Evaluation of platelet activation in patients supported by the Jarvik 2000* high-rotational speed impeller ventricular assist device

Christoph Löffler, MD,^{a†} Andreas Straub, MD,^{c‡} Nicole Bassler, BA,^{c‡} Katharina Pernice, MD,^b Friedhelm Beyersdorf, MD,^b Christoph Bode, MD,^a Michael P. Siegenthaler, MD,^{b§||} and Karlheinz Peter, MD^{c||}

Objective: The Jarvik 2000 (Jarvik Heart, Inc, New York, NY) is a thumb-sized high-speed impeller pump that is used as a ventricular assist device in patients with terminal heart failure. Because the Jarvik 2000 is designed for long-term use, it is a central question whether the mechanical forces inside the pump affect blood components. This study evaluated the potential association of the high rotational speed of the Jarvik 2000 with platelet activation, which may result in thromboembolic events.

Methods: The study group comprised patients with terminal heart failure who were supported with the Jarvik 2000. All were men and received 100 mg aspirin daily. In 8 patients, soluble platelet activation markers (P-selectin and sCD40L), platelet counts, and hemolysis markers (haptoglobin and lactate dehydrogenase levels) were determined. In 5 patients, P-selectin expression and platelet receptor glycoprotein IIb/IIIa activation were determined with flow cytometry and compared with a control group of 5 healthy men. Platelet activation was measured at various rotational device speeds.

Results: After Jarvik 2000 implantation, increased hemolysis was observed, but platelet activation markers and platelet counts were not affected. Increased rotational speed (8000 to 12,000 rpm) of the device also did not result in increased platelet activation.

Conclusion: The Jarvik 2000 was not associated with detectable platelet activation, despite high rotational impeller speeds.

Patients with congestive heart failure face a limited quality of life and a decreased life expectancy. Often cardiac transplant remains the ultimate step, despite maximal medical therapy. The Jarvik 2000 ventricular assist device (Jarvik Heart, Inc, New York, NY) was developed as a bridge to transplant but also as a long-term, lifetime mechanical circulatory support system for patients ineligible for or unwilling to undergo transplant. The Jarvik 2000 is a thumb-sized, silent, titanium, axial-flow impeller pump weighing 90 g, with a displacement volume of 25 cm³. The pump itself is implanted into the apex of the failing left ventricle, and a vascular graft conveys blood to the descending thoracic aorta or alternatively to the ascending aorta. The impeller is supported by mechanical bearings and spins within an electromagnetic field at between 8000 and 12,000 rpm,

delivering a systemic blood flow of 3 to 8 L/min, depending on the systemic vascular resistance.^{1,2}

Major complications of mechanical circulatory support with rotary blood pumps include bleeding, infection, late mechanical failure, and thromboembolism.^{3,4} Because of the high rotational speed of the impeller pump, blood elements are exposed to shear stress. Shear forces can cause activation of platelets, thereby promoting thrombotic events.⁵ It is therefore a central question whether platelet activation occurs in patients after implantation of the Jarvik 2000, because the induction of a prothrombotic state by the Jarvik 2000 could result in thrombotic and thromboembolic complications. This point is also of particular interest because potent antiplatelet drugs are available. We report here for the first time details about the platelet activation status in patients with the Jarvik 2000 assist device.

From the Departments of Cardiology and Angiology^a and Cardiovascular Surgery,^b University Hospital, Albert-Ludwigs-University, Freiburg, Germany, and the Baker Heart Research Institute, Melbourne, Australia.^c

*Jarvik Heart, Inc, New York, NY.

†These authors contributed equally.

§Currently at University of Pittsburgh Medical Center, Pittsburgh, Pa.

||These authors are equally contributing senior authors.

Received for publication May 6, 2008; revisions received Aug 16, 2008; accepted for publication Sept 6, 2008.

Address for reprints: Andreas Straub, MD, Centre for Thrombosis and Myocardial Infarction, Baker Heart Research Institute, PO Box 6492 St Kilda Rd Central, Melbourne, Victoria 8008, Australia (E-mail: Andreas.Straub@baker.edu.au).

