Platelet inhibition by aspirin after aortic valve replacement

Norbert Zimmermann, MD,^a Timothée Roussiekan, MD,^b Joachim Winter, MD,^c Muhamed Kurt, MD,^c Emmeran Gams, MD,^c Folker Wenzel, MD,^d and Thomas Hohlfeld, MD,^b Düsseldorf and Bonn, Germany

In spite of antithrombotic therapy, the thromboembolic risk after aortic valve replacement appears to be high for the first 3 months after surgical intervention (3.6%), especially during the first 10 postoperative days.¹

We have previously shown that 100 mg of aspirin, a dose that is effective for early antithrombotic treatment after coronary artery bypass grafting (CABG), did not sufficiently inhibit platelet function in patients subjected to CABG, indicating a remarkable resistance against the antiplatelet effect of aspirin in the early postoperative period.²

The present work determined platelet function early after aortic valve replacement and examined whether the antiplatelet effect of aspirin, based on the inhibition of platelet thromboxane production, is impaired in the early postoperative period.

Methods

Subjects and drug administration. This study was conducted in agreement with the Declaration of Helsinki and was approved by the institutional ethics committee. Fifteen consecutive patients were included who underwent an elective aortic valve replacement with bileaflet mechanical prostheses (St Jude Medical). Informed consent was obtained from each participant. Drugs affecting hemostasis (including aspirin) had been terminated at least 7 days before surgical intervention. Antithrombotic therapy was initiated the first day after surgical intervention with heparin ($3 \times 10,000$ IU administered subcutaneously). At day 3 after surgical intervention, anticoagulation with a vitamin K antagonist (phenprocoumon) was initiated, and heparin was terminated when a target international normalized ratio (INR) of 2.5 had been reached.

Measurement of platelet function. One day before and at days 1, 5, and 10 after surgical intervention arachidonic acid (1 mmol/L)-induced aggregation and thromboxane formation were determined in venous blood samples.² Because thromboxane formation by platelet cyclooxygenase is the pharmacologic target of aspirin, the sensitivity of platelets to aspirin in vitro was determined by means of addition of aspirin (100 μ mol/L).

Statistics. Data are presented as mean values $\pm$ the standard error of the mean. Statistical analyses were performed with 2-way analysis of variance for repeated measurements with the Tukey post-hoc test.

Results

Platelet counts decreased from $252 \pm 20/\text{nL}$ (before surgical intervention) to $143 \pm 14/\text{nL}$ (day 1 after CABG, $P < .05$) and increased to $239 \pm 22/\text{nL}$ at day 5 and $325 \pm 31/\text{nL}$ at day 10.

Before surgical intervention, arachidonic acid (1 mmol/L) caused a considerable platelet release of thromboxane (Figure 1). This was significantly reduced at day 1 after valve replacement, as shown by a decay of thromboxane to $39\% \pm 12\%$ of the control value ($P < .05$). Thereafter, platelet function recovered ($117\% \pm 25\%$ at day 5), and thromboxane formation was more than doubled at day 10 ($249\% \pm 55\%$, $P < .05$) compared with control values seen before surgical intervention.

From the Federal Institute for Drugs and Medical Devices, Bonn, Germany,^a and the Departments of Pharmacology and Clinical Pharmacology,^b Thoracic and Cardiovascular Surgery,^c and Hemostasis and Transfusion Medicine,^d Heinrich Heine—University Düsseldorf, Germany.

Received for publication Jan 3, 2006; accepted for publication Jan 24, 2006.

Address for reprints: Norbert Zimmermann, MD, Federal Institute for Drugs and Medical Devices, Kurt Georg Kiesinger Allee, D-53175 Bonn, Germany (E-mail: nzimmermann@bfarm.de).

J Thorac Cardiovasc Surg 2006;131:1392-3
0022-5223/\$32.00

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doi:10.1016/j.jtcvs.2006.01.029

* $p < 0.05$ vs. ASS 0 μM ; # $p < 0.05$ vs. control value (before surgery)

Figure 1. Arachidonic acid (1 mmol/l)-induced platelet thromboxane formation in platelet-rich plasma of patients ($n = 15$) before (control) and at the indicated times after aortic valve replacement. The measurements have been performed without (open bars) or with (filled bars) addition of aspirin in vitro (100 $\mu\text{mol/L}$). *Significant differences ($P < .05$) versus corresponding measurement without aspirin; #significant differences ($P < .05$) versus control values before surgical intervention. ASS, aspirin.

This activation of thromboxane formation was also reflected in the platelet aggregation (Figure 2). At days 1, 5, and 10 after surgical intervention, platelet aggregation was $38\% \pm 11\%$, $95\% \pm 15\%$, and $145\% \pm 14\%$, respectively, of the control value before surgical intervention.

Although the antiplatelet effect of aspirin was attenuated compared with the control value before surgical intervention, aspirin in vitro (100 $\mu\text{mol/L}$) inhibited platelet function significantly at days 5 and 10.

Discussion

The major finding of this study is that platelet thromboxane formation and aggregation are increased early after aortic valve replacement (with mechanical bileaflet prostheses), indicating remarkable platelet activation. This is in accordance with the increased risk of thromboembolism during the first weeks after valve replacement.¹ Our study is also, to the best of our knowledge, the first to show a significantly increased thromboxane biosynthesis.

The observed platelet hyperactivity after valve replacement might have resulted from an increased regeneration of young hyperactive platelets because of transient depletion caused by extracorporeal circulation. Shear stress-induced activation by the valve prosthesis might also have contributed. Indeed, the shear stress created by prosthetic heart valves has earlier been shown to induce platelet aggregation.³

American College of Chest Physicians Guidelines recommend vitamin K antagonists and heparin for patients with mechanical

* $p < 0.05$ vs. ASS 0 μM ; # $p < 0.05$ vs. control value (before surgery)

Figure 2. Arachidonic acid (1 mmol/l)-induced platelet aggregation in platelet-rich plasma of patients ($n = 15$) before (control) and at the indicated times after aortic valve replacement. The measurements have been performed without (open bars) or with (filled bars) addition of aspirin in vitro (100 $\mu\text{mol/L}$). *Significant differences ($P < .05$) versus corresponding measurement without aspirin; #significant differences ($P < .05$) versus control values before surgical intervention. ASS, aspirin.

valves in the aortic position until the INR is stable and within the therapeutic range for 2 consecutive days. Additional therapy with aspirin is presently recommended only for patients who have systemic embolism despite a therapeutic INR and in patients with additional risk factors.⁴ Nevertheless, aspirin appeared to prevent thromboembolism caused by mechanical bileaflet prostheses (eg, St Jude Medical) in the aortic position almost as efficiently as full anticoagulation, with a lower rate of bleeding.⁵

In conclusion, the increased thromboxane formation after valve replacement makes aspirin conceivable as an adjunct to vitamin K antagonists early after surgical intervention, especially in patients at high risk for thromboembolic events.

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