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# Analysis of Platelet Function during Left Ventricular Support with the Incor and Excor System

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## ABSTRACT

Improvements in pump technology and the scarcity of donor organs have led to an increased use of mechanical assist devices, but the problem of thromboembolism has still not been solved. We report on our initial experience with sequentially analyzing platelet function in patients provided with the Incor left ventricular assist device (LVAD) and the Excor LVAD system. Thirteen patients 5 to 61 years old with acute or end-stage heart failure were included in a pilot study. Five of the 10 Incor patients underwent LVAD placement under emergency conditions, and 5 were electively scheduled for surgery. All 3 patients with an Excor device had been connected to an extracorporeal membrane oxygenation system prior to insertion of the device. An anticoagulation protocol including heparin, aspirin, and clopidogrel was employed, and the patients were closely monitored with a special platelet-analyzing system that allows dose optimization for antiplatelet drugs. Initial platelet function was normal in only 2 patients (15%). During a follow-up period of 1770 days (cumulative >4.8 years), no early (<30 days) bleeding complications related to device implantation occurred. Late cerebral thromboembolic events were noted in 3 patients. One patient experienced severe stroke mandating neurosurgery during mechanical assist, and 1 patient experienced systemic embolism. The PAP platelet analyzer offers a cheap and reliable alternative to the more expensive thromboelastography method for adequately surveying the efficacy of aspirin and clopidogrel treatment, even if late thromboembolic events cannot be prevented.

## INTRODUCTION

Improvements in pump technology and the scarcity of donor organs have led to an increased use of mechanical assist devices, mainly as a bridge to transplantation but also for the recovery of impaired myocardial pump function in patients with acute and chronic end-stage heart failure [Goldstein 1998, Hetzer 2001]. Recently, the REMATCH study has shown that patients without a therapeutic alternative may undergo implantation of a left ventricular assist device (LVAD) as a definitive therapy [Rose 2001]. Independent of the individual indication for device placement, most cardiosurgical centers still use the rather bulky first-generation devices, and only a few institutions favor or have access to the considerably smaller axial-flow pumps. Regardless of the type of VAD, all systems are far from being perfect and are still associated with various complications [Deng 2003]. These problems, which are mainly associated with long-term use of the support systems, need to be addressed, especially in the view of an anticipated increase in permanent implantations.

In our opinion, thromboembolism is the most important issue to be solved. Because platelet function is generally assumed to play a key role in anticoagulant protocols, antiplatelet therapy is considered crucial for avoiding deleterious complications. However, up to now an optimal anticoagulant protocol has been lacking, there are no guidelines, and no gold standard is available.

We report on our initial experience with sequentially analyzing platelet function in patients provided with the Incor LVAD and Excor LVAD system (Berlin Heart AG, Berlin, Germany). The main intention was to reduce the incidence of early bleeding problems, but another goal was to improve the management of late bleeding and thromboembolic complications.

## PATIENTS AND METHODS

### *Patients*

Thirteen patients (8 male, 5 female) 5 to 61 years old with acute or end-stage heart failure were included in a pilot study (Table 1). Five patients had dilative cardiomyopathy, 4 patients had acute myocardial infarction, and 2 had ischemic heart disease. One patient who was referred to our institution with severe biventricular failure was suspected to have acute myocarditis (which could not be proved), and 1 patient, a 5-year-old boy, had postcardiotomy failure following the