J Thorac Cardiovasc Surg 2009;137:736-41

0022-5223/\$36.00

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doi:10.1016/j.jtcvs.2008.09.019

MATERIALS AND METHODS

Patients and Control Subjects

Patient selection. Patients with end-stage heart failure who were not transplant candidates and had deterioration despite maximal medical treatment were considered for Jarvik 2000 implantation at the University Medical Center Freiburg, Germany. Heart failure criteria for transplantation or mechanical left ventricular support⁶ had to be present. Between May 2001 and February 2004, a total of 8 male patients were enrolled in the study. The patients described in this report did not qualify for heart transplant because of advanced age (1 patient), amyloidosis (1 patient), elevated pulmonary vascular resistance (4 patients), patient request (1 patient); the final patient was unsuitable for a conventional left ventricular assist device because of a small body frame with a body surface area not greater than 1.5 m². Table 1 lists demographic and preoperative hemodynamic data.

Abbreviations and Acronyms

ADP = adenosine diphosphate
CI = confidence interval
GP = glycoprotein
LDH = lactate dehydrogenase

All but 1 patient, who had diastolic cardiac failure associated with amyloidosis, had either idiopathic dilated cardiomyopathy or ischemic cardiomyopathy with chronic heart failure (New York Heart Association functional class IV) despite maximal medical management. In our protocol, the Jarvik 2000 was not offered to patients with a fixed pulmonary vascular resistance greater than 7 Wood units because of the high risk of postoperative right ventricular failure. Inclusion and exclusion criteria for Jarvik implantation have been previously discussed.^{7,8}

Surgical methods, device management, and follow-up.

In all cases, the device was implanted and postoperative care was performed in accordance with previously published reports.^{2,9-11} After the initial postoperative period, the patients described in this report had anticoagulation with intravenous heparin; a week after the operation, anticoagulation was switched to phenprocoumon with the aim of achieving an international normalized ratio between 3.0 and 3.5. Angiotensin-converting enzyme inhibition and β -blockade were continued to support the native heart function, because these patients need continuous heart failure treatment and also to optimize pump flow by lowering systemic vascular resistance. In addition, all patients received aspirin at 100 mg/d. Patients were discharged home between 5 and 8 postoperative weeks. Most patients attended a rehabilitation center for a structured exercise program before returning home. Each patient was evaluated in a specialized outpatient clinic every 6 to 8 weeks. At these visits, laboratory and study parameters were evaluated and echocardiography was performed to monitor native heart and device function.

Blood sampling. All blood sampling procedures were approved by the ethics committee of the University Medical Center Freiburg (project number 58/01). Blood was collected by venipuncture with a 21-gauge butterfly needle from an antecubital vein. A 2-mL portion of blood was drawn and discarded before blood samples for analysis were drawn in further syringes and anticoagulated with citrate or ethylenediaminetetraacetic acid. In 8 cases preimplantation as well as postimplantation data were available for the soluble plasma platelet activation markers P-selectin and soluble CD40L and for standard laboratory markers. In 5 cases, flow cytometric data for platelet activation state after Jarvik 2000 implantation were available. Blood sampling after Jarvik 2000 implantation was performed between 3 weeks to 11 months after the operation. In some cases, several blood samples after Jarvik 2000 implantation were available at additional times. For the data depiction and analysis, data from the sampling point closest to the implantation date are shown.

Control group. We compared the flow cytometric data for platelet P-selectin expression and glycoprotein (GP) IIb/IIIa activation with normal platelet activation in 5 healthy men similar in age to the Jarvik patient group.

Flow Cytometry

Samples for flow cytometric analysis were prepared with a whole blood assay and evaluated according to the principle of a previously described method.¹² Whole blood anticoagulated with citrate was diluted 1:50 with modified Tyrode's buffer (150-mmol/L sodium chloride, 2.5-mmol/L potassium chloride, 1.2-mmol/L monosodium carbonate, 2-mmol/L calcium chloride, 2-mmol/L magnesium chloride, 1-mg/mL bovine serum albumin, and 1-mg/mL glucose). A 50- μ L aliquot of this blood-buffer dilution was added to 10 μ L of the appropriate antibody solution and to 10 μ L of the platelet activator adenosine diphosphate (ADP, final concentration

TABLE 1. Patient demographic characteristics (n = 8)

