UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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Abiomed, Inc. and Abiomed R&D, Inc.
Petitioners

v.

Maquet Cardiovascular, LLC
Patent Owner

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Case IPR2017-01204

U.S. Patent No. 9,561,314

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PATENT OWNER'S EXHIBIT 2021

MECHANICAL SUPPORT WITH MICROAXIAL BLOOD PUMPS FOR POSTCARDIOTOMY LEFT VENTRICULAR FAILURE: CAN OUTCOME BE PREDICTED?

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Objective: We sought to identify the indications of mechanical support in postcardiotomy left ventricular failure in patients who are unable to undergo transplantation.

Methods: From 1989 through 1997, 61 patients with postcardiotomy left ventricular failure beyond intra-aortic balloon pumping were assisted with the Hemopump cardiac assist system (Medtronic, Minneapolis, Minn). Their mean age was 64 ± 8 years. Comorbidity was prevalent; 47% underwent cardiac massage before pump support, and evolving myocardial infarction was diagnosed in 43% before surgery. Multivariable logistic regression of data known at the moment of pump insertion was performed to identify the risk factors for mortality.

Results: Sixty-five percent of the patients were weaned from the device, but only 30% were discharged home. Cardiac index evolution during the first hours after pump insertion ($P < .001$) is the only independent predictor for possibility to wean from the device in the multivariable analysis. Acute renal failure is the only variable retained in the model for 90-day mortality. Device-related complications were far more frequent with the femoral (54%) than with the transthoracic (6%) cannula. Only 13% of the patients had bleeding complications.

Conclusions: One third of the patients with postcardiotomy heart failure refractory to use of the intra-aortic balloon pump can be saved with the use of an endovascular axial flow pump. It is impossible to predict lethal outcome on preoperative data alone. The early hemodynamic response to support seems to be related to functional recovery of the heart and subsequent weaning from the device. (J Thorac Cardiovasc Surg 2000;120:393-400)

Postcardiotomy heart failure is the most troublesome condition in cardiac surgery. Patients unable to be weaned or patients undergoing failure in the first hours after surgery are generally treated with increased inotropic support and use of an intra-aortic balloon pump (IABP). Their survival to hospital discharge is reported to be around 50%.[1,2] At this moment, it is still unclear whether patients with heart failure should be treated immediately with more powerful assist devices and in which patients further therapy is useless. Since 1989 we used, in a consecutive series of patients with postcardiotomy left ventricular failure, the Hemopump cardiac assist system (Medtronic, Minneapolis, Minn) as the first-choice assist device in patients unsuitable for transplantation because of their age or comorbidity. We analyzed our data to delineate the indications for mechanical support in heart failure.

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Received for publication July 16, 1999; revisions requested Sept 13, 1999; revisions received April 12, 2000; accepted for publication April 12, 2000.

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0022-5223/2000 $12.00 + 0 **12/1/107833**
doi:10.1067/mtc.2000.107833

Methods

Left ventricular failure strategy. If a patient cannot be weaned from extracorporeal circulation, reperfusion is allowed for half an hour. In that period, an IABP is placed and

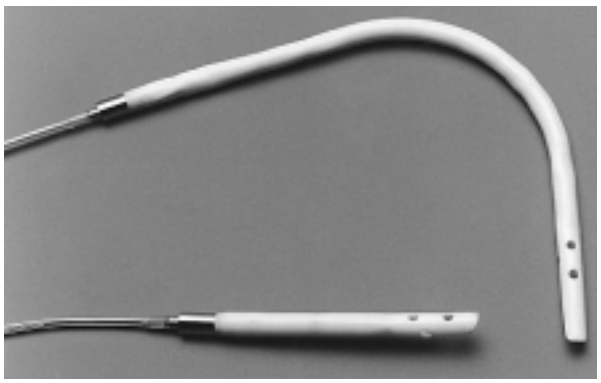

Fig 1. The Hemopump cardiac assist system is a miniaturized axial rotary blood pump. There were two cannulas in clinical use: the long femoral type and the short transthoracic type. Both are 8.1 mm wide.

medical therapy is optimized. Medical therapy comprises optimal filling; inotropic support with dobutamine, dopamine, and enoximone; and, in cases of vasodilation, norepinephrine. A second weaning attempt is undertaken. If signs of left ventricular failure are still obvious (ie, cardiac index < 2 L · m^{-2} · min^{-1} or systolic blood pressure < 90 mm Hg with increased left atrial pressures), the Hemopump device is inserted.

