Preclinical evaluation of a biolized temporary ventricular assist device[1]

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An external clinical temporary ventricular assist device (VAD) has been developed with the use of our universal, multipurpose cardiac prosthesis with specially designed inflow and outflow cannulas. The cannulas allow flexibility in application of the VAD, which can access the vascular system via either the atrium or ventricle for inflow, and the aorta or pulmonary artery for outflow. A high-pressure pneumatic actuator activates the pusher-plate of the VAD. The clinical drive system for this VAD has complete redundancy and automatic switching to a backup system in the event of any component failure. Six VADs were tested in calves as a temporary left VAD before clinical use and functioned well.

Index terms: Artificial organs • Heart, mechanical • Prosthesis, cardiac

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Circulatory support utilizing various forms of mechanical ventricular assist is now an accepted mode of therapy in refractory cardiogenic shock in several institutions.[1–6]

At The Cleveland Clinic Foundation, various forms of cardiac prostheses have been developed over several decades. In 1977 we began the development of a universal cardiac prostheses (UCP), which could be used for transient, interim, or permanent replacement of cardiac function. It was established that all components of such a device must be (1) adaptable and interchangeable for each of the above pump configurations, (2) mass producible, and (3) biocompatible and sterilizable.

Before development of a temporary ventricular assist device system (VAD), the blood pump had already been

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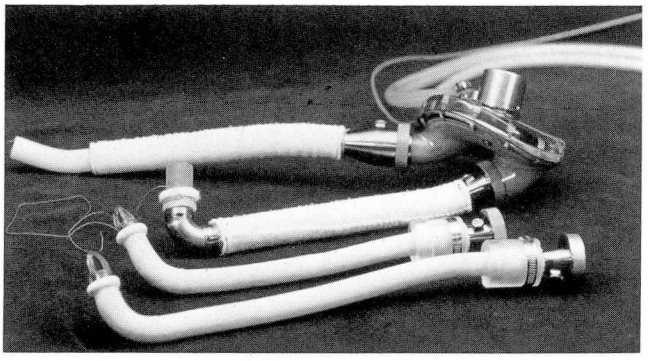

Fig. 1. The Cleveland Clinic Foundation temporary cardiac assist pump and cannula system.

evaluated as a long-term implantable (intrathoracic) left VAD in 11 calves for as long as seven months without the use of anticoagulants.[7,8] Based on these good results, a temporary VAD for clinical use was designed, built, and tested in calves.

This report summarizes the development of the temporary VAD system and the results of VAD performance evaluations.

Materials and methods

Blood pump

The convex circular blood pump consists of a rigid epoxy housing with inlet and outlet ports, pneumatic actuator, and polyolefin rubber diaphragm supported by a pusher-plate (*Fig. 1*). The polyolefin rubber was selected on the basis of its demonstrated high flex life.

All blood-contacting surfaces of the pump are coated with a thin (10–50 μm), smooth, and seamless aldehyde-treated protein to provide for blood compatibility. The stroke volume of the pump was designed to be 90 ml with a pusher-plate excursion of 1.5 cm. Regurgitation through the valves lowers the effective stroke volume to about 80 ml. The pusher-plate position transducer consists of a Samarium cobalt permanent magnet bonded to the pusher-plate and a Hall effect sensor (American Aerospace Control Model HI-5) bonded to the pump housing. The resultant voltage signal, which is proportional to the distance between the sensor and magnet, is linearized by a logarithmic amplifier and allows the continuous measurement of pusher-plate position and thus pump stroke volume.

Cannulas

We chose a cannula set that would allow the option of either ventricular apex to aorta or atrium to aorta vascular access, depending on the patient's condition. For the apical inflow site, a modified Bernhard system was used.[9] The outflow consisted of an 18mm low porosity Dacron graft protected by a series of metal rings embedded in a layer of silicone tube and covered with an outer Dacron fabric sleeve (*Fig. 1*).

