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Preclinical Studies on the Use of a Pulsatile Paracorporeal Assist Devices*)

Kazumi TAGUCHI[1)], Junji MURASHITA[1)], Shintaro FUKUNAGA[1)], Gen TAKEZAWA[1)], Shigeki TAGAMI[1)], Tomoyuki HIRONAKA[1)], Charles-Julian HAHN[2)], Jean-Pierre BRUGGER[2)] and Roland ODERMATT[2)]

1) *Research Institute for Artificial Heart, Hiroshima University School of Medicine, 1-2-3, Kasumi, Minami-ku, Hiroshima 734, Japan*
2) *Genolier Clinique, Genolier, Switzerland*

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ABSTRACTS

An assistance artificial heart was fabricated with blood compatible polyurethane having 3 different sizes and was evaluated by a series of preclinical experiment in calves. The following results were obtained.

1) The artificial heart was constructed in 3 sizes of 60, 80 and 100 cc in capacity and is activated by a pneumatic heart driver console.

2) The mock circulation revealed that this assistance heart has ejection fraction of 80-95%.

3) Safe use of assistance heart has been confirmed by implantation in 18 calves with intact or failured hearts over a period of 3 months.

4) Weaning could be performed in cases where myocardial necrosis of the left ventricle is induced less than 35% utilizing myocardial injection of 5N-NaOH. However pump dependency develops for a necrosis exceeding 35%.

5) Thus we concluded that this system can be safely employed for a one month cardiac assistance clinically and at most for a 3 months support in pump dependent cases.

6) The technique was developed to make the instant shift possible within a few minutes from the conventional non-pulsatile bypass assistance to the assistance heart.

INTRODUCTION

Pump dependency or progressive ventricular failure have often been observed in patients assisted by an intraaortic balloon pump (IABP). Therefore, we decided to provide circulatory assistance by either non-pulsatile or pulsatile pumping[1-5,10]. Our simple non-pulsatile ventricular bypass system was first evaluated in extensive animal experimentation; clinical application was initiated in September 1976[9]. Among 36 patients, 44% recovered normal ventricular function and were successfully weaned; 30% are long term survivors[7]. For the remaining 56%, a more powerful and effective circulatory assistance is required. Our experimental research on the artificial assistance heart (TAGUCHI-HAHN assistance heart) led us to perfect a pulsatile assistance system. Survival up to 523 days was achieved in calves[8]. Furthermore, our clinical experience with patients having failing hearts and low cardiac output syndroms indicated that patients with certain specific conditions would benefit from a pulsatile assistance heart. A clinical protocol was prepared accordingly[6].

*) 田口一美，村下純二，福永信太郎，武澤　厳，田上重喜，広中智之，C．ハーン，J．P．ブルガー，R．オーデルマット：胸壁外に設置した拍動型補助人工心臓に関する前臨床的研究

The purpose of this paper is to prepare the clinical application of the device based upon the experimental results obtained and on the clinical survey made on 134 patients requiring ventricular assistance.

PRECLINICAL STUDIES

a) *Materials and Methods*

Our assistance heart system mainly consists of a pneumatic paracorporeal diaphragm type artificial heart with two mechanical valves as shown on Fig. 1A. It has a capacity of 60, 80 or 100 cc (according to the weight and constitution of the patients) and is activated by a heart driver console. The polyurethane assistance heart is fabricated, using a one block dipping technique. The cannulae are made of flexible EPTFE (IMPRA-flex®) coated with polyurethane (Fig. 1B). Athrombogenic and compliant, they are built in four different sizes and two different shapes to fit the patient's weight and sites of connection.

The pneumatic prosthesis is air driven by a multipurpose artificial heart console (Fig. 2) consisting of:

1) A pulsatile pumping system
2) An electronic trigger circuit
3) A monitoring console
4) An automatic control system of the airline pressure contour capable of determining the complete filling or emptying of the assistance heart.