	95% Confidence		
	Mean	interval	Range
Age (y)	61	54.6–67.4	49–74
Body surface area (m ²)	2.0	1.8–2.2	1.5–2.3
Duration of heart failure (y)	8.6	3.3–13.8	3–18
Creatinine (mg/dL)	1.2	0.4–1.9	0.3–2.6
Heart failure severity score*	6.4	5.8–6.9	5.4–7.2
Cardiac index (L/[min $\cdot$ m ²])	2	1.7–2.2	1.5–2.3
Maximal oxygen uptake (mL/[min $\cdot$ m ²])	11.4	9.8–12.3	7.5–13.9
Pulmonary vascular resistance (Wood units)	3.4	1.7–5.1	0.8–7
Pulmonary capillary wedge pressure (mm Hg)	20	13–27	7–33
Left ventricular end-diastolic diameter (mm)	70.5	56.7–84.3	39–90†
Ejection fraction (%)	22	14–30	15–40†

All patients were male. *See reference 19. †Includes the values of the patient with amyloidosis with a small left ventricle, diastolic heart failure, and preserved systolic function.

20 μ mol/L; möLab GmbH, Langenfeld, Germany). In nonstimulated samples, the ADP solution was replaced with 10 μ L of modified Tyrode's buffer to achieve equal volumes. After gentle mixing, the samples were incubated at room temperature for 20 minutes and then diluted with 500 μ L of 1 $\times$ CellFix (BD Biosciences, Heidelberg, Germany) to achieve a stable fixation and to avoid platelet activation. Flow cytometry was performed on a FACS-Calibur cytometer (BD Biosciences) within 2 hours after the fixation step. The instrument was aligned with CaliBrite beads (BD Biosciences). Blood cells were examined with CellQuest software (BD Biosciences), and platelets were identified by light scatter characteristics. A gate was set around the platelet population, and platelet identity was confirmed with the anti-GP IIb antibody SZ22 (Beckman-Coulter GmbH, Krefeld, Germany). A total of 10,000 platelets were analyzed within this gate in each measurement. Platelet activation status was measured with a phycoerythrin-labeled antibody directed against P-selectin (BD Biosciences). The activation status of GP IIb/IIIa was investigated with the activation-specific fluorescein isothiocyanate-labeled immunoglobulin M monoclonal antibody PAC-1 (BD Biosciences).

Measurement of Soluble Activation Markers

Soluble P-selectin and soluble CD40L were measured by enzyme-linked immunosorbent assay (R&D Systems, Inc, Minneapolis, Minn) according to manufacturer recommendations. For soluble P-selectin, ethylenediaminetetraacetic acid–anticoagulated plasma was diluted 1:20, and for CD40L, ethylenediaminetetraacetic acid–anticoagulated plasma was diluted 1:5; 100 μ L diluted plasma was used per well. All measurements were performed in triplicate.

Measurement of Standard Laboratory Parameters

Platelet count, mean corpuscular volume, mean corpuscular hemoglobin concentration, and international normalized ratio, as well as haptoglobin and lactate dehydrogenase (LDH) levels, were determined in the clinical laboratory facilities of the University Medical Center Freiburg, Germany, according to standard laboratory methods.

Statistics

All data except the haptoglobin values are described by means, with 95% confidence intervals (CIs) or SEs as indicated. The results of the

FIGURE 1. Platelet activation in Jarvik patients compared with control subjects. Flow cytometric analysis did not show any difference in binding of phycoerythrin-labeled antibody against the platelet activation marker P-selectin (fluorescence in arbitrary units, *a.u.*) on nonstimulated (*n.s.*, $P = 0.11$ by *t* test) or on adenosine diphosphate-stimulated (*ADP*, $P = .22$ by *t* test) platelets from 5 male Jarvik patients relative to platelets from 5 healthy men of similar age. Data are shown as means with 95% confidence intervals.

flow cytometric measurements of the Jarvik patient group and the control group were compared with unpaired *t* tests. The preoperative and postoperative values of soluble platelet activation markers, platelet counts, mean corpuscular volume, and mean corpuscular hemoglobin concentration, as well as LDH levels, were compared with paired *t* tests. In 5 cases the haptoglobin levels after Jarvik implantation were below the detection limit of the measurement assay (<5 mg/dL). For the statistical analysis, these values were overestimated as 5 mg/dL, and the group values are described as medians and ranges. Preoperative and postoperative haptoglobin values were compared with a 1-sided Wilcoxon matched pairs test.