Two modifications were made. First, the Dacron graft attached to the apical inflow cannula was externally coated with Biomer to render the tube impervious to air during vacuum application. Second, the outer Dacron sheath that covers the inflow and outflow tubes where they pass through the chest wall was glued to the underlying silicone tube to minimize the potential for infection traveling inward alongside the cannula. The left atrial cannula, modified from that used by Pierce et al[3] was made with a Biomer-coated 51 French venous return cannula with a right-angle bend. Trileaflet tissue valves (22mm internal diameter) are used at the pump inflow and outflow for unidirectional flow and are fabricated from human dura mater.

Drive system

The drive console is a single integrated unit (*Fig. 2*). It consists of four subsystems: (1) power supply unit, (2) pneumatic unit, (3) control unit, (4) monitor and alarm unit.

1. *Power supply unit*: a battery power supply is included, which can function for as long as 35 minutes during patient transport from the operating room to the intensive care unit, and will automatically engage should AC power fail.
2. The *pneumatic unit* provides fail-safe operation with completely redundant backup pneumatics.
3. The *control unit* can operate in four different modes in order to cope with a variety of clinical situations and problems arising from both the patient and VAD. These are (a) manual mode, which allows the easy removal of residual air from the VAD during start up, (b) asynchronous (Asyn) mode (fixed rate), (c) synchronous (Syn) mode (electrocardiogram-triggered), (d) fill/empty (F/E) mode. In the last mode a Hall effect sensor used to indicate pusher-plate position triggers a circuit, which has adjustable end points, hence initiating filling at end ejection and ejection at end filling. This results in a pump with a preload- and afterload-dependent rate but a stroke volume that can be adjusted manually.
4. The *monitor and alarm unit* allows continual evaluation of physiological and VAD functions.

Electrocardiogram (ECG), blood pressure, pusher-plate position, or driving pressure signals can be selectively displayed on a long-persistence, dual-trace oscilloscope to aid in adjusting best VAD operation. Also, pump rate and flow are shown digitally.

The alarm panel conveniently displays complete system status, including pump performance, pneumatic and power-related failures, low pump rate, low pump flow, automatic 1:2 mode (when the heart rate exceeds 130 beat/min, the synchronous ratio is automatically reduced to 1:2 and an alarm sounds), pneumatic pressure loss, vacuum loss, back up pneumatic if in use, and battery operation (low voltage and over voltage).

In vitro studies

In vitro performance evaluations of this pump have been previously reported in detail.[7] In brief, in vitro dynamic performance and flow visualization studies were performed in a mock circulatory system.

This pump was designed to meet the criteria of the National Heart, Lung and Blood Institute (NHLBI, Department of Health, Education and Welfare, RFP HV-77-8, January 1977); it provides a flow rate of approximately 10 L/min at a pumping rate of 120 beats/min against a mean arterial pressure of 120 mm Hg with mean filling pressure of 15 mm Hg.

In vivo studies

These studies were designed to evaluate system performance and team readiness before initiation of clinical application. Six VADs were positioned externally through a left thoracotomy in healthy calves weighing 80–110 kg.

In three cases, the apex was cannulated, while in the other three, the left atrial appendage was accessed. The outflow cannula was sutured to the side of the midthoracic aorta. The two cannulas were passed through percutaneous transthoracic holes made in the 6th intercostal space (*Fig. 3*).

The assist pump, previously flushed with saline, was attached to the cannulas, and placed externally on the lateral chest wall. Slow manual pumping was initiated to completely remove residual air from the system. When the air was removed, the pumping mode was switched to either Syn, F/E, or Asyn mode.

Arterial pressure, left atrial pressure (Statham P-23 pressure transducer, Gould) and left ventricular pressure (Konigsberg transducer Model P-20) were continuously monitored throughout the experiments. Hematologic studies and circulating blood volume (Volumetron, Miles Labs, Inc) were checked periodically. The assist pump was examined on removal and complete autopsies were performed at the end of the experiments.