Our pulsatile assistance heart system was experimentally applied in 18 Holstein and Japanese black calves weighing from 80 to 120 kg. To initiate the pulsatile ventricular assistance, a thoracotomy was performed through the bed of the left fourth or fifth rib. The proximal portion of the descending thoracic aorta was dissected and an aortic cannula was sutured in place. For the left ventricular connection, the apex was infiltrated with 2% Xylocaine solution prior to the placement of Ticron® 2-0 sutures around the apex in order to anchor the ventricular cannula. Under full heparinization (3 mg/

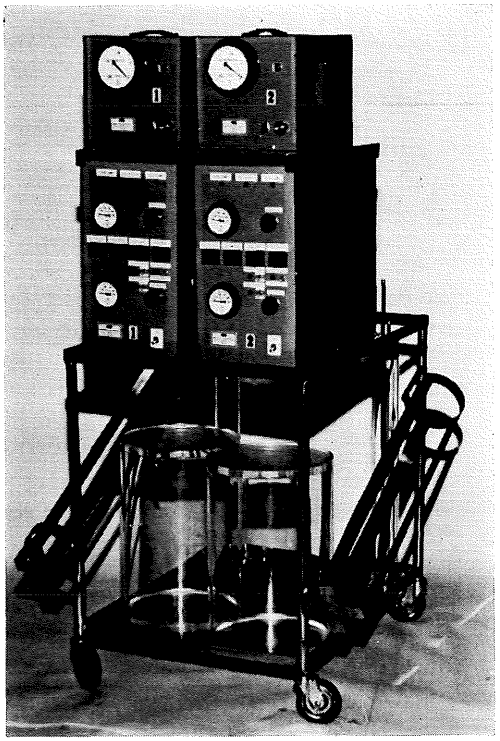
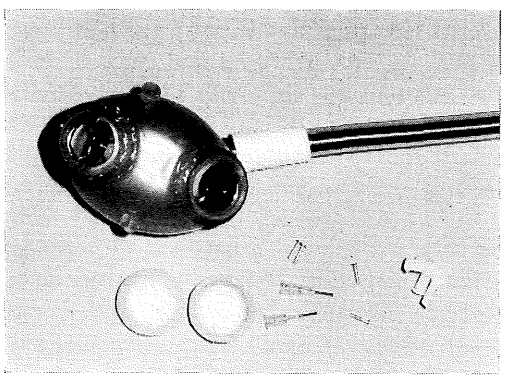
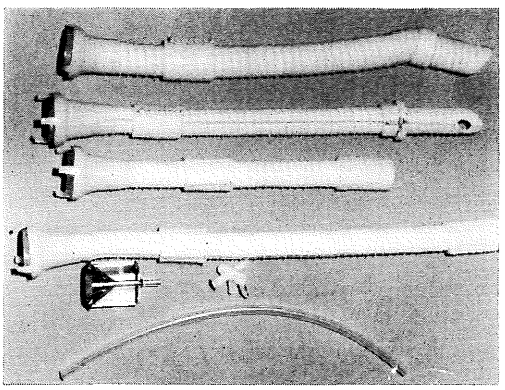


Fig. 2. The artificial heart driver (HHD-III)



A) TAGUCHI-HAHN Heart (HAAH-D-82-IV-S-100-B)



B) Atrial, ventricular and aortic cannulae made of IMPRA-Flex coated with polyurethane, and a dummy connector.

Fig. 1. The clinical assistance artificial heart and accessory cannulae

kg), the cannula was then inserted into the left ventricle after the apical myocardium has been partly resected. In the atrium, the left atrium appendage was sutured twice with purse string sutures. An angled atrial cannula was inserted into the left atrium and tied in position. The cannulae were then connected to the assistance heart and the left aorto-ventricular or aorto-atrial bypass was initiated. The activated coagulation time was maintained at 150–200% of the control level with protamine. The chest was closed and the calves were allowed to recover.

The total of 18 calves was divided into the following groups:

—Group I : 8 calves with intact hearts.

—Group II : 5 calves with 25 to 32% necrosis of the LV produced with myocardial injection of 5N-NaOH.

—Group III: 5 calves with 38 to 45% necrosis of the LV produced with same technique as in group II.

