Resistance to aspirin after external ventricular assist device implantation

Rémi Houël, MD,[a] Elisabeth Mazoyer, MD,[b] Matthias Kirsch, MD, PhD,[a] Bernadette Boval, MD,[b] Ludovic Drouet, MD, PhD,[b] and Daniel Y. Loisance, MD,[a] Créteil and Paris, France

Anticoagulation in patients implanted with ventricular assist devices is widely performed with aspirin, heparin, and anti–vitamin K therapy. Nonetheless, a variable antiplatelet effect of aspirin is well-known in healthy subjects. Moreover, the efficacy of aspirin may be reduced in the days after coronary artery bypass grafting surgery.[1] Its efficacy has not been reported during the chronic phase of mechanical support with an external ventricular assist device. We report a resistance to aspirin that did respond to an increased daily oral intake and that could be observed as long as 6 weeks after device implantation.

Methods

Patient selection. Fifteen patients were studied prospectively during 6 weeks after implantation of an external ventricular assist device (Thoratec Laboratories Corporation, Pleasanton, Calif). Two patients were female. Median age was 44.3 years, range was 16.6 to 58.6 years. Indications for emergent device implantation were persistent primary cardiogenic shock complicating acute myocardial infarction in 7 patients, acute myocarditis in 2 patients, and end-stage dilated cardiomyopathy in 6 patients. Seven patients were supported by an intra-aortic balloon pump before device implantation. Median duration of support was 72 days (range 28-360 days). Mechanical support was biventricular in 10 patients. Three patients died while on support of sepsis in 1 case, intracranial hemorrhage in 1 case, and device dysfunction in 1 case.

Surgical technique and anticoagulation protocol. Implantation was performed by a standard technique. All patients were implanted under cardiopulmonary bypass and moderate hypothermia. Median cardiopulmonary bypass duration was 162 minutes (range 96-339 minutes). After surgery, anticoagulation was started within 8 to 12 hours with intravenous heparin to achieve an anti-Xa activity between 0.3 and 0.4 IU/L. Aspirin was started after 24 hours with a starting dose of 250 mg daily (except for 1 patient who had a starting dose of 400 mg daily). Aspirin doses were then adjusted according to in vitro platelet function tests and depending on clinical and biologic status. Anti–vitamin K therapy was started after removal of chest drains and extubation to maintain the international normalized ratio between 3 and 4. Fresh blood drawn for platelet function studies was collected once every week after implantation. A resistance to aspirin therapy was considered to have occurred when in vitro testing showed a persistent platelet aggregation in the presence of arachidonic acid despite daily administration of aspirin.

From the Department of Thoracic and Cardiovascular Surgery, Hôpital Henri Mondor, Créteil, France,[a] and the Department of Hematology, Hôpital Lariboisière, Paris, France.[b]

Received for publication Feb 28, 2003; accepted for publication April 22, 2003.

Address for reprints: Rémi Houël, MD, Department of Thoracic and Cardiovascular Surgery, Hôpital Henri Mondor, 51 Avenue du Maréchal de Lattre de Tassigny, Créteil, France.

J Thorac Cardiovasc Surg 2003;126:1636-7

Copyright © 2003 by The American Association for Thoracic Surgery

0022-5223/2003 $30.00 + 0

doi:10.1016/S0022-5223(03)01194-2

Results

Figure 1 shows the numbers of patients during follow up after device implantation with persistent in vitro platelet aggregation in the presence of arachidonic acid and despite daily aspirin administration. This was observed in 6 of 15 patients.

An increase in daily aspirin dose up to 500 mg was associated with disappearance of platelet aggregation in the presence of arachidonic acid in vitro. Three patients had a recurrence of this phenomenon, despite this increased daily aspirin intake in 2 cases. In 3 patients this observation was done from the first week of treatment after implantation.

Figure 2 shows the mean dose of aspirin administered per day and its temporal trends after device implantation. Two patients had an interruption in treatment because of severe bleeding complications in the third and fourth postoperative weeks (hemothorax and intracranial bleeding).