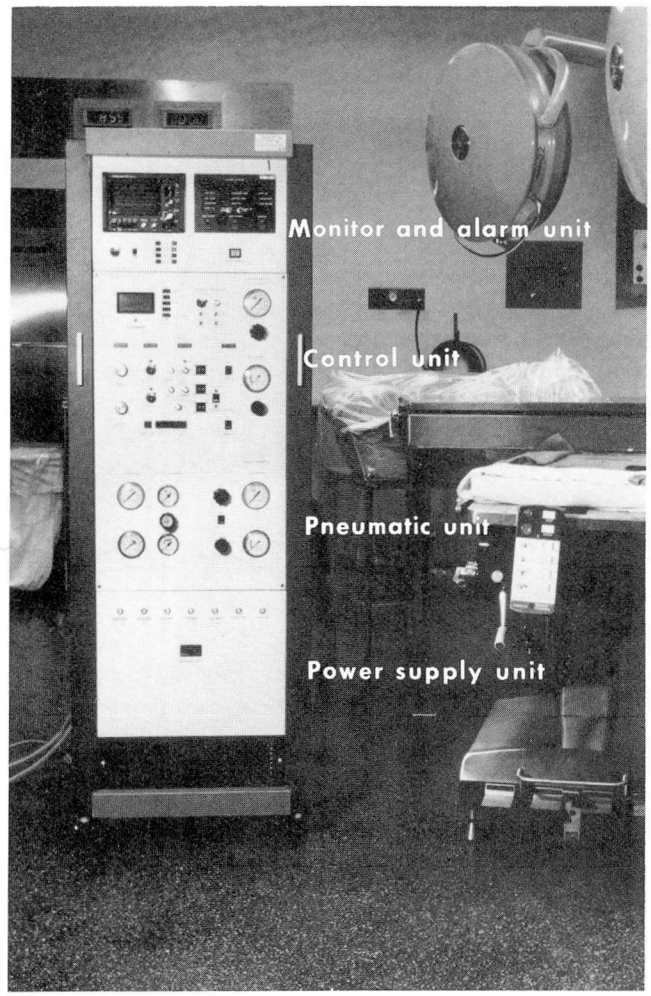

Fig. 2. Drive console.

Results

In vitro studies

Testing of the pump indicates that a net maximum stroke volume of 80 cc was obtained. Complete filling of the pump takes place in 230 msec with an inlet pressure of 15 mm Hg, resulting in a flow of 9.6 L/min at a pumping rate of 120 beats/min. Flow visualization studies demonstrated good filling and ejection flow patterns with good washing of all surfaces.

In vivo studies: clinical course

The results of the six in vivo experiments are summarized in *Table 1.* The average period of continuous pumping in each calf was 12 days.

