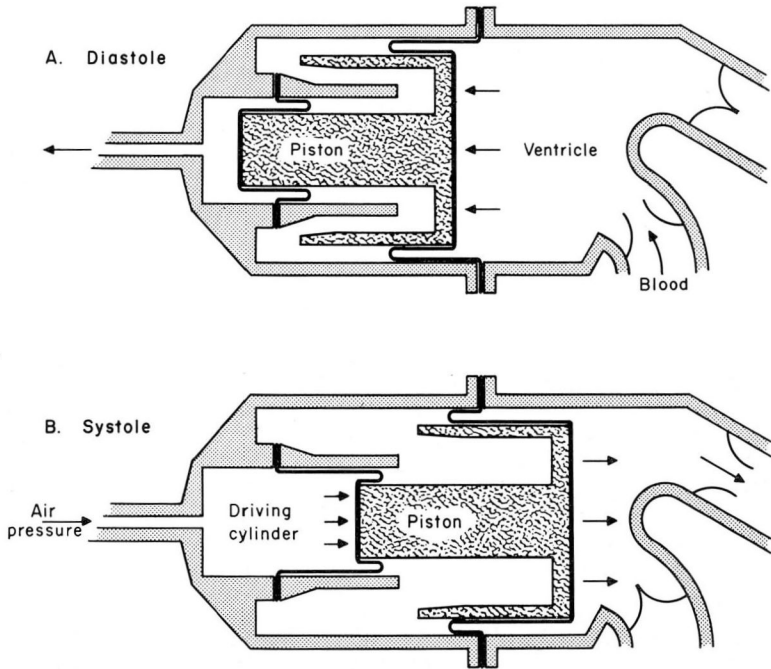


Fig. 2. Diagram that shows how the small (driving) Bellofram drives the larger (blood) Bellofram. The Belloframs roll from the outer cylinder onto the inner cylinder, and only a narrow fold of the material is exposed to the pressure without being supported. (Courtesy of Seidel, W.; Akutsu, T.; Mirkovitch, V.; Brown, F., and Kolff, W. J.; Tr. Am. Soc. Artificial Int. Org. 7: 376-385, 1961.)

approach seems to be to provide a negative surface charge to the plastic either by making new polymers or by grafting. Grafting is not a coating in the mechanical sense of the word but an actual chemical binding; a plastic with good electric properties is grafted to a plastic with good bulk properties. This can now be done, and has been done to a limited extent at Battelle Memorial Institute in Columbus, Ohio.

We prepared a motion picture with sound track. It is entitled "Study of Intra-cardiac Thrombosis in Dogs Leading to Development of a Mitral Valve"; it is available upon request.

The valves³ that we have used so far in the artificial hearts have not fulfilled our expectations, because small thrombi originate in the commissures between the leaflets. Valves with silastic balls have been prepared, which can be interchanged with the other types of valves in the artificial hearts. However, there might be causes other than thrombosis for the deterioration of the clinical condition of the dog after the artificial heart functions inside the chest for from 5 to 10 hours. Such deterioration might be caused by unphysiologic, undesirable pressure waves or flow characteristics in the dog's arteries.

Together with Mr. Kirby Hiller of NASA, a sophisticated type of air-driven heart¹⁸ was developed. The necessity to be able to change the form of the pressure curve at will was foreseen. To do this, methods in common use by rocketry engineers but novel to us were used. The NASA machine first generates an electric function the curve of which can be changed by 24 potentiometers for each ventricle into any desired shape. The electric function curve is transposed to an air pressure wave of almost identical shape. A feedback mechanism maintains this shape when it tends to change under different circumstances. A special piston heart, the Bellofram heart, was slightly modified, and a linear transducer was inserted in each of the two ventricles.¹⁸ These linear transducers determine the piston movements, which can be projected on an oscilloscope (*Fig. 3*). The piston movement can be combined