The group I was used to experimentally test an instant shift method from non-pulsatile to pulsatile assistance. Specially designed Teflon connectors were made, permitting the connection between the previously described continuous flow circuit and the cannulae designed for pulsatile flow (Fig. 3). After 1 to 5 hours of non-pulsatile assistance, it was possible, within a few minutes, to remove the Teflon connectors and to connect the pulsatile assistance heart.

b) *Experimental Results*

For all eight calves of group I with intact healthy hearts (Table 1), the shift from non-pulsatile to pulsatile bypass was performed. In the initiation stage of the experiments, non-pulsatile flow assistance was mantained for 1–5 hours and then instantaneously shifted to the pulsatile assistance heart. This shift could be made in all cases within 2 or 3 minutes and pulsatile pumping has been initiated. They were then chronically supported by the pulsatile assistance heart up to 92 days. In two experiments, intractable infection developed after 20 to 35 days of pumping and therefore the bypass assistance was discontinued. In all the remaining animals, the schedule pumping period was completed.

In group II and III (Table 2), 10 calves with induced cardiac failure were chronically assisted. Cardiac failure was produced by injecting a solution of 5N-NaOH into the myocardium. For the first 5 calves of group II, a 25 to 32% necrosis of the left ventricular wall, including the ventricular septum, was made. Four calves were still weaned successfully after 8 to 21 days. In one of the four calves, ventricular fibrillation was induced but the sinus rhythm was restored spontaneously after a period of pumping. The last one was pump dependent and died of gastrointestinal bleeding after 38 days.

In the remaining 5 calves of group III, with an induced necrosis of 38 to 45%, weaning could not be achieved. They were all pump dependent and had to be sacrificed 3 to 6 weeks after the beginning of the experiment.

Demonstration has been made with this animal experimentation that safe chronic pumping with an assistance heart was possible for up to 3 months without any technical problems of abnormal pathophysiologic occurences.

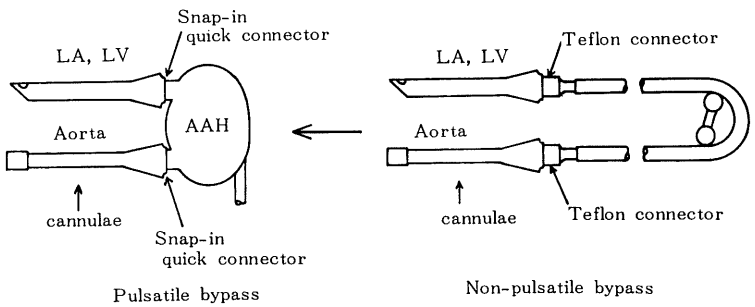


Fig. 3. Schema for instant shift from the non-pulsatile bypass to the pulsatile bypass
Abbreviations: AAH-Artificial assistance heart
LA-Left atrium
LV-Left ventricle

Table 1. Chronic experiments of Taguchi-Hahn assistance heart in 8 calves with intact heart

# calves	Body weight (kg)	Types of connection	Mode of pumping	Flow in average (L/M)	Period of pumping	Outcome	Complication
1	105	LA-Thoracic aorta	Full stroke	6.65	90 days	Weaned off & survived	(−)
2	98	LV-Thoracic aorta	Full stroke	6.25	20 days	Sacrificed	Intractable systemic infection
3	112	LA-Abdominal aorta	Full stroke	4.75	72 days	Sacrificed	Mild local infeciton
4	92	LA-Thoracic aorta	Full stroke ECG trigger	5.87 ?	83 days	Sacrificed	Mild renal infarction
5	95	LV-Thoracic aorta	Full stroke	6.05	60 days	Weaned off & survived	(−)
6	115	LA-Thoracic aorta	Full stroke ECG trigger	6.75 ?	35 days	Sacrificed	Intractable local infection
7	102	LA-Thoracic aorta	Full stroke	4.85	75 days	Weaned off & survived	(−)
8	100	LV-Abdominal aorta	Full stroke	5.50	92 days	Weaned off & survived	(−)