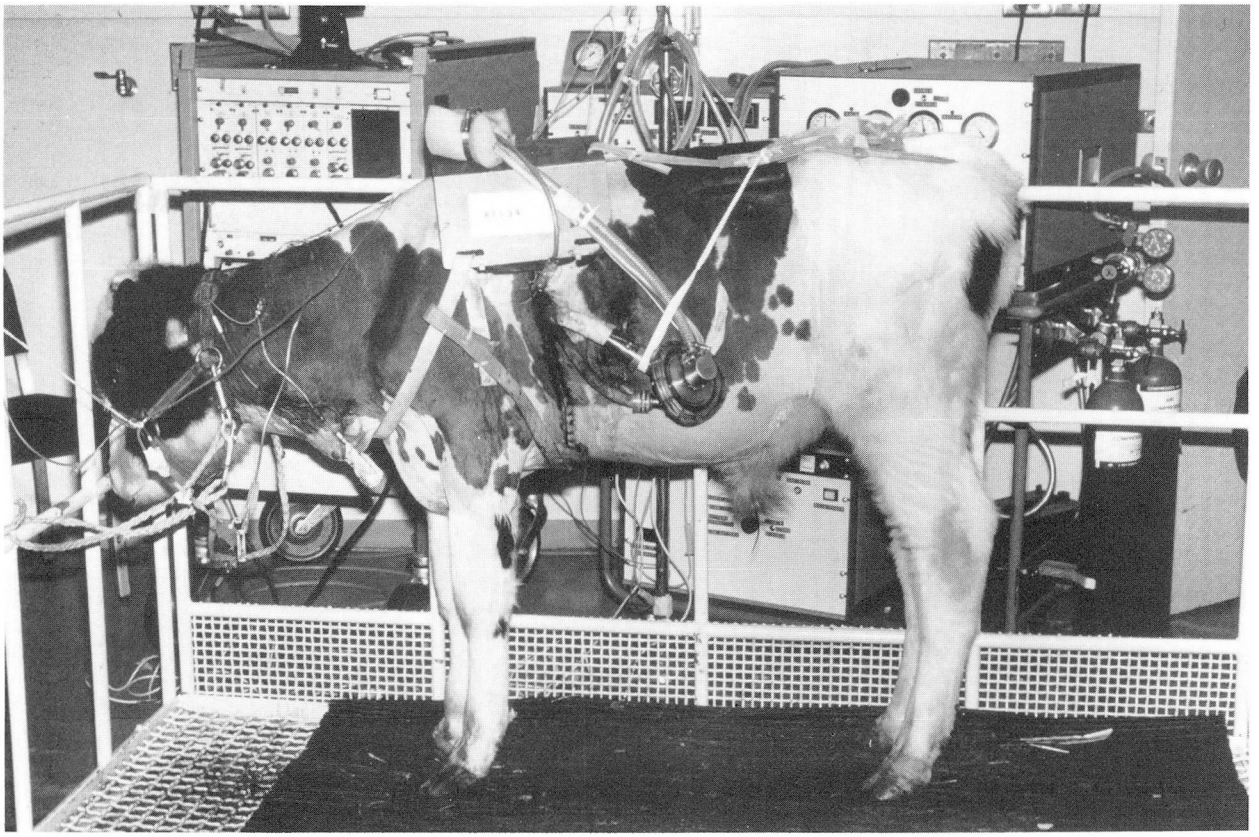

Fig. 3. Preclinical calf experiment (81534). Temporary left ventricular assist device is connected to the calf.

There were no unexplained deaths during the experiments. One calf (81491) was sacrificed after nine days of pumping because of massive hemorrhage due to dehiscence at the ventricular cannulation site, which was a direct result of overwhelming infection (*Pseudomonas aeruginosa*). In calf 81534, an attempt was made at 12 days to remove the VAD, because of declining pump flow. However, hemorrhage-induced ventricular fibrillation ensued and the experiment was terminated. Autopsy confirmed that the cause of the low-flow state was partial obstruction of the left atrial cannula tip by the atrial appendage. This was attributed to improper fit of the cannula

Table 1. Summary of preclinical experiments

Experiment no.	Cannulation	Duration of pumping (days)	Survival after pump removal	Cause of termination	Pumping mode
79365	Apical	14	No; pump removal not attempted	Elective	Syn
79376		11	No; pump removal not attempted	Elective	Syn
81491		9	No; pump removal not attempted	Hemorrhage due to infection	Syn
81507	Atrial	14	Yes; sacrificed 14 days later	Elective	Syn, F/E, Asyn
81534		12	No; ventricular fibrillation at pump removal	Ventricular fibrillation	F/E, Asyn
81536		13	Yes; sacrificed 14 days later	Elective	F/E

Syn = synchronous, F/E = fill/empty, Asyn = asynchronous.

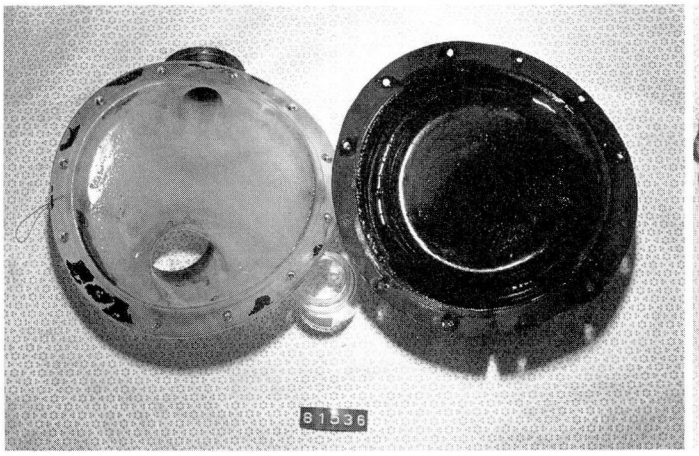

Fig. 4. Pump from preclinical experiment (calf 81536).