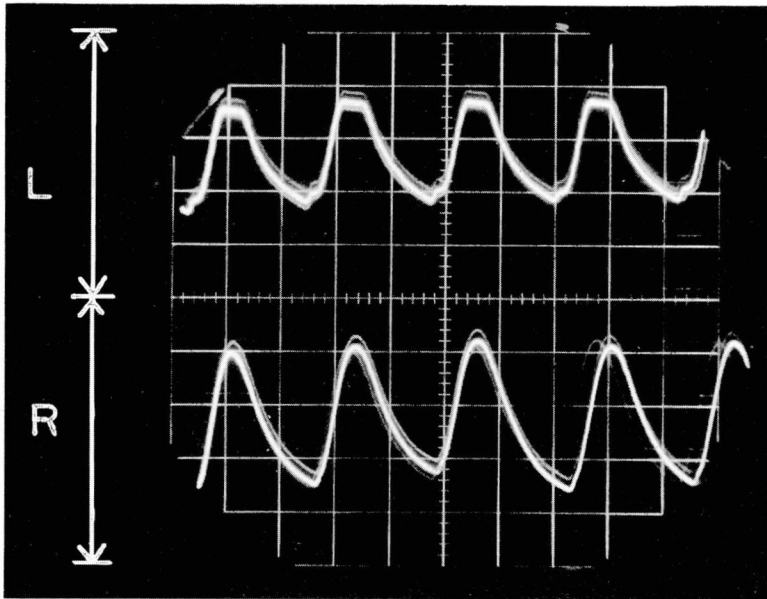


Fig. 3. Oscilloscopic tracings from the Bellofram heart. Upper tracing (L) represents the movements of the piston of the left ventricle. Lower tracing (R) represents movement of the piston of the right ventricle while the artificial heart is sustaining the dog's circulation and the chest has been closed. Only the midportion of the maximal excursion of each piston is used. The left piston hesitated in the up (systole) position while this picture was taken.

with piston velocity or with strokes per minute, and can be integrated to cardiac output. Cardiac output can be read continuously on a meter for the right and one for the left heart. Various electric functions set in the equipment will result in gas pressure curves similar to them. These gas-pressure curves, in turn, will result in various shapes of the ventricular pressure and various shapes of aortic and femoral pulse contours. Most important, piston movement and cardiac output are directly readable.

The deterioration of our dogs was sometimes preceded by a drop in pressure in

the early diastolic phase of the arterial pressure curves. Such drops in diastolic pressure are nonspecific. Similar drops in diastolic pressure have been observed in animals in shock¹⁹ or in animals after the injection of pressor drugs, when the initial rise in pressure is overcome. It seems to indicate an increased peripheral resistance. This fascinated one of us. He designed an electric analogue of the natural circulation. The heart is represented by a source of energy, the blood inertia by an inductance, the peripheral vascular system by a resistance, and blood reservoirs by capacitors. What would happen when this electric analogue was pulsed with waves of energy having sharp peaks? This would be the worst thing that could happen to it, as the resistance would increase and the electric energy would be pooled in the capacitors. This is exactly what had happened in our dogs. Peripheral resistance increased and the organs received less perfusion, leading to deterioration of the animal's brain, to acidosis, and related imbalances. The blood became pooled in the analogue of the capacitors—in the spleen and in the portal system—resulting in the so-called "portal syndrome" described by Clowes,²⁰ and well known to heart-lung machine experimenters. The answer seemed simple. Turning to the 24 potentiometers of the NASA equipment and by feeding in an electric function curve resembling an "h," one can reproduce a similar-shaped air pressure curve that results in a square ventricular-pressure curve. This shape resembled a ventricular-pressure curve registered from a normal dog.

The cylindrical Bellofram heart mentioned was made for two reasons: (1) to obtain more experience with Belloframs, and (2) to allow the use of a linear transducer, which greatly simplifies projection of piston movement on the oscilloscope, and the determination of the cardiac output. It has performed well, and has made it possible to determine cardiac output while pumping inside the dog's chest.

Meanwhile, another form of air-driven heart, the sac heart, proved to fit much better in the chest (*Fig. 4*). From studies to determine hemolysis in pumps, which were initiated some years ago²¹ in our laboratory²² we knew that this was one of the most desirable shapes a ventricle can have to minimize damage to the blood.