Table 2. Chronic experiments of Taguchi-Hahn assistance heart in 10 calves with induced cardiac failure model by 5N-NaOH myocardial injection

	Size of Myocardial necrosis (%)	Types of connection	Mode of pumping	Flow in average (L/M)	Period of pumping	Outcome and complication	Pump dependency
			Moderate myocardial necrosis				
1	25.2	LA-Th. Ao.	Full stroke	5.85	198 hrs	wean off	(−)
2	25.5	LV-Th. Ao.	Full stroke	6.48	187 hrs	wean off	(−)
3	28.3	LV-Th. Ao.	Full stroke	5.55	12 days	wean off	(−)
4	29.5	LV-Ab. Ao.	Full stroke	4.87	21 days	wean off, infection	(−)
5	32.0	LA-Th. Ao.	Non-full stroke	4.90	38 days	died of gastrointestinal bleeding	(+)
			External myocardial necrosis				
6	38.4	LA-Th. Ao.	Full stroke	6.77	24 days	wean off and died immediately	(+)
7	42.5	LA-Ab. Ao.	Full stroke	6.59	27 days	unsuccessful weaning, sacrificed	(+)
8	39.6	LV-Th. Ao.	Full stroke	6.85	42 days	wean off and died 3 hrs later	(+)
9	44.3	LV-Th. Ao.	Full stroke	7.26	35 days	unsuccessful weaning, sacrificed	(+)
10	40.7	LV-Ab. Ao.	Full stroke	7.05	40 days	unsuccessful weaning, sacrificed	(+)

* Size of myocardial necrosis was calculated by a regression curve which has been determined experimentally evaluating the used volume of NaOH and the resulted myocardial necrosis against total LV and Septum in weight.

Abbreviations: Th. Ao. -Thoracic aorta
Ab. Ao. -Abdominal aorta, subrenal

CLINICAL STUDIES

a) *Classification of patients*

In order to simplify as much as possible the clinical protocol, the patients are classified into 7 groups (Table 3B). These groups have been established according to the following criteria (cf Table 3A):

—cardiac output
—aortic pressure
—urine flow
—acid base balance etc

patients belonging to groups 5 to 7 will first undergo non-pulsatile flow assitance. If adequate ventricular bypass flow cannot be achieved (CI 1.9 l/min/m^2) it is planned to immediately shift to the pulsatile assistance using the assistance heart. These groups have been established empirically based on the clinical results obtained from 134 patients who underwent assisted circulation (AC). Ninety-eight were supported by IABP, VA pumping and the remaining 36 patients by continuous flow ventricular bypass assistance. Additional 100 patients treated with vasoactive drug therapy served as control group in this study.

b) *Control Study*

Scoring indexes were calculated from the hemodynamical findings of the patients and the grouping were made as a function of the cardiac index (CI) in 234 patients with critical cardiac conditions. The control group consisting of the 100 patients under pharmaceutical therapy was first reviewed. A scoring index based on 7 variable parameters was then established (Table 2A). The 68 survivors scored 18.14±2.8, the remaining non-survivors 8.91±1.65. Individual scores were plotted as a function of the CI to divide the patients into 7 categories (Table 2B). This control study showed that the patients belonging to the groups 2 and 3 responded to pharmaceutical treatment and that the patients in groups 4 to 7 needed circulatory support. Furthermore, we integrated 134 patients who rececived circulatory support into this classification. This leads to the following observations: The 98 patients who underwent

Table 3-B. Definitions of patient's groups according to C. I. and score indices

Groups	Definition
Group 1	C. I. : 2.5 L/m/m^2 or above Score: 14.0 or above
Group 2	C. I. : 2.5 L/m/m^2 or above Score: 14.0–9.5
Group 3	C. I. : Less than 2.5 L/m/m^2 Score: 15.0 or above
Group 4	C. I. : 2.5–1.75 L/m/m^2, Score: 14.0–9.5
Group 5	C. I. : Less than 1.75 L/m/m^2 Score: Less than 9.5
Group 6	C. I. : Less than 1.75 L/m/m^2 Score: 14.0–9.5
Group 7	C. I. : Less than 1.75 L/m/m^2 Score: Less than 9.5