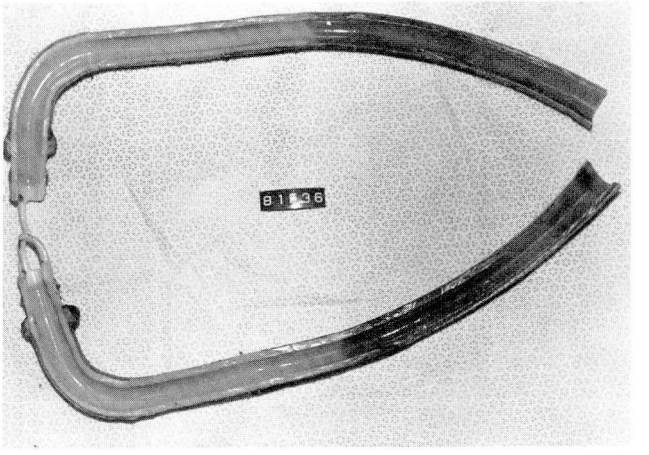

Fig. 5. Left atrial inflow cannula (calf 81536).

tip in the small left atrium of the normal calf. After changing the design of the Dacron collar on the cannula tip to properly fit a calf, there was no recurrence of this problem. Two animals (81507, 81536) were kept alive for 14 more days after removal of the pump. No calf showed clinical evidence of central nervous system emboli or renal emboli. Good tissue anchoring of the outer Dacron covering of the inflow and outflow cannulas was observed in most cases. The six pairs of tissue valves and cannulas were clean. In two pumps some minor deposition was observed on the diaphragm consistent with a low-flow state (<3 L/min, 81534) or with severe infection (81491). The other four pumps were clean (*Figs. 4 and 5*).

Hematologic studies

In most cases, the hematocrit decreased slightly during the first week after implantation, followed by a gradual return to the preoperative value. Blood trauma was minimal as evidenced by the low values for plasma hemoglobin (*Fig. 6*) and constant value of red blood cell osmotic fragility.

Fibrinogen values remained unchanged from preoperative values. A moderate reduction in platelet count was observed (first postoperative day, $P < 0.01$), but returned to the preoperative level within seven days (*Fig. 6*). The serum electrolytes, serum proteins, bilirubin, blood urea nitrogen, and creatinine values were not different from preoperative values in all experiments.

Hemodynamics

Pump flow for each animal is shown in *Figure 7*. Average pump flow was 7.8 L/min with ven-