RESULTS

P-selectin Expression on Circulating Platelets

The activation status of circulating platelets was determined by flow cytometry. P-selectin (CD62P) is an adhesion molecule that is localized in α -granula of non-stimulated platelets. After stimulation, P-selectin is mobilized to the cell membrane, and thus its flow cytometric detection on the platelet surface can be used as marker of platelet activation. The comparison of 5 Jarvik patients with control subjects did not show a significant increase in P-selectin expression on platelets in Jarvik patients in either nonstimulated or ADP-stimulated samples (Figure 1).

FIGURE 2. Activation of platelet receptor glycoprotein (GP) IIb/IIIa in Jarvik patients compared with control subjects. Flow cytometric analysis with fluorescein isothiocyanate-labeled antibody PAC-1 that binds only to activated glycoprotein IIb/IIIa showed no differences in activation state of platelet glycoprotein IIb/IIIa receptor (fluorescence in arbitrary units, *a.u.*) in either nonstimulated (*n.s.*, $P = .57$ by *t* test) or adenosine diphosphate-stimulated (*ADP*, $P = .45$ by *t* test) platelets from 5 Jarvik patients relative to platelets from 5 healthy men of similar age. Data are shown as means with 95% confidence intervals.

GP IIb/IIIa Activation on Circulating Platelets

In addition to the surface expression of P-selectin, another major change in platelets during their activation is a conformational switch of the platelet fibrinogen receptor integrin GP IIb/IIIa from a low-affinity state to a high-affinity state. This conformational change can be detected with the monoclonal immunoglobulin M antibody PAC-1, which binds only to the high-affinity GP IIb/IIIa receptor. The comparison between control subjects and Jarvik patients did not demonstrate differences in the binding of PAC-1 on platelets in either nonstimulated or ADP-stimulated samples (Figure 2). According to two sensitive parameters, circulating platelets in patients with the Jarvik 2000 assist device were not activated.

Platelet Activation Status With Different Rotational Speeds of the Jarvik 2000 Axial Impeller

To investigate the influences of the Jarvik 2000 impeller speed and pump flow on platelets, both P-selectin expression and GP IIb/IIIa activation were determined in 1 patient with the Jarvik 2000 assist device at five different impeller

FIGURE 3. Influence of rotation speed of Jarvik impeller pump on platelet activation. To investigate influence of rotation speed of impeller pump on platelets, expression of platelet activation marker P-selectin and glycoprotein IIb/IIIa activation (PAC-1) were determined by flow cytometry (fluorescence in arbitrary units, a.u.) in 1 patient with Jarvik 2000 assist device at different rotational speeds. There were no increases in platelet activation markers during stepwise increase in Jarvik impeller rotational speed from 8000 to 12,000 rpm. Data are shown as means and SEs of triplicate measurements.

rotational speeds. Notably, there were no increases in anti-P-selectin antibody and PAC-1 antibody binding on platelets during the stepwise increase of the rotation of the Jarvik axial impeller pump from 8000 to 12,000 rpm (Figure 3).

Soluble Markers of Platelet Release as Memory of Platelet Activation

Soluble P-selectin. Because mild activation of platelets may not be detectable by flow cytometric analysis of circulating platelets, soluble markers of platelet activation were determined. Soluble P-selectin is shed from the platelet membrane during platelet activation, and its plasma level thus is also a marker of platelet activation. There was no difference in plasma levels of soluble P-selectin after implantation of the Jarvik 2000 relative to preoperative values (Figure 4).

Soluble CD40L. CD40L is a membrane molecule that becomes mobilized to the platelet surface during platelet activation. Similar to P-selectin, this molecule is also shed from the platelet surface and can be detected as soluble CD40L in plasma. There was no difference in plasma levels of soluble CD40L after implantation of the Jarvik 2000 relative to preoperative values (Figure 4).

FIGURE 4. Levels of soluble P-selectin (P-sel) and soluble CD40L (sCD40L) as markers of platelet activation in patients with Jarvik devices. P-selectin is shed from platelet membrane during activation and therefore indicates platelet activation status. There was no difference in plasma level of soluble P-selectin after implantation of Jarvik 2000 relative to preoperative values ($P = .53$ by paired t test). CD40L is expressed on platelets on activation and also shed from platelet surface, thereby becoming detectable as soluble CD40L in plasma. There was no difference in plasma level of soluble CD40L after implantation of Jarvik 2000 relative to preoperative values ($P = .7$ by paired t test). Data are depicted as means and SEs of 8 patients.

