Platelet inhibition by aspirin is diminished in patients during carotid surgery: a form of transient aspirin resistance?

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Summary
The majority of patients who suffer peri-operative thromboembolic complication while undergoing vascular procedures do so despite taking aspirin. This study examined the antiplatelet effect of aspirin during surgery in patients undergoing carotid endarterectomy (CEA). Fifty patients undergoing CEA were standardised to 150 mg aspirin daily for ≥2 weeks. Platelet aggregation in response to arachidonic acid (AA) was measured in platelet rich plasma prepared from blood taken prior to, during, and at the end of surgery. Spontaneous platelet aggregation was also studied, as was the role of physiological agonists (ADP, collagen, thrombin, and epinephrine) in mediating the in vivo and in vitro responses to AA. Eighteen patients undergoing leg angioplasty, also on 150 mg aspirin, without general anaesthesia, served as a control group. In the CEA patients aggregation induced by AA (5 mM) increased significantly from 7.6 ± 5.5% pre-surgery to 50.8 ± 29.5% at the end of surgery (p <0.0001). Aggregation to AA was even greater in samples taken mid-surgery from a sub-set of patients (73.8 ± 7.2%; p = 0.0001), but fell to 45.9 ± 7.4% by the end of surgery. The increased aggregation in response to AA was not due to intra-operative release of physiological platelet agonists since addition of agents that block/neutralise the effects of ADP (apyrase; 4 µg/ml), thrombin (hirudin; 10 units/ml), or epinephrine (yohimbine; 10 µM/l) to the samples taken at the end of surgery did not block the increased aggregation. The patients undergoing angioplasty also showed a significant rise in the response to AA (5 mM), from 5.6 ± 5.5% pre-angioplasty to 32.4 ± 24.9% at the end of the procedure (p <0.0001), which fell significantly to 11.0 ± 8.1% 4 hours later. The antiplatelet activity of aspirin, mediated by blockade of platelet arachidonic acid metabolism, diminished significantly during surgery, but was partially restored by the end of the procedure without additional aspirin treatment. This rapidly inducible and transient effect may explain why some patients undergoing cardiovascular surgery remain at risk of peri-operative stroke and myocardial infarction.

Keywords
Aspirin, platelets, surgery, carotid artery, aspirin resistance

Introduction
Long-term aspirin therapy has a proven role in reducing the relative risk of stroke, myocardial infarction and peripheral vascular disease (1). Its main antiplatelet effect is mediated by irreversible inactivation of cyclo-oxygenase-1 (COX-1) activity, preventing the conversion of arachidonic acid (AA) to the prostaglandin endoperoxides PGG₂/PGH₂; intermediate metabolites in the formation of Thromboxane-A₂, (TxA₂), a potentiator of platelet aggregation (2). Aspirin is effective at preventing platelet adhesion and aggregation at the site of endothelial disruption in patients undergoing cardiovascular intervention, leading to a reduction in the risk of arterial thrombo-occlusive events (3). Similarly, the use of aspirin prior to carotid surgery confers beneficial effects in reducing cardiovascular related post-operative morbidity and mortality (4-6). However, despite aspirin’s effi-
cacy, perioperative thromboembolism is still a significant cause of stroke and myocardial infarction following cardiovascular interventions (7).

The reason why aspirin fails to prevent thromboembolic events in some patients remains unclear. Studies in healthy and patient populations have shown variations in the response to aspirin, with a proportion of individuals being non-responsive or ‘aspirin resistant’ (8-11). Other individuals who have initially been sensitive to the effects of aspirin have gone on to develop progressively increasing dosage requirements or even total ‘aspirin resistance’ (12). Further variation has been seen in patients following coronary artery bypass grafting (13, 14) resulting in a form of induced ‘aspirin resistance’ appearing within a few days of surgery. No comment is made in these studies on the efficacy of aspirin during surgery itself. The aim of this study was to determine the effectiveness of aspirin at preventing arachidonic acid mediated platelet aggregation in patients undergoing a standardised surgical procedure (carotid endarterectomy; CEA).

Materials and methods

Subjects

Approval was gained from the Leicestershire Health Authority Research Ethics Committee for an open prospective cohort study on all patients listed for CEA who were on long-term aspirin therapy. Patients undergoing leg angioplasty served as a control group. Patients were excluded if they had: not been taking aspirin (indicated by history or platelet response to AA); reported aspirin intolerance or hypersensitivity; a history of bleeding abnormalities; a platelet count <100 × 10^6/dl; been treated with alternative antithrombotic or antiplatelet therapy, or were taking non-steroidal anti-inflammatory drugs in the two weeks prior to admission. Compliance was checked by questioning the patient on admission to the ward and subsequently checking platelet aggregation in response to arachidonic acid.