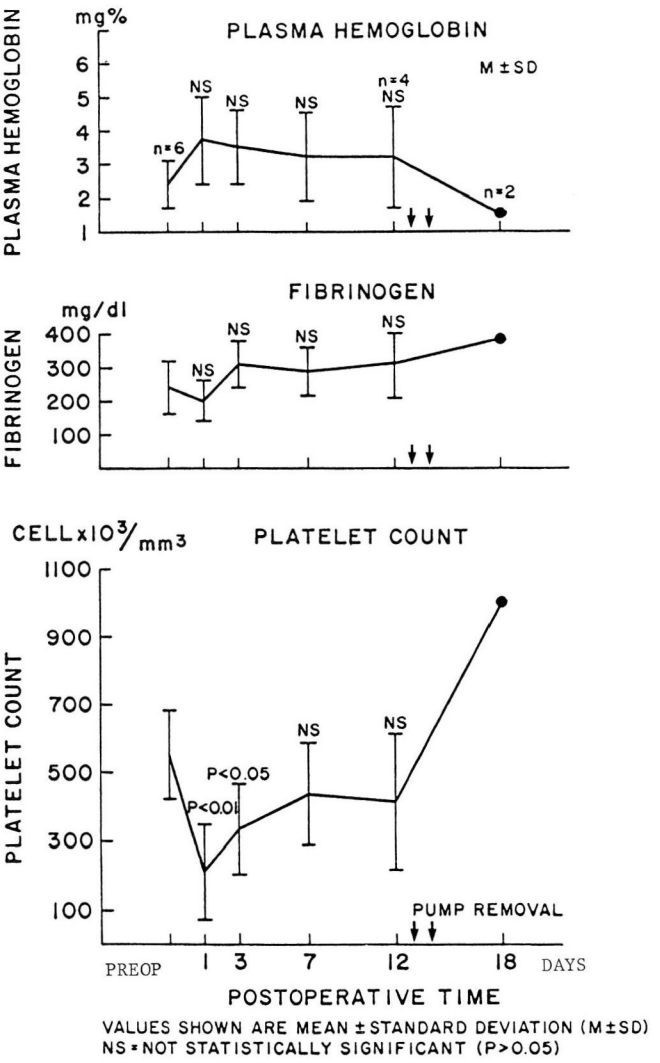

Fig. 6. Serial determinations of plasma hemoglobin, fibrinogen, and platelet count.

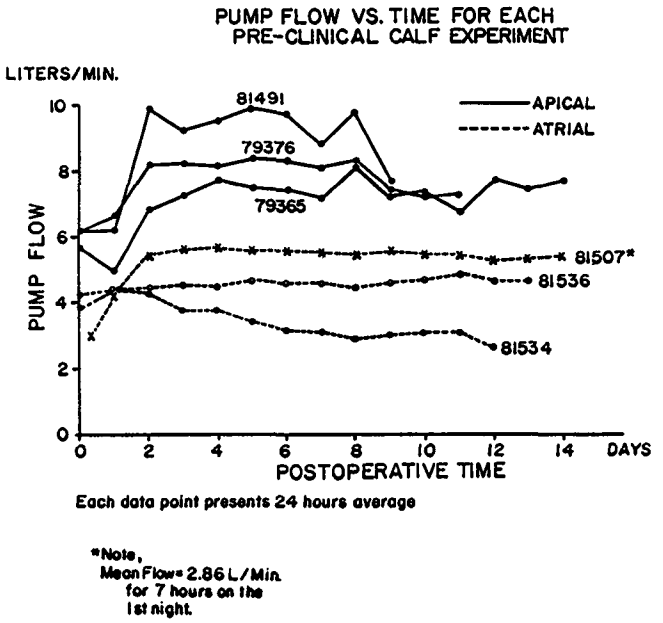

Fig. 7. Pump flow versus time for each preclinical calf experiment.

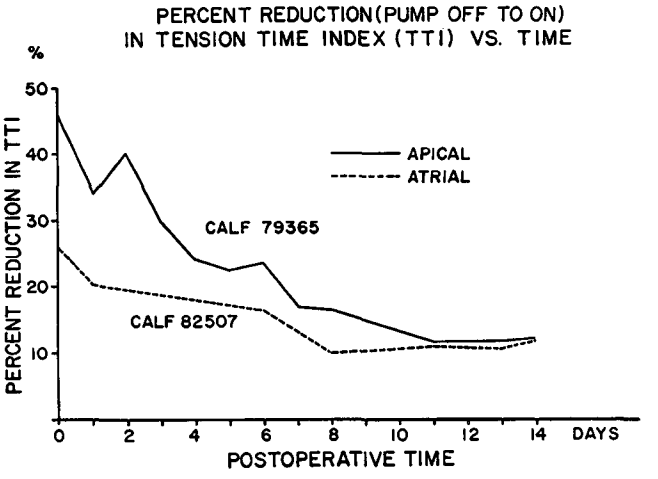

Fig. 8. Percent reduction (pump off to on) in tension time index (TTI) versus time.

tricular cannulation and 4.4 L/min with atrial cannulation. The calves with apical cannulation maintained better VAD filling and consistently higher flow without assist vacuum to the pump diaphragm. For atrial cannulation in any mode, assist vacuum (10–30 mm Hg) had to be used to enhance pump filling and flow during the entire period of pumping. Circulating blood volume did not change postoperatively from preoperative value ($P > 0.05$). Hemodynamic parameters during pump on/off studies are shown in *Table 2.* Under pumping conditions with apical cannulation in the synchronic mode, heart rate ($P < 0.01$), left atrium (LA) and left ventricular end-diastole (LVED) pressure ($P < 0.05$) decreased, while aortic (Ao) pressure increased ($P < 0.05$), compared to values with the pump off.