An analysis of soluble platelet activation markers in patients with blood samples from additional time points that could be analyzed revealed no relationship between platelet activation and time since the Jarvik 2000 was implanted (data not shown).

Platelet Counts and Hemolysis

Because the high rotational speed of the impeller pump may damage corpuscular blood elements, single platelet counts and potential signs of hemolysis were investigated in Jarvik patients. There was no statistically significant difference ($P = .8$ by paired t test) regarding preoperative values of single platelet counts (mean 273.3×10^3 cells/ μ L, 95% CI 206.7 – 339.8×10^3 cells/ μ L) and postoperative values (mean 268.1×10^3 cells/ μ L, 95% CI 188.9 – 347.4×10^3 cells/ μ L). Haptoglobin levels decreased from a preoperative median of 167 mg/dL (range 50–222 mg/dL) to a postoperative median of 5 mg/dL (range 5–77 mg/dL, $P = .008$). There was only a mild and statistically nonsignificant increase ($P = .219$) in LDH from preoperative (271.9 U/L, 95% CI 168.2–375.5 U/L) to postoperative (420.4 U/L, 95% CI 170.5–670.3 U/L) measurements. Mean corpuscular volume and mean corpuscular hemoglobin concentration did not differ between preimplantation and postimplantation measurements (data not shown).

Anticoagulation and Correlation With Thrombotic Events

The mean international normalized ratio at the time of blood sampling after Jarvik 2000 implantation was

2.5 ± 0.5 . There was no obvious relationship between the degree of anticoagulation and platelet activation in individual patients. One patient with a dissection of the thoracic aorta who had only minimal anticoagulation because of this fresh aortic dissection had an early debilitating stroke. Taking into account that we did not observe any platelet activation, the stroke was not correlated with platelet activation.

DISCUSSION

Ventricular assist devices are used for treatment of end-stage heart failure, either for bridging to transplant or for lifetime mechanical circulatory support. Assist devices may be associated with major complications, however, including thromboembolism. Axial rotary blood pumps are designed to reduce complications because of their size.^{3,4} To provide sufficient blood flow, however, an axial impeller pump with high rotational speed has to be used, and there is concern that such high speed could be associated with adverse platelet activation. In our cohort of 8 Jarvik patients, we were unable to demonstrate that the high rotational speed of the Jarvik 2000 impeller pump was associated with either platelet activation or a loss of circulating platelets. In this context, however, it should be taken into account that all patients investigated in this study were receiving continuous aspirin treatment, which may have had a protective effect on platelet function against damage and activation by the impeller pump.

All rotary blood pumps seem to be associated with risks of thrombosis and thromboembolism. The assist device Jarvik 2000 is placed directly in the left ventricle, and thus there is no need for an inlet cannula. This decreases the potential for blood stasis and thereby reduces the risk of thromboembolic events.³ Although autopsy studies have revealed no thrombotic apposition to the pump,⁷ thrombus formation within the left ventricle has occasionally been reported.¹³ The position of the outflow graft may also influence the incidence of thromboembolism. There is no consensus regarding whether to connect the outflow cannula to the ascending or descending thoracic aorta.¹¹ The first provides better washout of the aortic root, whereas the second reduces the risk of cerebral thromboembolism, because small particles are less likely to embolize to the brain.⁹ In addition to the administration of anticoagulation therapy, the risk of stasis in the aortic root may be lessened by minimizing pump flow to only unload the ventricle partially to allow opening of the aortic valve. As another solution, a so-called intermittent low-speed controller for this device has been released in Europe to provide better aortic root washout. This controller automatically reduces the pump speed every minute for a few seconds to a low rotational setting, which leads to an increased preload on the native heart and an ejection from the native heart for a few heart beats.

The miniaturized pump design is based on a unique axial impeller pump that revolves at extraordinarily high speeds of

8000 to 12,000 rpm. Cellular blood components may become activated or even damaged, however, by the mechanical forces caused by the impeller rotation. Indeed, decreased haptoglobin levels, mild increases in LDH and plasma free hemoglobin levels have been reported after Jarvik implantation,^{2,8} indicating hemolysis and thus damage to blood cells. In our study, we could confirm significantly reduced haptoglobin levels; however, we only saw a mild and nonsignificant LDH increase and no decrease in circulating platelet counts. Nevertheless, in this context platelets are still of particular interest, because shear forces can induce platelet activation,⁵ resulting in a procoagulatory state and an increased risk of thromboembolism. Therefore the question of whether high rotational impeller speed, such as in the Jarvik 2000, activates platelets is important for the clinical use of all rotary blood pumps and could also provide a rationale for the use of platelet inhibitors.