Surgical procedure

A standardised carotid endarterectomy was performed using normotensive, normocarbic general anaesthesia, as described elsewhere (15). Intra-operatively, unfractionated heparin (5000 u) was administered via the arterial line prior to clamping the carotid artery and insertion of a Pruitt Inhara shunt. The time of the operation varied between 1 and 2.5 hours.

The control group, undergoing leg angioplasty were standardised to 150 mg aspirin. The procedure was carried out without general anaesthetic and a bolus of unfractionated heparin (2500-3500 u) was administered iv during the procedure.

Blood collection

Immediately before surgery, blood samples were taken from the CEA patients via the antecubital fossa via a 21-gauge butterfly needle into vacutainer tubes (Becton Dickinson, Oxford, UK) using a standardised phlebotomy technique employed to minimise artefactual platelet activation. Further samples were taken at the end of surgery following restoration of blood flow through the endarterectomised artery via the arterial line. In a subset of patients, intra-operative samples were taken via the arterial line, after clamping the carotid artery. This was selected as a practically accessible mid-operation time point, after general anaesthesia and heparinisation. Although the differences in the route of blood collection can have small effects on the baseline level of platelet activation there was no significant effect on platelet responsiveness to agonist stimulation in samples collected via these two routes (data not shown).

In the angioplasty group three samples of venous blood were collected from the ante cubital fossa; prior to, immediately following, and 4 hours after the procedure.

For all samples the first 3 ml of blood taken into EDTA (5.4 mg) and used to obtain a full blood count (A^TM Diff® Analyser, Coulter Electronics Ltd, Luton, UK). Subsequent samples were taken into tri-sodium citrate (3.2% w/v) for analysis of platelet function.

Platelet studies

Born-type platelet aggregometry was carried out within one hour of sampling. In all experiments, aggregation was measured in platelet rich plasma (PRP) in a PAP4C aggregometer (Bio Data Corp. Horsham, USA) and in all cases is reported as the percentage maximum aggregation at 10 minutes compared to autologous platelet poor plasma. PRP was prepared and stimulated with arachidonic acid 2.5, and 5 mmol.L^-1 (Sigma, Poole, Dorset, UK). In the CEA patients PRP was also stimulated with ADP 0.05, 0.1, 0.2 and 0.4 µM (Sigma), collagen 0.5 and 1.0 µg.ml^-1 (Horm collagen; Nycomed, München, Germany) and thrombin receptor agonist peptide (TRAP; SFLLRN) 6 µmol.L^-1 (PNAC Laboratory, University of Leicester). Spontaneous platelet aggregation was measured in a sub-set (n = 28) of the CEA patients and in all of the angioplasty group.

Additional studies were undertaken in sub-sets of the CEA patients to determine whether the increased platelet aggregation activation to AA was the result of increased levels of the physiological platelet agonists ADP, thrombin or epinephrine in vivo. For these investigations the ADP-degrading enzyme apyrase (4 µg.ml^-1), the thrombin inhibitor hirudin (4 µM), and the α2-adrenergic receptor antagonist yohimbine (10 µM) (all from Sigma) were added to PRP samples taken at the end of surgery, which were then stimulated with AA. All inhibitors were used at concentrations that had been demonstrated to completely block the maximum effects of exogenous agonist. The effects of two potential
intra-operative mediators of platelet activation; epinephrine 200 ng.ml⁻¹ (Phoenix Pharma Ltd, Gloucester, UK) and heparin 1 u.ml⁻¹ (CP Pharmaceuticals Ltd, Wrexham, UK), alone or in combination, were also assessed by their addition to PRP from pre-operative blood samples then stimulated with AA.

**Statistical analysis**
All paired data were analysed using paired Student’s t-test. When more than one concentration of platelet agonist was used, the two-way ANOVA test was employed for statistical analysis. Correlation of data was performed using linear regression. A P value of ≤0.05 was considered as statistically significant.

