PRECLINICAL STUDIES

An Expandable Percutaneous Catheter Pump for Left Ventricular Support

Proof of Concept

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OBJECTIVES
We sought to evaluate the performance of a newly designed percutaneous catheter with expandable pump.

BACKGROUND
The device was designed as a percutaneously insertable temporary support system for patients with acute left ventricular failure.

METHODS
The pump catheter (introduction diameter 9-F) is positioned in the left ventricle. The rotor is driven by an external motor through a flexible drive shaft. A model circuit was used to assess pump performance, hemolysis tests, and particle image velocimetry. The feasibility of the catheter placement and pump operation were examined in 12 anesthetized sheep. Cardiogenic shock was induced in seven of the animals. Cardiac output (CO) and mean aortic blood pressure (MAP) were recorded before and during shock, and during catheter pump action.

RESULTS
The catheter pump delivered a flow of 4.1 l/min at a differential pressure of 60 mm Hg. The average modified index of hemolysis was 11.6 (optimum, 1.8). Fluoroscopically and echocardiographically guided in vivo placement and deployment of the device were quick and uncomplicated. Under simulation of acute left ventricular failure (CO 43 ± 22% and MAP 55 ± 16% of the baseline value), the catheter pump significantly improved CO to 67 ± 12% and MAP to 74 ± 18%. Maximum in vivo duration of operation was 6 h (average, 3.1 ± 1.4 h). These animal studies revealed: 1) no significant hemolysis (average plasma-free hemoglobin 26 ± 4 mg/l after 3 h); 2) no thrombotic deposits at rotor or pump housing; and 3) no damage to the endocardium or aortic valve.

CONCLUSIONS
A percutaneously insertable, expandable catheter pump is technically and clinically feasible. Our first experimental results are encouraging. (J Am Coll Cardiol 2005;45:1856–61) © 2005 by the American College of Cardiology Foundation

Mortality rates resulting from cardiogenic shock, which is the state of inadequate tissue perfusion resulting from acute myocardial infarction, and other causes of heart failure remain in the 50% to 80% range, despite coronary interventions (1). During the past two to three decades, no significant change in the incidence of cardiogenic shock as a complication of acute myocardial infarction has been observed (2). However, patients selected to receive early revascularization with percutaneous transluminal coronary angioplasty or coronary bypass grafting during this time had lower in-hospital mortality rates than those not selected (3). The rate of mortality of the critically ill with acute left ventricular failure is mainly due to multiple organ failure caused by inadequate tissue oxygenation.

Temporary left ventricular support may increase myocardial oxygen supply and improve oxygen delivery to dependent organ systems, thereby preventing multiple organ dysfunction and subsequent death. A non-surgical, percutaneously implantable device may save time and resources because it could be managed by interventional cardiologists while executing percutaneous coronary intervention. The purpose of this project was the development and initial experimental evaluation of a percutaneously insertable blood pump for temporary left ventricular support.

MATERIALS AND METHODS

Percutaneous catheter pump. The expandable pump unit is located at the tip of the catheter and consists of an expandable rotor, concentrically located within an expandable housing. Both of these components are made of the shape memory alloy (Nitinol, Euroflex, Pforzheim, Germany). The middle segment of the housing, between inflow and outflow tracts, has a polyurethane coating that extends to the catheter shaft as a tubing with outlet slits (Fig. 1). The rotor is connected to a flexible shaft, driven by an external motor unit with a rotation speed of 32,000 rpm. The device is introduced via the percutaneous femoral arterial route. A 9-F delivery sheath is placed with its tip in the left ventricle, and the device is pushed through the

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Manuscript received September 1, 2004; revised manuscript received February 9, 2005, accepted February 22, 2005.
sheath. Consecutively, the compressed pump unit, at the catheter tip, is released by partial withdrawal of the sheath. The correct positioning of the pump unit is assisted by a fluoroscopic or transesophageal echocardiography (TEE) guidance. The inflow tract of the pump unit and the expanded pump housing (diameter, 6.5 mm) are placed within the left ventricle, the outlet tubing in a transvalvular aortic position, and the outflow tract (tubing slits) in the ascending aorta (Fig. 2). Before its removal, the pump unit is compressed by withdrawing it back into the sheath. The sheath with the pump unit is removed, and the puncture site closed via manual compression.