During pumping with atrial cannulation in fill/empty mode, LA pressure and heart rate decreased significantly ($P < 0.05$). Ao pressure varied according to pump timing. It was lower when the pump was counter pulsating and higher when the heart and pump ejected simultaneously (co-pulsation).

Percent reduction (pump off to on) in tension time index (TTI) is shown in *Figure 8.* In general, greater percent TTI reduction was observed in the early postoperative period. Moreover, percent TTI reduction with apical cannulation was greater than with atrial cannulation during the first week. However, by the tenth postoperative day, percent TTI reduction was approximately the same for both cannulation methods.

Table 2. Hemodynamic comparison of pump on versus pump off with apical and atrial cannulation

Cannulation (Exp. No.)	Pump on/off (n = 3)	Mode	Pump flow (L/min)	Heart rate (beats/min)	Pressure (mm Hg)			% TTI↓
					LA (mean)	LVED	Ao	
Apical (79365)	On	Syn	5.4 ± 0.8	94 ± 6[a]	2.7 ± 2.4[b]	3.3 ± 2.8[b]	145 ± 5[a]/90 ± 7[a] (108 ± 7)[a]	47 ± 5
	Off	...	...	101 ± 5	4.8 ± 2.6	16 ± 1.1	128 ± 8/84 ± 6 (94 ± 9)	...
Atrial (82507)	On	F/E	5.0 ± 1.3	98 ± 4[a]	3.7 ± 1.2[a]	6.3 ± 2.0	138 ± 8/81 ± 7 (103 ± 9)	26 ± 2
	Off	...	...	101 ± 4	5.3 ± 2.6	8.0 ± 1.4	124 ± 4/74 ± 5 (89 ± 8)	...

LA = left atrium; Ao = aorta; LVED = left ventricular end-diastole; Syn = synchronous; F/E = fill/empty; %TTI↓ = percent reduction in tension time index.

[a] Significance: $P < 0.05$ compared with pump off (paired t test).

[b] Significance: $P < 0.01$ compared with pump off (paired t test).

Data above taken on the day of surgery (M ± SD).

Discussion

The efficacy of mechanical circulatory assistance in the treatment of profound left ventricular (LV) failure has been documented from both a theoretical basis and from laboratory studies. The intra-aortic balloon pump (IABP) has been used in a significant number of patients with LV failure; however, some patients cannot survive with this form of cardiac assistance and require escalating degrees of cardiovascular support. The VAD is more effective than IABP which is a volume-displacement device that augments existing circulation. The VAD is a true blood pump, which can temporarily replace the function of the failing heart to allow a period of rest and recovery. The currently available pumps vary in design (concentric tube, sac, or pusher-plate type), blood contacting surface (flocked, highly smooth polymer, or highly smooth protein), and valve type (tissue or mechanical); but all models have proved safe and effective in normal calves for periods of use exceeding the intended duration of clinical use.

Berger et al[4] employed an axisymmetric pump with a flocked surface and tissue valves, while Pierce et al[3] used a sac-type device with a highly smooth polymer surface and mechanical valves. The unique feature of our temporary VAD is a pusher-plate pump that facilitates control, and blood-contacting surfaces coated with a seam-free, highly smooth protein. The trileaflet valves are fabricated from human dura mater. Anticoagulants are not required with this pump.

The pneumatic drive system to be used for clinical work is the same basic device as that developed and used for several years in long-term VAD experiments under National Institutes of Health (NIH) contracts at our laboratory. The purpose in repackaging this unit for clinical use was to design a drive system that could be easily used by clinical personnel, with the capability for mobile operation, and sufficient flexibility to cope with varying circulatory assist situations. A new control mode, F/E, was developed as an alternative to Syn or Asyn operation.[10] It was recognized that the F/E mode was preferable with atrial cannulation (to maintain sufficient flow), and could also be used with ventricular cannulation when natural heart conditions preclude use of the synchronous mode, such as tachyarrhythmia or poor ECG signals. F/E mode has also been found to be the most sensitive to preload and afterload. When the VAD stroke volume is adjusted properly, excellent synchronization can be achieved without the use of an ECG signal.