**Results**
During a 12-month period, fifty patients undergoing CEA fulfilled the inclusion criteria. Patients were aged between 50 to 80 years, (mean 68 years). The male to female ratio was 35:15. Patients’ demographics are shown in Table 1. The control group comprised 18 consecutive patients undergoing elective leg angioplasty. They were similar in age (46 to 86; mean 67 years) and male to female ratio (13:5) to the CEA group (p >0.5 for both).

**Ex-vivo platelet aggregation in the CEA patients**

**Response to arachidonic acid**
Pre-operative aggregation in response to arachidonic acid (5 mM) was low (7.6 ± 5.5%) in all subjects, and none had an aggregation response >25%. Despite this effective blockade of the cyclo-oxygenase pathway in all patients prior to surgery the response of platelets to arachidonic acid (5 mM) increased significantly at the end of surgery to 50.8 ± 29.5% (range 5-94%; p <0.0001); an increase of 570% (Fig. 1). An increased response to AA following surgery was seen in every patient. A similar pattern was seen with 2.5 mM arachidonic acid, rising from 3.0 ± 2.2% prior to surgery to 10.9 ± 8.6% (p <0.0001) at the end of the procedure.

**Effects of physiological agonists**
Platelet aggregation in response to ADP, collagen and TRAP also increased after surgery (p ≤0.01) but to a much smaller extent (<40%) compared with the increase in the response to AA. Figure 2 shows data for a single concentration of each agonist but similar levels of increase were seen with all concentrations used. These data suggest that it is unlikely that the release, or generation, of these physiological agonists in vivo could account for the large increase in platelet aggregation seen in response to AA during surgery. To substantiate this, the in vitro addition of agents that prevent the response to ADP (apyrase), thrombin (hirudin) and epinephrine (yohimbine), either alone or in combination, to samples taken at the end of surgery, did not significantly reduce the response of arachidonic acid (5 mM) increased significantly at the end of surgery to 50.8 ± 29.5% (range 5-94%; p <0.0001); an increase of 570% (Fig. 1). An increased response to AA following surgery was seen in every patient. A similar pattern was seen with 2.5 mM arachidonic acid, rising from 3.0 ± 2.2% prior to surgery to 10.9 ± 8.6% (p <0.0001) at the end of the procedure.

**Spontaneous platelet activation**
Spontaneous platelet aggregation, studied in a subset of 28 CEA patients, increased from a pre-operative level of 0.8 ± 0.9% to

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**Table 1: Demographics of CEA patients.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (mean ± SD)</td>
<td>68 ± 9</td>
</tr>
<tr>
<td>Ratio Male: Female</td>
<td>35:15</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>8 (16%)</td>
</tr>
<tr>
<td>Amaurosis fugax</td>
<td>11 (22%)</td>
</tr>
<tr>
<td>Transient ischaemic attack</td>
<td>23 (46%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>8 (16%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>35 (70%)</td>
</tr>
<tr>
<td>Ex-Smokers</td>
<td>24 (48%)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>16 (32%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>14 (28%)</td>
</tr>
<tr>
<td>Angina</td>
<td>10 (20%)</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>12 (24%)</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>31 (62%)</td>
</tr>
</tbody>
</table>
Payne, et al.: Loss of aspirin effect during surgery

4.2 ± 4.5% at the end of surgery (p <0.001) (Fig. 3). This small increase was seen in all patients in the sub-set studied. A correlation was noted between this and AA-induced aggregation (r = 0.37, p = 0.04), suggesting that those patients whose platelets were most activated during surgery were the same patients in whom the loss of aspirin effectiveness during surgery was greatest.

Effects of adrenergic hormones and heparin
To test whether the increased response to AA could be due to adrenergic hormones released during surgery, epinephrine (200 ng.ml⁻¹) was added in vitro to pre-operative samples. This gave only a small (12%) and non-significant increase in AA-induced aggregation, reinforcing the view that the increased platelet response to AA was not the result of release of epinephrine in vivo during surgery. Similarly, addition of unfractionated heparin in vitro, which is known to increase platelet response to agonists such as ADP (18-20), gave only a small (14.9%) and non-significant increase in AA response. Even with a combination of epinephrine and heparin the increase was only 23.5% (p >0.05 for all) (Fig. 4).

Platelet count
There was no increase in the number of platelets during surgery. In fact there was a small drop in platelet number from 251.7 ± 69.6 x 10⁶ /µl before surgery to 219.4 ± 60.6 x 10⁶ /µl at the end of the operation, which was significant (p <0.0001). There was no correlation between the drop in platelet count and the increased aggregation in response to AA.