The drawback of this sac heart was that its cardiac output could not be followed on the oscilloscope of the NASA equipment. After trying strain gauges, induction coils, and capacitors, the last approach seemed promising. The two sides of the artificial ventricle and the housing were coated with the same material—0.0005-inch Mylar, vaporcoated with aluminum—which is well known since it has been used in the satellite *Echo*. The conductive surfaces separated by air in the housing form a capacitor. The capacitance is a function of the filling, and can be used to record objectively stroke volume and, unless the valves leak, cardiac output.

Our ultimate goal is not a patient with an air-driven heart inside his chest accompanied by a tower of electronic equipment on wheels. Our purpose is to obtain equipment that will help us to define the shape of the air pressure curves required, and to obtain initial experience with the dog. Once the curves were defined, and as a preliminary stunt, one third of the NASA tower of electronic

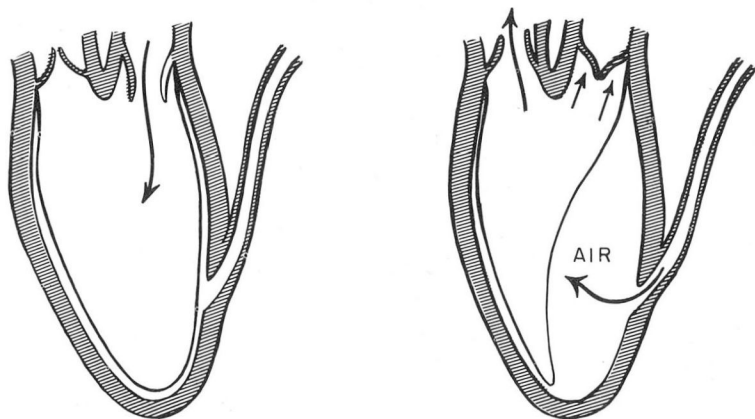


Fig. 4. Diagram of the sac heart, smallest, lightest, and simplest of all present-day artificial hearts. (Courtesy of Seidel, W.; Akutsu, T.; Mirkovitch, V.; Brown, F., and Kolff, W. J.; *Tr. Am. Soc. Artificial Int. Org.* 7: 376-385, 1961.)

equipment was miniaturized into a little box 3 in. by 2 in. by 2 in. It generates the same electric function that was selected as optimum.

Fluid amplification technics also derived from rocketry may offer the most compact solution for the regulation of air pressure. This approach is being followed.*

Although we sometimes seemed to have strayed from our original path, we always came back to it, and invariably when we did return to it, we were wiser and better equipped for the main attack.²³ In the meantime, experiences have been obtained and discoveries have been made which are useful in other fields: a pulsed solenoid,¹¹ improved valves,⁹ better understanding of blood clotting on plastics, stand-by pumps for treatment of medical heart failure,¹³ a modification of a new membrane oxygenator,¹² a useful pump for heart-lung machines, and a powerful tool for those interested in the basic study of the circulation.

References†

1. Dreyer, B.; Akutsu, T., and Kolff, W. J.: Aortic grafts of polyurethane in dogs. *J. Appl. Physiol.* 15: 18-22, 1960.
2. Schollenberger, C. S.: Properties of estane VC, urethane material that is under study in prostheses, p. 166-171, in Merendino, K. A., editor: *Prosthetic Valves for Cardiac Surgery*, Springfield, Illinois: Charles C Thomas, 1961, 586 p.
3. Akutsu, T.; Dreyer, B., and Kolff, W. J.: Polyurethane artificial heart valves in animals. *J. Appl. Physiol.* 14: 1045-1048, 1959.

*In cooperation with Mr. Kenneth Woodward, Fluid Amplification Division of the Diamond Fuse Ordnance Laboratory, Washington, D.C.

†Additional references may be obtained from the author.

