Detection and duration of aspirin resistance after coronary artery bypass grafting

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Aspirin resistance is associated with a significant increase in major adverse cardiovascular events.1,2 We have previously reported an insufficient antiplatelet effect of aspirin in most patients after coronary artery bypass grafting (CABG).3 Nevertheless, the duration of aspirin resistance after CABG remains unknown, and the suitability of available tools to discriminate those with reduced response to aspirin is controversial. This work determined the antiplatelet effect of aspirin at the time of CABG and 6 months later and examined the reliability of different methods for the diagnosis of aspirin resistance.

Materials and Methods

Subjects and Drug Administration. This study was conducted in agreement with the Declaration of Helsinki and was approved by the institutional ethics committee. Twenty-five consecutive patients undergoing elective CABG for stable three- vessel disease were included. Informed consent was obtained from each participant. Drugs affecting hemostasis had been discontinued at least 10 days before surgery. Starting on day 1 after CABG, 100 mg aspirin (Aspirin 100; Bayer AG, Leverkusen, Germany) was administered every morning.

Measurement of Platelet Function. The following parameters were determined: platelet counts (automated counting), arachidonic acid– (1 mmol/L) or collagen (1 μg/mL)–induced aggregation (turbidimetry), thromboxane formation (radioimmunoassay), and membrane closure times (platelet function analyzer PFA-100) before and on days 1, 5, and 10 after surgery, as well as after a follow-up period of 6 months. Because thromboxane formation is the pharmacologic target of aspirin, platelet function was investigated in vitro in the absence and presence of 30 μmol/L aspirin, a concentration comparable to or exceeding plasma levels after oral aspirin treatment.4 Aspirin resistance during oral antiplatelet treatment was defined as less than 90% inhibition of thromboxane synthesis (vs before aspirin) or PFA-100 closure times less than 171 seconds.

Statistical Analysis. Data are shown as mean ± SEM. Statistical analyses were performed by t test or analysis of variance, as appropriate.

Results

Platelet counts decreased after extracorporeal circulation, from 251 ± 30 cells/nL before CABG to 167 ± 15 cells/nL at day 1 after CABG, and subsequently increased to 256 ± 13 cells/nL (day 5) and 414 ± 31 cells/nL (day 10). At 6-month follow-up, platelet counts were comparable to values before surgery (268 ± 45 cells/nL).

Before CABG, arachidonic acid effectively induced platelet aggregation in vitro and evoked a marked platelet thromboxane release (Figure 1). Addition of aspirin in vitro significantly inhibited platelet function. At day 1 after surgery, platelet function was blunted, probably as a result of extracorporeal circulation. On days 5 and 10 after CABG, platelet aggregation was not significantly different from values before surgery (despite oral aspirin therapy), and 30 μmol/L aspirin failed to inhibit platelet function in vitro. Platelet function was nearly completely inhibited, however, 6 months after CABG. The results obtained after stimulation with collagen were similar to those with arachidonic acid (not shown).

The PFA-100 method did not detect the blunted platelet function at day 1 after CABG. Measurements obtained by this technique remained unchanged at days 5 and 10 after CABG. Closure times were nearly doubled (vs before surgery) at follow-up (Figure 2).

The incidences of aspirin resistance on day 5, on day 10, and 6 months after surgery were 93%, 86%, and 0%, respectively, in the thromboxane assay and 100%, 75%, and 33% in the PFA-100 test. Moreover, thromboxane values were not significantly different between those with and without response according to PFA-100 (18 ± 5 ng/mL vs 34 ± 14 ng/mL).

Discussion

These data show aspirin resistance early after CABG but a sufficient antiplatelet effect 6 months thereafter. This pattern may explain why the elevated risk of graft thrombosis declines within the first months after surgery.2 Another important finding is that the thromboxane assay and PFA-100 test showed comparable results early after CABG, whereas these methods differently classified the responder status of a third of the patients at follow-up. In accordance with thromboxane, arachidonic acid- and collagen-induced aggregations showed near-complete platelet inhibition at follow-up.

The observed differences between thromboxane and turbidimetry on one hand and PFA-100 on the other hand may be explained by variables unaffected by aspirin, such as von Willebrand factor.
which may outweigh platelet inhibition by aspirin in the PFA-100 method. Our results agree with the unfavorable correlation between PFA-100 and optical aggregation described in other study populations.5

In conclusion, PFA-100 is a convenient bedside test. This advantage, however, seems outweighed by its reduced accuracy in comparison with turbidimetry and the criterion standard of thromboxane.

References