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Table 1. Patient Data*

| Patient No. | Age, y | Sex | Cause of Heart Failure | Prior Interventions | Device Implanted |
|---|---|---|---|---|---|
| 1 | 43 | M | Acute myocarditis | — | Incor LVAD |
| 2 | 40 | F | Dilative cardiomyopathy | — | Incor LVAD |
| 3 | 54 | F | Acute myocardial infarction | IABP, PTCA | Incor LVAD |
| 4 | 58 | M | Ischemic heart disease | Redo CABG | Incor LVAD |
| 5 | 32 | M | Acute myocardial infarction | — | Incor LVAD |
| 6 | 34 | M | Dilative cardiomyopathy | — | Incor LVAD |
| 7 | 51 | F | Ischemic heart disease | CABG | Incor LVAD |
| 8 | 59 | M | Dilative cardiomyopathy | — | Incor LVAD |
| 9 | 58 | M | Dilative cardiomyopathy | — | Incor LVAD |
| 10 | 62 | M | Dilative cardiomyopathy | — | Incor LVAD |
| 11 | 5 | M | Subaortic stenosis | AVR, ECMO | Excor LVAD |
| 12 | 39 | F | Acute myocardial infarction | PTCA, IABP, ECMO | Excor LVAD |
| 13 | 30 | F | Acute myocardial infarction | CABG, ECMO | Excor LVAD |

*LVAD indicates left ventricular assist device; IABP, intra-aortic balloon pump; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting; AVR, aortic valve replacement; ECMO, extracorporeal membrane oxygenation.

replacement of the aortic valve with a homograft. Five of the 10 Incor patients underwent LVAD placement under emergency conditions, and 5 were electively scheduled for surgery. All 3 patients with an Excor device had been connected to an extracorporeal membrane oxygenation system prior to insertion of the device.

Mechanical support lasted from 27 to 485 days (mean ± SD, 141 ± 122 days). Two patients were successfully weaned from their devices after recovery of native pump function after 77 days and 97 days. Four patients underwent heart transplantation, and 2 patients are still under support.

### *Devices*

The Incor LVAD is a new axial-flow pump with special technologic features. Its inflow conduit is inserted into the left ventricular apex, and the outflow conduit is attached to the ascending aorta. The weight of the device is approximately 200 g, which allows it to be placed inside the pericardium. No separate device pocket is required. The impeller has magnetic bearings; that is, there is no friction to compromise the long-term function of the device. The conduits are made of silicone and are connected with clip connectors that can easily be reopened at any time. Because the conduits are perfectly sealed, no oozing from the conduits is seen after implantation. The driveline exits the right lower quadrant of the abdominal wall and is attached to a portable controller and batteries. The controller allows the speed of the turbine to be varied from 5000 to 10,000 rpm. The capacity of the 2 batteries guarantees an untethered use of the device for 8 hours.

The Excor device is a pneumatically driven extracorporeal system comparable to the well-known Thoratec device (Thoratec, Pleasanton, CA, USA). It can be used to support the left or right heart and is available in various sizes to support any patient from the neonate to the large and obese adult. The inflow and outflow cannulas are similarly made of silicone, allowing cannulation of the left and right atrium as well as the left ventricular apex.

### *Postoperative Anticoagulation Management and Assessment of Platelet Function*

No anticoagulation therapy was administered for 12 to 24 hours after device placement. Thereafter, intravenous heparin was administered to achieve a partial prothrombin time of 60 to 80 seconds. Prior to adding aspirin with a starting dosage of 100 mg per day, usually following removal of the drains, platelet function was assessed with a platelet analyzer (PAP; Mölab, Hilden, Germany). This analyzer allows a selective survey of arachidonic acid–, adenosine diphosphate (ADP)- and collagen-induced platelet aggregation. The dosage of aspirin was increased until arachidonic acid–triggered platelet aggregation dropped to levels below 30%. If the patient remained clinically stable and did not need further invasive interventions, clopidogrel was added. The dosage was similarly adjusted to lower ADP-induced platelet aggregation to levels below 30%. The collagen aggregation curve was noted, with levels of 70% to 100% considered optimal; however, the aggregation curve could not be influenced by an additional antiplatelet medication. Oral anticoagulation treatment with phenprocoumon was started in parallel with the removal of the venous central line and aimed at an international normalized ratio of 2.5 to 4. Further medication including dipyridamole and ticlopidine was prescribed only in cases of thromboembolic adverse events despite an assumed optimal antiplatelet therapy.

### *Statistics*

All data had been prospectively entered in the institutional database. A retrospective analysis was undertaken, and values were expressed as the mean and SD.