One of the most reliable techniques to determine the platelet activation status is flow cytometry. On platelet activation, P-selectin is mobilized from intracellular α -granula to the platelet surface and can be detected by directly labeled anti-CD62P antibodies. The determination of P-selectin expression on the platelet surface has been repeatedly used as a marker of platelet activation in various experimental and clinical settings.^{14,15} The conformational change of GP IIb/IIIa from a low-affinity binding state for its ligand fibrinogen to a high-affinity binding state is the final common pathway of all types of platelet stimulation. The activated GP IIb/IIIa receptor can be detected in flow cytometry with the monoclonal immunoglobulin M antibody PAC-1, an approach that has been extensively used for experimental and clinical studies.¹⁶ In our study, both markers of platelet activation, P-selectin expression and the high-affinity conformation of GP IIb/IIIa, did not demonstrate any activation of circulating platelets in patients with the Jarvik 2000 assist device. This finding is important in determining potential prothrombotic properties of the Jarvik 2000. It indicates that despite the high rotational speed of the impeller pump of the Jarvik 2000, no activation of circulating platelets was detectable by flow cytometry.

Soluble forms of platelet adhesion molecules are also plasma markers of platelet activation. P-selectin and soluble CD40L are both molecules that are mobilized to the platelet cell membrane on platelet stimulation. Both molecules are transmembranous molecules, and both are shed by cleavage of the extracellular domain close to the transmembrane domain. The soluble parts of these molecules continue to circulate in the blood and thus constitute a kind of measurable memory of platelet activation. Indeed, both platelet activation markers have also been proved to be prognostically important in clinical settings, such as instable coronary artery disease. Notably, especially in those patients with positive results for soluble CD40L, antiplatelet therapy improved overall prognosis.¹⁷ Our finding that the soluble markers

of platelet activation were not increased in Jarvik 2000 patients parallels the finding of our flow cytometric evaluation of platelet activation and is another indicator that the Jarvik 2000 does not activate platelets in the clinical setting.

Favorable properties regarding platelet activation and hemolysis have also recently been reported from a study in juvenile sheep that evaluated the function of the pediatric Jarvik 2000 heart, in which the pump configuration was adapted from its adult counterpart.¹⁸ After an initial maximum increase in LDH and plasma free hemoglobin levels at 1 week after implantation, the degree of hemolysis stabilized. The LDH level returned to baseline, and the plasma free hemoglobin level stayed around 50% above baseline throughout the remainder of the study period. This is quite encouraging, especially considering that ovine red blood cells are more fragile than are human red blood cells. Likewise, P-selectin expression on platelets followed a similar pattern, with maximal effects 1 week after implantation and normalization to minimal values by 2 weeks after surgery.¹⁸

Our finding that platelet activation markers were not increased after Jarvik 2000 implantation in patients receiving low-dose aspirin therapy suggests that additional antiplatelet therapy is not necessary for these patients. It is yet unclear whether low-dose aspirin treatment, as administered to our patients, inhibited some platelet activation associated with a rotary blood pump. Aspirin, however, is not capable of fully blocking platelet activation. Furthermore, our data address the controversy regarding the clinical suitability of high-rotational speed impeller pumps and indeed support their use. Thus the enormous advantage that is provided by the small size of high-rotational speed impeller pumps does not appear to be counteracted by the activation of platelets.

CONCLUSIONS

Despite the high rotational speed of the Jarvik 2000 left ventricular assist device, no activation of circulating platelets could be detected in patients receiving low-dose aspirin therapy, even with sensitive methods including flow cytometry and the determination of soluble platelet activation markers. Overall, considering the major clinical benefits of the Jarvik 2000 in terminal heart failure and our finding that platelet activation was not associated with its use, high-rotational speed impeller pumps such as that used in the Jarvik 2000 represent a promising technology. The Jarvik 2000 and, potentially, similar rotary blood pumps do not seem to be associated with platelet activation.

We thank Drs I. Ahrens and J. Martin for their help in obtaining patient samples and Dr B. Balkau for advice regarding the statistical analysis of the data presented in this article.

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