**Hydraulic and hemolysis bench test.** The catheter pump was evaluated using bench tests for compressibility and expandability of the pump unit, pump performance, and hemolysis. It was delivered via a 9-F sheath into a flow model. Within the test loop, the device was operated at different rotation speeds to determine the flow-differential pressure relationship and the hemolysis rate. Hemolysis was determined by the modified index of hemolysis (MIH), which represents the ratio of red blood cells destroyed during passage through the pump to the total number of red blood cells in the system, according to the American Society for Testing and Materials regulations (4).

**In vitro flow field studies.** To assess the flow condition of the pump (stall, vorticity, backflow) tests were performed using particle image velocimetry in a translucent test circuit (Fig. 3). The rotor was positioned along the center line of a transparent pump housing. The central part of the flow channel had an inner diameter of 6 mm and a divergent nozzle at the downstream end to simulate outflow conditions at the downstream end of the catheter. To reduce flow disturbances upstream, a flow straightener and a contraction nozzle were placed in the inflow chamber. A water-glycerine mixture of 30% vol glycerine was used as a test fluid with a viscosity of 3.6 cP (similar to human blood at 37°C). A thin laser sheet was focused in axial planes, which crossed the rotor blade at different angles during rotation. Small fluorescent tracer particles were added to the fluid and recorded in the light sheet with a digital double-shutter camera (PCO Optics, Munich, Germany). The motion of the tracer particles was frozen by a double-pulse of the laser onto two separate images of the camera and digitally processed with cross-correlation methods to obtain the vector field of velocity distribution.

**Animal trials.** The catheter pump was tested in 12 sheep (average body weight 73 kg). Approval for the study was obtained from the regional council in accordance with the German Animal Welfare Act. The animals were premedicated with natriumpentobarbital (20 to 30 mg/kg intravenously), intubated, and mechanically ventilated (isofluorane 0.5 to 1.5%, supplemented with oxygen and N2O). Surface electrocardiographic leads were attached, and a gastric tube inserted. All investigations were performed with the animals in a supine position.

In 5 of the 12 sheep, pump delivery, deployment, and operation, as well as the resulting hemolysis were tested. In seven of the animals, a 4-mm balloon catheter was placed in the left anterior descending coronary artery and inflated to induce myocardial infarction (Fig. 4). For measurement of cardiac output (CO), a Swan-Ganz catheter (131F7, Edwards Lifesciences, Irvine, California) was inserted into the pulmonary arteries. Measurements were performed in triplicate using ice-cold saline solution. Successful implementation of acute cardiac insufficiency was confirmed by a subsequent reduction of CO.
Mimicking the clinical approach for the treatment of acute myocardial infarction, systemic anticoagulation and antiplatelet therapy were provided. All animals received a bolus of 5,000 International Units (IU) unfractionated heparin intravenously, followed by a continuous infusion adjusted to obtain an activated partial thromboplastin time ratio of 1.8 to 2.5. Subsequently, an intravenous bolus of 500 mg aspirin and 300 mg of clopidogrel were administered orally. Following the Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE) protocol, we initiated glycoprotein IIb/IIIa inhibition (i.e., 10 µg/kg bodyweight tirofiban over the course of 3 min followed by a maintenance infusion of 0.15 µg/kg/min) (5).

The catheter pump was inserted percutaneously via the right femoral arterial route, using a 9-F sheath that was 100 cm in length. In the animals with myocardial infarction, the pump was set into operation as soon as cardiac insufficiency (evidenced by a significant reduction of CO and presence of tachycardia) developed. Cardiac output and mean aortic blood pressure (MAP) were recorded before and during cardiac insufficiency and subsequently with catheter pump support. In six of the 12 animals, positioning of the pump in relation to the aortic valve was monitored by TEE. At the completion of the trial, the animals were killed, and the hearts and aortas were harvested, allowing the endocardium and aortic valve to be inspected macroscopically.