In cases in which left ventricular failure becomes obvious some hours after surgery in the intensive care unit, medical therapy is optimized, and an IAPB is inserted as a measure of intensive care. If hemodynamics again indicate a persistently failing ventricle, the patient is taken back to the operating room, and the Hemopump device is inserted.

The device. The Hemopump cardiac assist system is a miniaturized rotary blood pump mounted on a catheter (Fig 1). The rotor is driven by an electric motor. The bedside-installed console allows regulation of the pump speed from 17,000 to 26,000 rotations per minute. Once the cannula is placed over the aortic valve, it sucks the blood out of the left ventricle and expells it into the ascending aorta. Two cannulas were used in this series: a femoral device and a transthoracic device. Both are 8.1-mm wide, but the femoral cannula has a longer inflow tip and is less performant (maximum flow of 3.5 L/min for the femoral and 5.1 L/min for the transthoracic cannula). The nonpulsatile flow delivered by the Hemopump device is continuously influenced by the underlying cardiac activity.[3,4] The Hemopump console does not display the actually delivered flow, but a performance indicator shows the varying motor current. From 1989 through 1992, the femoral cannula was used. From the first of January 1993, we switched to the transthoracic cannula.

Patients. From 1989, the date of introduction of the Hemopump device in our institution, through December 31, 1997, 12,163 patients underwent cardiac surgery. Three hundred eighty-eight (3.2%) patients received an IABP in the perioperative period, and 108 (0.9%) patients were supported with a more powerful assist device. If bridging to heart transplantation was the first option, the patient was assisted with a medium-term pulsatile assist device (either Abiomed from Abiomed Cardiovascular, Inc, Danvers, Mass, or Medos from Medos, Stollberg, Germany). The Hemopump is a short-term assist device and was only considered in cases of isolated left ventricular failure, with the intention of recovering the cardiac function. Patients with clinical signs of right ventricular or biventricular failure received a right or biventricular assist device other than the Hemopump device (centrifugal pump, Abiomed, and Medos). The assessment of right ventricular function was based on hemodynamic status (central venous pressure, pulmonary artery pressure, and cardiac output), on echocardiographic assessment of the right ventricular contractility, and on clinical background. Therefore, 61 patients received the Hemopump system for isolated left ventricular failure in a postcardiotomy setting, with recovery of the heart as the only possible outcome.

Table I summarizes the biographical data of these 61 patients with a mean age of 64 ± 7.9 years. Many of them were operated on under emergency conditions. Almost half of these patients (47%) underwent cardiopulmonary resuscitation before the Hemopump insertion, and in 43% of them, the diagnosis of evolving myocardial infarction was known at the moment of Hemopump initiation.

Important comorbidity is present with predominantly vascular pathology and diabetes. The comorbidity and age were exclusion criteria for heart transplantation for each of these patients.

Surgical technique. The femoral Hemopump device is inserted through a cutdown of the femoral artery. Bleeding on insertion is controled by means of a 12-mm Dacron graft sutured to the artery. The cannula is introduced through the graft and then passed across the aortic arch and the aortic valve under fluoroscopic guidance.

The transthoracic Hemopump device is inserted through a graft sutured onto the ascending aorta. The cannula is passed over the aortic valve under direct palpation of the ascending aorta. The position of the cannula is confirmed by means of transthoracic echocardiography. Occluding plugs around the drive cable prevent blood loss through the graft once the cannula is in place. Tying one plug close to the ascending aorta secures the position of the cannula and prevents displacement.

Hemopump assist systems are inserted without extracorporeal circulation, with the exception of the patients unweanable from bypass. The transthoracic drive cable is positioned with a smooth curve in the right pleural space and leaves the chest through the caudal end of the sternotomy.

Removal of the transthoracic device requires resternotomy. The graft is occluded as low as possible and sutured.