Controversy remains over the best method of vascular access during left VAD pumping for patients with severe LV failure. Our experiments in calves have demonstrated the superiority of apical cannulation over atrial cannulation in decompressing the left ventricle and reducing myocardial oxygen consumption. However, these studies were not performed in animals with severe LV failure. A review of clinical VAD experience reveals more survivors of atrial cannulation than apical cannulation,[3,11] suggesting that left atrial perfusion may be more effective in instances of severe LV failure. Because of the difficulty in achieving a reliable LV failure model in laboratory animals, further clinical experience is necessary to reach a conclusion as to the best method of vascular access.

There has been steady progress in the development of assist devices. Some systems are presently in clinical use ranging from simple centrifugal pumps to sophisticated electronically controlled pumps.[11-13] Golding et al[2,14] reported 11 cases in which centrifugal pumps were employed in patients who could not be weaned from cardiopulmonary bypass after cardiac surgery. Eight of the 11 patients were weaned, with 2 long-term survivors. More recently, Pierce et al[3] reported a 50% survival rate with the use of VAD after cardiac surgery in patients who could not be weaned. In general, the overall survival rate in these patients is about 20%.[15]

We are encouraged by the high degree of success of our temporary VAD experiments. The Food and Drug Administration has approved this device for human use, and current clinical studies are underway for patients requiring temporary support of ventricular function in accordance with NIH clinical protocol.

References

1. Norman JC. Mechanical ventricular assistance; a review. Artif Organs 1981: 5(2):103–117.
2. Golding LR, Jacobs G, Groves LK, Gill CC, Nosé Y, Loop FD. Clinical results of mechanical support of the failing left ventricle. J Thorac Cardiovasc Surg 1982; **83**:597–601.
3. Pierce WS, Parr GVS, Myers JL, Pae WE Jr, Bull AP, Waldhausen JA. Ventricular-assist pumping in patients with cardiogenic shock after cardiac operations. N Engl J Med 1981; **305**:1606–1610.
4. Berger RL, McCormick JR, Stetz JD, et al. Successful use of a paracorporeal left ventricular assist device in man. JAMA 1980; **243**:46–49.

5. Litwak RS, Koffsky RM, Jurado RA, et al. Use of a left heart assist device after intracardiac surgery. Technique and clinical experience. Ann Thorac Surg 1976; **21:**191–202.
6. Pennington DG. Clinical experience with a centrifugal pump ventricular assist device. Circulatory assistance and the Artificial Heart. The USA-USSR Joint Symposium, Tbilisi, USSR, September 20–22, 1979. NIH Publication No. 802032.
7. Nose Y, Kiraly R, Ozawa K, et al. Development and evaluation of cardiac prostheses. Annual Report to the NIH Contract NO1-HV-4-2960, April 1979.
8. Ozawa K, Snow J, Sukalac R, et al. Totally implantable left ventricular assist device for human application. Trans Am Soc Artif Intern Organs 1980; **26:**461–465.
9. Radvany P, Pine M, Weintraub R, Abelmann WH, Bernhard WF. Mechanical circulatory support in postoperative cardiogenic shock. J Thorac Cardiovasc Surg 1978; **75:**97–103.
10. Yozu R, Golding L, Jacobs G, et al. A new control method for ventricular assist devices (abst). Artif Organs 1983; **7:**4.
11. Bernhard WF. Clinical evaluation of left ventricular assist devices. NHLBI Devices and Technology Branch Contractors Meeting Program, December 6–9, 1982, p 63.
12. Golding LA, Nose Y, Phillips DF, et al. Clinical evaluation of ventricular assist devices. NHLBI Devices and Technology Branch Contractors Meeting Program, December 6–9, 1982, p 64.
13. Pennington DG, Williams G, Bashiti H, et al. Clinical application of ventricular assist devices. NHLBI Devices and Technology Branch Contractors Meeting Program, December 6–9, 1982, pp 65–66.
14. Golding LR, Loop FD, Gill CC, Jacobs G, Nose Y. Clinical mechanical ventricular support. Artif Organs 1981; **5**(suppl):22.
15. Golding LA. Mechanical assist of the failing heart. Cardiovasc Clin 1981; **12**(no. 2): 153–164.