## RESULTS

The first analysis of platelet aggregation after device placement showed normal platelet function in only 2 patients (15%). From the 3 recordings of the PAP analyzer indicating platelet aggregation under the various stimuli, 1 tracing was

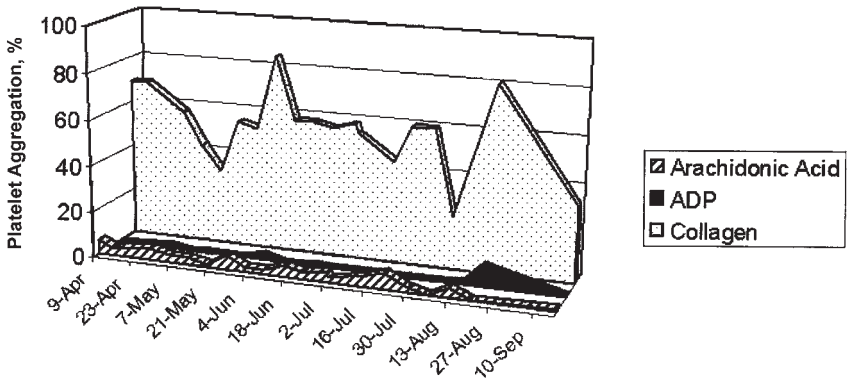


Figure 1. Analysis of platelet function. Incor patient was completely stable and treated on an ambulatory basis. After 470 days, no clinical adverse events had occurred.

altered in 4 patients (31%), 2 tracings were altered in 1 patient (8%), and all 3 tracings were altered in 6 patients (46%).

With the appropriate treatment of patients to have both recordings (arachidonic acid– and ADP-triggered platelet aggregation) within the suppression level of 0% to 30% platelet function, a total follow-up period of 1770 days (cumulative >4.8 years) was obtained. During that follow-up, no early bleeding complication (<30 days) related to the device implantation occurred. Moreover, no cerebral hemorrhage was noted (Figure 1). A mild hematothorax following puncture of pleural effusions developed in 2 patients, 1 of whom experienced heparin-induced thrombocytopenia type 2 and was treated with danaparoid. Gastrointestinal bleeding complications were seen in 2 more cases, both requiring endoscopic interventions and even laparotomy in 1 case.

Cerebral thromboembolic events were noted in 3 patients. One patient experienced severe stroke and later underwent cortical decompression via neurosurgery during mechanical assist with the anticoagulation therapy critically lowered (Figure 2). This patient required rather long care in the intensive care unit but finally had a favorable outcome. The other 2 patients had only mild symptoms, which were fully reversible within days. One patient had a systemic embolism into the middle colic artery that mandated colon resection.

A complete pump stop was suspected in 1 patient. This patient had a defective system after struggling with and unintentionally pulling firmly on his driveline. The line was partially torn, but this damage did not affect the impeller function. The patient was scheduled for high-urgency transplantation, but he died suddenly a week later after cardiovascular

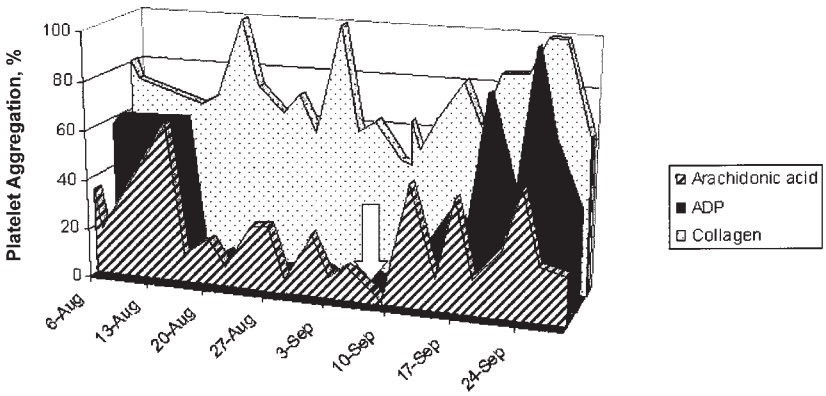


Figure 2. Analysis of platelet function. Incor patient with antiplatelet therapy that was difficult to optimize. Arrow indicates intracerebral bleeding with subsequent neurosurgery during ongoing left ventricular assist.