Statistics. Results are presented as mean values ± SD. All variables were tested for normal distribution by the Kolmogorov-Smirnov test. Repeated-measures analysis of variance was used for comparison of continuous and normally distributed data. A non-parametric test (Friedman test) was applied to non-normally distributed data. Statistics were analyzed using SPSS 11.0 (SPSS Institute, Chicago, Illinois).
RESULTS

Bench tests. Flow model tests revealed a maximum flow of 4.1 l/min at 32,000 rpm with a differential pressure of 60 mm Hg (Fig. 5). With an optimal rotor design, the average MIH was calculated as 11.6. By improving coaxial guidance of the rotor within the housing, MIH was reduced to a minimum value of 1.8. Maximum duration of rotation was 10 h.

Flow studies. The post-processing of measurement data yielded velocity fields over different angular rotor positions. An example of the flow structure in the central plane along the flow axis (x-axis) is shown in Figure 6, indicating the position of the horizontal leading edge of the blade (phase 0°). Velocity vectors show both flow direction and magnitude at the entrance of the rotor. Backflow was generated upstream of the blade tip, in the gap between the rotor blade edge and the housing. The main flow along the blade was well directed axially over the complete blade surface. The downstream end of the rotor reveals a small flow separation near the rotor axis.

Animal trials. Fluoroscopically guided placement and deployment in 12 sheep was straightforward and quick. Expansion and rotation of the pump at 32,000 rpm was technically feasible. The correct pump position could be confirmed by fluoroscopy as well as by TEE. In seven animals, the model of acute cardiac insufficiency worked well. Cardiac output decreased to 43 ± 22% and MAP to 55 ± 16% of the baseline value. With pump support, CO increased to 67 ± 12% and MAP to 74 ± 18% (Figs. 7 and 8).

Using TEE and color Doppler revealed no significant mitral valve insufficiency, aortic valve regurgitation, or insufficiency during pump support. Maximum in vivo duration of pump operation was 6 h (average in 12 animals, 3.1 ± 1.4 h). There was no clinically significant hemolysis. Average baseline value of plasma-free hemoglobin (PFH) of 12 animals was 21 ± 2 mg/l. After 30 min of pump action, PFH accounted for 25 ± 5 mg/l, and after 3 h of pump action, 26 ± 4 mg/l. With sufficient anticoagulation and antiplatelet therapy, no thrombotic deposits at the rotor, the pump housing, or the drive shaft were observed.

Compression of the pump housing, by catheter withdrawal into the delivery sheath and percutaneous removal of the device, was simple and uneventful. Autopsy and inspection of heart and aorta did not show any macroscopic signs of damage to the endocardium or aortic valve.

DISCUSSION

A percutaneously insertable device for left ventricular support must meet certain medical requirements, which prompt

Figure 5. Pump performance chart: flow versus pressure at operating rotation speed of 32,000 rpm.

Figure 6. Instantaneous vector field of velocity distribution in the central plane at the entrance of the blade’s passage. Coordinates are normalized with the rotor diameter. The origin of the axis system is fixed with the leading edge of the rotor. The vortex structure indicates the typical tip clearance vortex observed in fluid dynamics of turbines.
demanding technical solutions. To avoid complications at the puncture site, the maximum introduction diameter is limited to 9-F (3 mm). The pump unit had to be expandable to provide for sufficient pump performance (a minimum flow rate of 2.5 l/min with a differential pressure of 60 mm Hg) at an acceptable rotation speed (in the range of 32,000 rpm), with regard to drive shaft durability. Therefore, the expandable rotor and pump housing were the “critical” technical components. They required a sophisticated, durable design that allowed for successful percutaneous positioning and deployment.

Our bench tests demonstrated that an expandable axial flow pump is technically feasible. An adequate pump performance was achieved with a rotor diameter of 6 mm at a rotation speed of 32,000 rpm. A pump flow of more than 4 l/min, at a mean pressure of 60 mm Hg, in a fluid with a viscosity comparable with blood indicates its potential to provide for significant circulatory support in cardiac insufficiency. The average in vitro hemolysis rate of the optimized version is less than the MIH threshold of 20, which is considered to be the upper limit for use of a blood pump in a clinical setting (4).