4. Merendino, K. A., editor: *Prosthetic Valves for Cardiac Surgery*. Springfield, Illinois: Charles C Thomas, 1961, 586 p.
5. Dreyer, B.; Akutsu, T., and Kolff, W. J.: Testing of artificial heart valves. *J. Appl. Physiol.* **14**: 475-478, 1959.
6. Finelli, A. F.; Mayor, R. H., and Pierson, R. M.: Urethane rubber heart valves made by casting techniques, p. 176-198- *in* Merendino, K. A., editor: *Prosthetic Valves for Cardiac Surgery*. Springfield, Illinois: Charles C Thomas, 1961, 586 p.
7. Akutsu, T.; Mirkovitch, V.; Seidel, W., and Kolff, W. J.: Monocusp aortic valvular prosthesis in dogs. *Am. Heart J.* **61**: 783-789, 1961.
8. Mirkovitch V.; Akutsu, T., and Kolff, W. J.: Intracardiac thrombosis on plastics in relation to construction of artificial valves. *J. Appl. Physiol.* **16**: 381-384, 1961.
9. Mirkovitch, V.; Akutsu, T.; Seidel, W., and Kolff, W. J.: Study of thrombosis on plastics placed inside heart resulting in mitral valve with chordae tendineae. *Tr. Am. Soc. Artificial Int. Org.* **7**: 345-349, 1961.
10. Kolff, W. J.; Akutsu, T.; Dreyer, B., and Norton, H.: Artificial heart in chest and use of polyurethane for making hearts, valves and aortas. *Tr. Am. Soc. Artificial Int. Org.* **5**: 298-300, 1959.
11. Bindels, J., and Grigsby, J.: Considerations and calculations about optimum solenoid to be used for intrathoracic artificial heart. *Tr. Am. Soc. Artificial Int. Org.* **7**: 369-373, 1961.
12. Kylstra, J. A.; Mouloupoulos, S. D., and Kolff, W. J.: Further development of ultra-thin Teflon membrane gas exchanger. *Tr. Am. Soc. Artificial Int. Org.* **7**: 355-360, 1961.
13. Murphy, W. P., Jr.: Cardiac programmer to trigger arterial pump. *Tr. Am. Soc. Artificial Int. Org.* **7**: 361-368, 1961.
14. Akutsu, T.; Houston, C. S., and Kolff, W. J.: Roller type of artificial heart within chest: preliminary report. *Am. Heart J.* **59**: 731-736, 1960.
15. Houston, C. S.; Akutsu, T., and Kolff, W. J.: Pendulum type of artificial heart within chest: preliminary report. *Am. Heart J.* **59**: 723-730, 1960.
16. Akutsu, T.; Seidel, W.; Mirkovitch, V.; Feller, J., and Kolff, W. J.: Electromotor-driven pendulum-type artificial heart inside chest. *Tr. Am. Soc. Artificial Int. Org.* **7**: 374-377, 1961.
17. Seidel, W.; Akutsu, T.; Mirkovitch, V.; Brown, F., and Kolff, W. J.: Air-driven artificial hearts inside chest. *Tr. Am. Soc. Artificial Int. Org.* **7**: 378-385, 1961.
18. Seidel, W.; Hiller, K., and Kolff, W. J.: Intrathoracic artificial hearts. *Tr. Am. Soc. Artificial Int. Org.*: In press.
19. Olmsted, F.: New techniques for continuous recording of cardiovascular functions in unrestrained dogs. *J. Appl. Physiol.* **17**: 152-156, 1962.
20. Clowes, G. H. A., Jr.: Extracorporeal maintenance of circulation and respiration. *Physiol. Rev.* **40**: 826-919, 1960.
21. Cahill, J. J., and Kolff, W. J.: Hemolysis caused by pumps in extracorporeal circulation (in vitro evaluation of pumps). *J. Appl. Physiol.* **14**: 1039-1044, 1959.

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22. Brown, F.; Seidel, W., and Kolff, W. J.: Hemolysis caused by pumps at flow rates of 2 liters. Tr. Am. Soc. Artificial Int. Org. 7: 350-354, 1961.
23. Kolff, W. J.: Integrated program for treatment of patients in desperate heart failure. Tr. Am. Soc. Artificial Int. Org. 7: 343-344, 1961.