Table 2. Coagulation Parameters during Adverse Events*

| | Pump Data | | | Plasmatic Coagulation | | | | | | Platelet Function Test, % | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Adverse Event | Flow, L/min | RPM | Power, W | aPTT, s | AT III, % | INR | Fibrinogen, mg/dL | D Dimer, µg/mL | Platelet Count, $\times 10^3/\mu L$ | Arachidonic Acid | ADP | Collagen |
| Hematothorax (pleural puncture) | 4.3 | 6450 | 3 | 110.5 | 58 | <1.5 | 390 | — | 306 | 16 | 6 | 77 |
| Hematothorax (pleural puncture) | 3.7 | 8000 | 2.3 | 42 | 57 | <1.5 | 397 | — | 96 | 17 | 1 | 46 |
| Intracranial bleeding | 4.3 | 7000 | 1.1 | 80 | 78 | <1.5 | — | 4.6 | 483 | 1 | 1 | 46 |
| Cerebral thromboembolism | 3.9 | 6950 | 2.8 | 61 | — | <1.5 | — | — | 229 | 19 | 12 | 59 |
| Cerebral thromboembolism | 4.7 | 6350 | 2.3 | 55 | — | <1.5 | — | — | 211 | 8 | 3 | 37 |
| Mesenterial/splenic infarction | 4.3 | 6000 | 1.7 | 64 | — | <1.5 | 647 | 1 | 213 | 18 | 16 | 57 |
| Sudden death | N/A | N/A | N/A | 62 | — | <1.5 | 731 | — | 247 | 23 | 69 | 65 |

*aPTT indicates partial prothrombin time; AT III, antithrombin III; INR, international normalized ratio; ADP, adenosine diphosphate; N/A, not available.

collapse. A pathologic examination revealed a small mural thrombus inside the left ventricle, which might have been able to temporarily occlude the pump inflow. However, the hypothesis remains to be proved.

There were no significant correlations between adverse events, coagulation parameters, and platelet function or antiplatelet therapy (Table 2).

## DISCUSSION

The main obstacle hindering long-term VADs in gaining widespread acceptance to treat patients with end-stage heart failure is their associated complications. Although the degree of infectious problems has declined with miniaturization of the devices (ie, since the introduction of the small axial-flow pumps), bleeding and thromboembolism still jeopardize patients, especially over the long term [Song 2003]. It is well known that patients supported with an LVAD, although successfully sustained with or without systemic anticoagulation therapy, have evidence of activation of coagulation [Spanier 1996, Dewald 1997]. Moreover, excessive anticoagulation treatment not infrequently leads to bleeding complications requiring a reduction in or even the halting of anticoagulation therapy, which increases the risk of thromboembolism, and finally may induce a deleterious vicious cycle. The most devastating complication is device thrombosis, which has been repeatedly reported for the MicroMed DeBakey device (MicroMed Technology, Houston, TX, USA) [Rothenburger 2002, Vitali 2003].

As the experience among implant surgeons and treating physicians has grown, the important role that platelets play in this regard has become clear. In our own early VAD experience, in which mainly the Novacor system (Novacor, Oakland, CA) was implanted, the high incidences of thromboembolism were treated with increasing dosages of aspirin [Schmid 1998a, 1998b, 2000]. However, this kind of management did not result in an adequate improvement of complication rates because more patients than expected were in part resistant to aspirin medication. Consequently, the anticoagulation protocol had to be widened in a much more sophisticated fashion. Having become aware of centers that have taken extraordinary efforts to optimize anticoagulation therapy, we discussed several aspects of a modified treatment protocol.