Flow field study results showed the distribution of inflow and outflow velocity vectors. The lack of flow separation along the expanded rotor blades emphasizes their well-designed profile. The backflow observed upstream of the blade tip, in the gap between the rotor blade edge and the housing, is well known in turbine fluid dynamics as the tip clearance vortex. The small flow separation near the rotor axis at the downstream end of the rotor is due to the positive pressure gradient generated at the exit of the pump. Both the clearance vortex and downstream flow separation are inevitable side effects.

The results of our experiments on animals confirmed the proof of concept and indicate that the procedure is technically feasible and has the potential to be clinically beneficial. Percutaneous fluoroscopy or TEE-guided pump delivery, correct placement, and removal were straightforward and uneventful. The pump performance under cardiac insufficiency, as evidenced by CO and MAP measurements, was convincing. Transesophageal echocardiography images during pump support showed neither significant impairment of left ventricular outflow nor induction of aortic valve insufficiency. Additionally, TEE did not show any disturbance of the mitral valve leaflets by the pump unit. Animal experimental hemolysis rate (PFH 26 ± 4 mg/l) was considerably less than the clinically significant threshold of 200 to 400 mg/l. However, these promising results, obtained after an average support duration of 3.1 h, have to be confirmed in further trials of extended duration.

Despite a standard regimen of anticoagulation and platelet inhibition, no significant bleeding was observed. Furthermore, no thrombotic deposits related to the pump unit occurred. By autopsy, no evidence of thrombus was found in the heart and adjacent large vessels. However, assessment of thromboembolic events by necropsy of other organs was not performed and will be the subject of further study.

Our device joins a growing assortment of miniaturized axial flow rotary blood pumps. Blood pump design has a history of more than two decades, beginning with the hemopump in the late 1970s (6). None of these devices featured an expandable pump unit, other than the Reitan pump, which was designed for operation in the descending aorta (7) and whose unconventional concept led to reduced perfusion of carotid and coronary arteries, thus making it unsuitable for the clinical setting.

A recently introduced, non-expandable axial flow pump (with a pump performance comparable with our device) is the rotary blood pump by Impella (Aachen, Germany) with an outer diameter of 6.4 mm (8). The use of the Impella
device in 26 sheep with myocardial infarction revealed a significantly reduced infarct size in the pump-supported animals. The pump produced a maximum CO of 4.1 l/min and significantly increased mean blood pressure. The reduction in infarct size correlated with the degree of “unloading” during reperfusion. In another study by Meyns et al. (9), the same device was applied in 16 patients with cardiogenic shock. Cardiac output before support was 4.1 l/min and increased by pump action to 5.5 l/min after 6 h and 5.9 l/min after 24 h. However, 6 of 16 patients revealed a hemolysis rate of more than 1,000 mg/l PFH, and only 6 of the 16 patients (37%) survived.

Stolinski et al. (10) addressed the interaction between the native heart and a rotary blood pump in a transvalvular aortic position. Although a number of hypotheses were generated, none was experimentally proven. Neither the concept of “unloading” nor other aspects of preload and afterload changes was explicitly tested.

**Study limitations.** The goal of our study was to demonstrate the feasibility of a new technical concept. Fluid mechanics of pump-heart interaction and investigation of the effects of non-pulsatile flow generated by the pump in conjunction with pulsatile flow of the heart for peripheral organ perfusion (e.g., kidney, liver, gut) initially were not addressed. Hemodynamic improvement as a result of pump intervention cannot rule out the possibility that recruitment of collaterals may have contributed to observed positive effects. Further studies should be targeted to resolve these issues.

All examinations were performed in animals with healthy aortic valves. Whereas aortic insufficiency would presumably not impair pump placement and ventricular support, it may be complicated or impossible in case of severe aortic stenosis. One major technical task still to be addressed is the further design optimization of our device. This will focus on increasing the fatigue strength of the expandable components to extend the in vivo operating period up to 72 h. This duration would allow for a more effective bridging, e.g., in cardiogenic shock after myocardial infarction.

**Conclusions.** The present study confirms the feasibility of a newly designed, percutaneous expandable blood pump in vitro and in vivo. Positioning, short-term results of pump performance and hemolysis rates were very encouraging. The device could serve as a short-term mechanical support in acute left ventricular failure, a concept that could meet the requirements of contemporary interventional cardiology.

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