Patient management. Inotropic support is stopped as soon as possible. Vasopressors are continued in cases of vasodilation. Hemodynamic goals are a mean aortic blood pressure of 70 mm Hg, with left atrial and right atrial pressures of 10 to 15 mm Hg. Filling volume is primarily triggered by the right

Table I. *Biographic data of the patients supported with the Hemopump device (n = 61)*

	No.	*Observations*	*%*	*Mean ± SD*
Age (y)	61			64 ± 8.0
Male sex	61	45	74	
CPR before assist device	61	29	47	
Acute myocardial infarction	60	27	45	
Left ventricular hypertrophy	59	19	32	
Acute renal failure	60	20	33	
Peripheral vascular disease	59	16	27	
Diabetes	59	13	22	
Chronic obstructive pulmonary disease	60	4	7	
Chronic renal failure	60	3	5	
Duration of shock (h)	58	Median, 1	(25%-75%: 0.25-2.3)	
Weight (kg)	52			73 ± 0.8
Length (cm)	52			169 ± 0.4
Cardiac index before assist device ($L \cdot m^{-2} \cdot min^{-1}$)	39			1.8 ± 0.8
Mean blood pressure before assist device (mm Hg)	41			54 ± 12
Left atrial pressure before assist device (mm Hg)	35			19 ± 5
Cardiac index after assist device ($L \cdot m^{-2} \cdot min^{-1}$)	47			3.3 ± 0.9
Mean blood pressure after assist device (mm Hg)	53			7.5 ± 4
Left atrial pressure after assist device (mm Hg)	51			10 ± 3

CPR, Cardiopulmonary resuscitation.

atrial pressure because the right ventricular function is considered to be the limiting factor. Cardiac output by the thermodilution method indicates right ventricular output and reflects the sum of both Hemopump and left ventricular output. Besides the hemodynamic status and clinical signs, plasma lactate levels are monitored to estimate peripheral organ perfusion. In cases in which an IABP is present, we leave it in place because we assume a beneficial effect to myocardial blood flow.[5]

All patients remain sedated and mechanically ventilated during Hemopump support.

Once the drainage through the chest tubes indicates a dry surgical field, we start a continuous heparin infusion to obtain activated clotting time between 180 and 200 seconds.

The antibiotic routine consists of 3 · 2 g of a second-generation cephalosporin the day of surgery. Additional antibiotic therapy is only initiated on guidance of clinical signs of infection.

When recovery of the heart becomes obvious (by increasing pulsatility of the arterial blood pressure), we wean the patient gradually over several days by reducing the pump speed. Transesophageal echocardiography is performed on indication (like clinical suspicion of cardiac tamponade). On the last day, with minimal Hemopump support, transesophageal echocardiography is performed to judge myocardial contractility and to plan the pump removal.

Statistical analysis. Continuous data are presented as means and SD. Paired data are analyzed with the paired Student *t* test. A Kaplan-Meier life-table curve was constructed with the statistical software package Statistica (StatSoft Inc, Tulsa, Okla). Because mortality occurred in a rather short period of time, a logistic regression analysis was performed to predict 90-day mortality.

Simple logistic regression and multivariable logistic regression (SAS; SAS Institute Inc, Cary, NC) were performed to analyze the influence of different clinical variables on the possibility of weaning the patients from the pump and on 90-day mortality. The following variables known by the surgeon at the time of urgent surgery, existing largely of crude historical and hemodynamic data, were considered: age; weight; length; the need for cardiopulmonary rescucitation before surgery; the duration of shock before surgery (ie, shock is a cardiac index <2 $L \cdot m^{-2} \cdot min^{-1}$ or systolic pressure < 90 mm Hg with elevated filling pressures); cardiac index before surgery; mean blood pressure before surgery; left atrial pressure before surgery; peripheral vascular disease; diabetes; chronic renal failure (creatinine >2.5 mg/dL or hemodialysis); acute renal failure (no urine output in the last hour); chronic obstructive lung disease; redo surgery; left ventricular hypertrophy; known severe reduction of ventricular ejection fraction; and evolving acute myocardial infarction at the moment of surgery. Furthermore, additional information gained by the immediate hemodynamic response to the pump insertion were also considered. These variables are cardiac index in the first 6 hours after insertion of the device, mean arterial blood pressure in the first 6 hours after insertion of the device, and left atrial pressure in the first 6 hours after insertion of the device. The variables for which more than 25% of the data were missing were not allowed into the multivariable model.