Pavie, Szefner, and others postulated a rather extensive protocol, the multisystem La Pitie Hospital protocol [Szefner 1995]. These authors stated that most bleeding complications are biological in origin and are essentially the result of disseminated intravascular coagulopathy (DIC) in its later phases. Instead of filling up the reservoirs, the authors adopted a radically different strategy than that of other centers considering different phases of DIC. They considered thromboelastography on recalcified whole blood to be the only sensitive test to allow the study of global coagulability and the different phases of coagulation. With regard to platelet function, these authors stated that platelets are permanently activated throughout the implantation of any mechanical circulatory support. Accordingly, their patients were treated with dipyridamole to render the platelets less receptive to the usual inductors, thereby preventing the release of platelet secretion products.

Synder et al [2002] thoroughly investigated platelet activation, aggregation, and life span in calves implanted with axial-flow VADs. Calves with uneventful VAD implant periods had early transient elevations in levels of platelet microaggregates and prolonged elevations in levels of activated platelets that did not recover to preoperative values during the study. Daily platelet consumption in VAD-implanted calves was increased by 20% ± 3%. Calves that had thrombotic deposition within the VAD and elevated thromboembolism observed at autopsy experienced increases in levels of circulating activated platelets and microaggregates.

Matsubayashi et al [2000] investigated changes in platelet activation associated with left ventricular assist system placement by using flow cytometry to evaluate the expression of CD62P and CD63 as markers of platelet activation. Patients'

platelets showed increased levels of CD62P and CD63 expression, whereas annexin V binding was not increased. These workers also demonstrated during LVAD support the suppression of thrombin activation, which was a consequence of heparin treatment. Treatment with aspirin or dipyridamole gave no evidence of such an effect.

Because we wanted to intensify antiplatelet therapy and had no thromboelastography capability available in our institution, we started using the PAP platelet analyzer, a much cheaper alternative that was readily available. The analyzer costs approximately $20,000, and costs of approximately $2 per study have to be considered. After investigating all of the patients who were being treated with aspirin, it became apparent that some patients did not respond or inadequately responded to the aspirin treatment. Higher dosages of up to 1000 mg daily did not lower the incidence of adverse thromboembolic events. In this situation, we started adding clopidogrel to the anticoagulant regimen. This step proved rather effective. Thus, clopidogrel became an integral part of treatment for all patients with axial-flow pumps because of their increased procoagulant properties (the reason is still unknown) and became the drug of second choice in cases of aspirin resistance in all other devices. This protocol worked quite acceptably but still did not prevent thromboembolism. If patients experienced further thromboembolic adverse events despite optimal levels of aspirin and clopidogrel, we then medicated the patient with dipyridamole to further intensify the antiplatelet therapy. This triple therapy certainly posed a not-underestimated risk of bleeding complications. Although iatrogenic complications can be reduced when one is aware of them, gastrointestinal bleeding problems cannot be dealt with in a satisfactory manner. If severe gastrointestinal bleeding did occur, the administration of all antiplatelet drugs was halted. In cases of minor bleeding, only clopidogrel and dipyridamole therapies, if used, were withdrawn until stabilization of the clinical situation.

The real value of the PAP analyzer used in this study is still not clear. We were quite successful in abolishing early bleeding complications and consecutive early thromboembolic events. However, late adverse events remained a challenge to the physician. It was interesting to see that intraventricular thrombus formation does occur despite high-grade antiplatelet therapy. With regard to the analyzer system, we now focus on the collagen-induced aggregation curve. As stated before, this curve or the underlying physiologic process cannot be altered by specific drugs in a manner similar to that with the other 2 recordings. Theoretically, the level of this curve should be maximal, because collagen is assumed to be exposed only in cases of endothelial injury, which does not occur under normal circumstances. If an endothelial laceration occurs, the action of not inhibiting platelet aggregation at that site should be taken to prevent a bleeding complication.

In conclusion, antiplatelet therapy is fundamental in LVAD patients. The PAP platelet analyzer offers a cheap and reliable alternative to the more expensive thromboelastography method for adequately surveying the efficacy of aspirin and clopidogrel treatment.

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