Abbreviation: C. I. -Cardiac index

Table 3-A. Criteria for scoring indices

Scores*	1	2	3	4
Mean pulmonary capillary pressure (mmHg)	20	13–20	8–13	8
Central venous pressure (cmH_2O)	20	15–20	10–15	10
Systemic vascular resistance (dyne/sec/cm^{-5})	2500	1800–2500	1400–1800	1400
Urine flow (cc/hr/m^2)	20	20–40	40–60	60
Base Excess (mEq/L/1/2 hrs)	−15	−5−−15	−1−−5	−1.0

Scores*	0.75	1.5	2.25	3.00
PaO_2 (mmHg)	75	75–90	90–110	110
$PaCO_2$ (mmHg)	48 28	43–48 28–32	40–43	32–40

* These scoring indices were plotted against cardiac index (L/min/m^2) and the patient's conditions were classified into 7 groups.

various kinds of AC (for 3 to 340 hrs) were all in groups 4 to 7. Marked differences were seen during the final 3 hours of support between survivors and the non-survivors. Patients in group 4 had a survival rate of 50 to 70%, whereas none of those classified in groups 5 to 7 survived. Finally, in the remaining 36 pateints supported by non-pulsatile assistance, 35 belonged to group 7 and one to group 5 during the initial 3 hours of non-pulsatile support. The 16 successfully weaned patients were in groups 4 to 7 for 24 to 96 hours. They gradually improved their CI and their scoring indexes. Weaning could take place when the patients reached groups 3 to 1. Ultimate recovery failed in 25 patients, being classified in groups 5 to 7, mainly because of the following facotrs:

1) Brain damage, and respiratory and renal failure,
2) Unusual anatomic or physiologic condition (i. e. stone heart)
3) Infection and recurrent cardiac failure

DISCUSSION

Surgeons and cardiologists in the operating room and cardiac intensive care unit should be aware of the fact that there exist currently cardiac assistance techniques beyond modern therapeutics such as intensive vasodilator therapy and IABP.

The purpose of this paper is to describe the recent improvements in cardiac assistance permitting a progressive ventricular support from continuous to pulsatile bypass flow whenever the conventional techniques prove to be ineffective.

Four aspects of this new approach concerning cardiac assistance should be emphasized:

—From our experimental results, the use of the Taguchi-Hahn's extracorporeal assistance heart is proven to be safe for a period of at least three months. Five animals survived over one year with the device implanted intrathoracically[9]. However, for clinical use we recommend to limit the application of the extracorporeal heart to a maximum period of 30 days (In particular cases such as pump dependency this period could be extended to 90 days). This limitation should be observed for the following reasons: With a paracorporeal device the infection risk in high, furthermore, indication as well as limitation of the use of this type of assistance heart is currently not well defined.

The calf experiments showed that if the size of myocardial infarction is over 35% (mass of infarcted muscle vs total mass of the left ventricle), the probability of pump dependency is high. Therefore, we foresee that there will be a limitation in the clinical application of this type of system.

—To simplify the clinical use of our cardiac assistance and in order to provide a progressive assistance from non-pulsatile to pulsatile flow bypass, we developed the instant shift technique. Since the shift can be made in a few minutes, we consider that progressive support of cardiac function is easily achievable.

—In our view, the most important advancement of this cardiac assistance technique is its simplicity. Starting the ventricular support under cardiopulmonary bypass is safe and weaning from this support is simple. Furthermore, the driving system is easy to handle. The present technical approach is therefore considered to be ready for clinical use.

—By evaluating cardiac index, left atrial pressure or pulmonary capillary pressure, central venous pressure, aortic pressure, urine flow, acid base balance etc. based on the categorisation as shown in Table 3, the patients can be classified into the group 1 to group 7. Patients belonging to groups 5, 6 and 7 will first receive the non-pulsatile bypass assistance and if adequate flow cannot be attained (less than 1.9 l/min/m^2 including patient's own cardiac output), it is planned to immediately shift to the assistance heart.

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