Results

Weaning from the device. Immediate hemodynamic recovery was obvious, with a significant increase in cardiac index (from 1.8 ± 0.7 to 3.3 ± 0.8 $L \cdot m^{-2} \cdot min^{-1}$; $P < .0001$) and mean arterial blood pressure

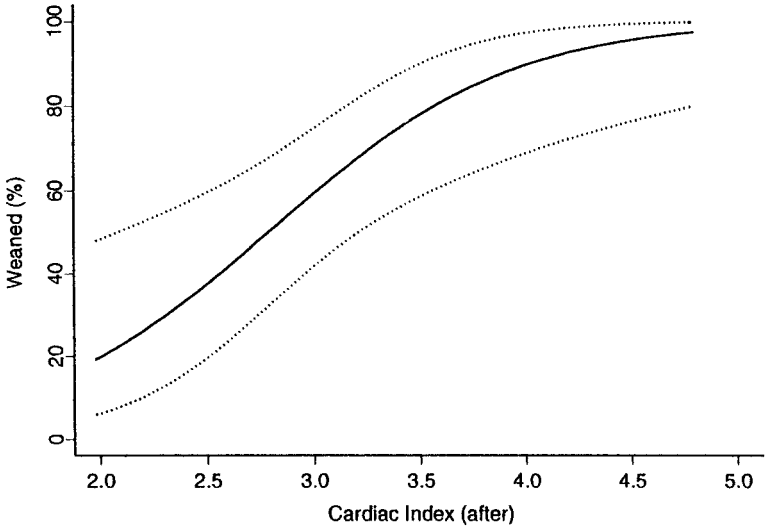

Fig 2. The relation (with 95% confidence limits) between cardiac index in the first 6 hours after Hemopump support and the possibility of weaning the patient from the device.

Table II. *Simple and multivariable logistic regression of risk factors indicating the possibility of weaning the patient from the device*

	OR	*95% CI*	P *value*
Univariate analysis weaning			
Sex (female vs male)	1.336	0.396-4.510	>.3
Age	0.952	0.884-1.025	.17
Weight	0.924	0.855-0.999	.04
Length	0.969	0.894-1.049	>.3
CPR	1.111	0.389-3.177	>.3
Duration of shock	1.012	0.954-1.074	>.3
Cardiac index*	0.966	0.396-2.353	>.3
Arterial blood pressure*	1.023	0.968-1.081	>.3
Left atrial pressure*	1.000	0.860-1.163	>.3
Peripheral vascular disease	1.179	0.345-4.029	>.3
Diabetes	0.510	0.145-1.796	.30
Chronic renal failure	0.000	0.000-1.244	.07
Acute renal failure	0.135	0.040-0.448	<.001
Chronic pulmonary disease	1.667	0.162-17.100	>.3
Redo surgery	1.120	0.366-3.428	>.3
Left ventricular hypertrophy	0.54	0.172-1.701	.29
Poor ejection fraction	0.583	0.189-1.803	>.3
Acute myocardial infarction	0.85	0.293-2.465	>.3
Cardiac index (after)	5.861	1.881-18.264	<.001
Mean blood pressure (after)	1.056	1.004-1.110	.02
Left atrial pressure (after)	0.982	0.817-1.181	>.3
Multivariable model weaning			
Cardiac index (after)	5.861	1.881-18.264	<.001

OR, Odds ratio; *CI,* confidence interval; *CPR,* cardiopulmonary resuscitation before insertion of the device; *after,* hemodynamic values obtained in the first 6 hours after insertion of the device.
*Variable that is excluded from the multiple model because greater than 25% of the data are missing.

(from 54 ± 12 to 74 ± 14 mm Hg; $P < .0001$) and a decrease in left atrial pressure (from 19 ± 5 to 10 ± 3 mm Hg; $P < .0001$). Weaning from the device was possible in 39 (65%) of the patients. Weaning was intended within the first week (longest duration on the device was 10 days). Twenty percent of the patients died the very first day of support. In all these cases a technical pump failure was excluded. Mode of death in these

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