Discussion

Aspirin resistance has been reported in patients after coronary artery bypass grafting and was associated with an increased recruitment of new platelets in the days after surgery.[1] After ventricular assist device implantation, we did observe a persistent in vitro platelet aggregation as late as 6 weeks after implantation and despite high doses of aspirin (>150 mg/d). In healthy subjects a dose of 100 mg/d is associated with the absence of in vitro platelet aggregation.[2] When flow conditions are changed, however, as in patients with atherosclerosis, a higher dose of aspirin is necessary to preserved the absence of thromboxane A_2 production by platelets. This mechanism of resistance to aspirin has been associated with a prothrombotic effect of erythrocytes on platelet reactivity.[3] Also, experimentally increased shear stress has been seen to overcome the effect of intravenous aspirin.[4] Finally, increased platelet activation is also produced by thrombin generation and cytokine

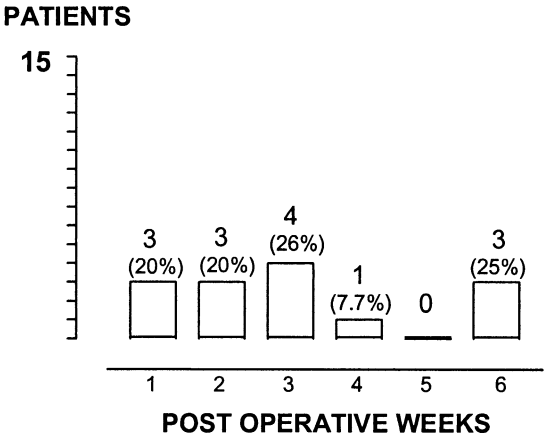

Figure 1. Numbers and percentages of patients with persistent in vitro platelet aggregation in presence of arachidonic acid during weekly follow-up after implantation.

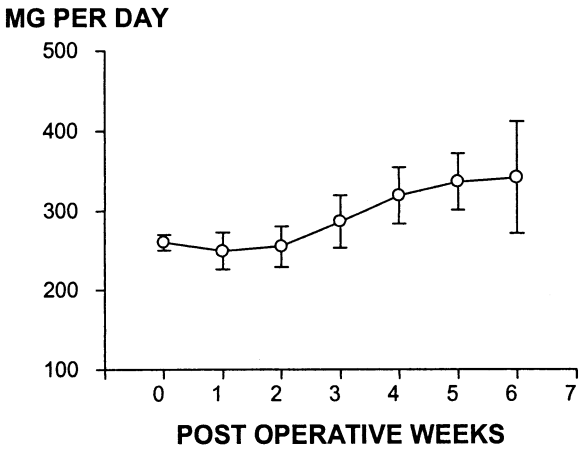

Figure 2. Temporal trend of daily dose of aspirin administered per patient after device implantation. *Data points* represent mean; *error bars* represent SEM.

production (interleukin 6 and 8) independently of thromboxane production.[5] In patients with external ventricular assist device, all these conditions (increased shear stress, prolonged inflammatory reaction, prolonged cytokine production, thrombin generation) combine to induce a persistent platelet activation and resistance to the antiplatelet effect of aspirin. Although our observation was expected, we observed as many as 30% of patients with a persistent platelet response to arachidonic acid. However, a higher dose of aspirin restored the efficacy of aspirin regarding in vitro platelet aggregation.

Aspirin resistance in the prolonged postoperative course of patients implanted with external ventricular assist device is frequent and necessitates close monitoring. However, it will respond to increased oral intake of aspirin up to 500 mg/d.

References

1. Zimmermann N, Kienzle P, Weber AA, Winter J, Gams E, Schrör K, Hohfeld T. Aspirin resistance after coronary artery bypass grafting. *J Thorac Cardiovasc Surg*. 2001;121:982-4.
2. Pappas JM, Westengard JC, Bulls JS. population variability in the effect of aspirin on platelet function. Implications for clinical trials and therapy. *Arch Pathol Lab Med*. 1993;118:801-4.
3. Valles J, Santos MT, Aznar J, Osa A, Lago A, Cosin J, et al. Erythrocyte promotion of platelet reactivity decreases the effectiveness of aspirin as an antithrombotic therapeutic modality: the effect of low-dose aspirin is less than optimal in patients with vascular disease due to prothrombotic effects of erythrocytes on platelet reactivity. *Circulation*. 1998;97: 350-5.
4. Maalej N, Folts JD. Increased shear stress overcomes the antithrombotic platelet inhibitory effect of aspirin in stenosed dog coronary arteries. *Circulation*. 1996;93:1201-5.
5. Lumadue JA, Lanzkron SM, Kennedy SD, Kuhl DT, Kikler TS. Cytokine induction of platelet activation. *Am J Clin Pathol*. 1996;106:795-8.