Intra-operative response
In 10 patients, blood samples were taken intra-operatively, following anaesthesia and heparin administration. The rise in platelet aggregation in response to AA was even greater in these samples, from 7.6 ± 1.6% pre-operation to 73.8 ± 7.2% intra-operation (p = 0.0001), but then decreased significantly to 45.9 ± 7.4% at the end of the operation (p = 0.0112), but to a level that remained significantly higher than the pre-operative sample (p = 0.0002) (Fig. 5). Thus the platelet response to AA peaks, and inhibition by aspirin of platelet AA metabolism is least, at the mid-point of surgery, diminishing by the end of the

Figure 2: Platelet aggregation in response to (a) ADP 1 µM, (b) collagen 0.5 µg.ml⁻¹ and (c) TRAP 6 µM prior to and at the end of surgery. Bar represents the mean [n = 50].

Figure 3: Spontaneous platelet aggregation prior to and at the end of carotid surgery. Bar represents the mean [n = 28].
operation, suggesting a rapidly inducible but transient form of ‘aspirin resistance’. The aggregation induced by AA in these intra-operative samples could be completely blocked by the GPIIb-IIIa antagonist abciximab (data not shown).

Ex vivo platelet aggregation in control (angioplasty) group
In the patients undergoing leg angioplasty under local, rather than general anaesthetic, platelet aggregation in response to AA (5 mM) rose significantly from 5.6 ± 4.5% prior to the procedure to 32.4 ± 24.9% at the end of the procedure (p < 0.0001). Four hours afterwards the response had fallen to 11.0 ± 8.1% which was significantly lower than the post-procedural level (p = 0.001) but still higher than the level prior to the procedure (p = 0.02).

Discussion
As aspirin therapy inhibits platelet COX-1 irreversibly (2), it is reasonably assumed that long-term aspirin therapy, when combined with intra-operative heparin, produces optimal anti-thrombotic protection throughout surgery and during the immediate post-operative period. This study clearly indicates that despite demonstrably effective aspirin treatment before surgery the inhibitory effect of aspirin on platelets is diminished or bypassed significantly during carotid endarterectomy.

‘Aspirin resistance’ has been reported to occur in a sub-set of patients on long-term aspirin therapy, either from the start of treatment (9-12) or developing over time (12). There are also reports of a form of ‘aspirin resistance’ occurring in the hours or days following surgery (14). This present study has however, revealed a novel form of transient aspirin resistance that is not

Table 2: Effects of inhibitors on AA-induced platelet aggregation in samples taken at the end of the operation. Platelet aggregation (percentage of max) in response to AA (5 mM). Mean ± SD.

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Without inhibitor</th>
<th>With inhibitor</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apyrase (n=18)</td>
<td>56.2 ± 32.4</td>
<td>61.2 ± 24.6</td>
<td>0.49</td>
</tr>
<tr>
<td>Hirudin (n=22)</td>
<td>55.2 ± 32.2</td>
<td>54.1 ± 26.3</td>
<td>0.87</td>
</tr>
<tr>
<td>Apyrase + hirudin (n=12)</td>
<td>61.8 ± 29.8</td>
<td>63.6 ± 21.3</td>
<td>0.82</td>
</tr>
<tr>
<td>Yohimbine (n=15)</td>
<td>41.5 ± 28.6</td>
<td>43.6 ± 30.0</td>
<td>0.84</td>
</tr>
</tbody>
</table>

Figure 4: Addition of epinephrine (200 ng.ml⁻¹) or heparin (1 u.ml⁻¹) alone, or in combination, to pre-operative blood samples. Aggregation in response to AA (5 mM) before and after surgery is shown for comparative purposes [n = 5].

Figure 5: Platelet aggregation in response to arachidonic acid (5 mM), pre-operation, intra-operation, and at the end of the operation [n = 10].
only rapidly induced by the mid-point of surgery, but also appears to diminish significantly at the completion of the operation, without any further aspirin intake.

Several approaches have been advocated to demonstrate the effects of aspirin ex vivo or to detect ‘aspirin resistance’ including measurement of plasma or urinary levels of thromboxane metabolites (10, 16-18), generation of thromboxane by the platelets in vitro (19) increased aggregation in response to AA, ADP or collagen (8, 11) and measurement of bleeding time, either in vivo (13) or in vitro, using the PFA100 (11). In this study effective inhibition by aspirin prior to surgery was defined as aggregation of <25% of maximum, over a 10-minute period, in response to AA (5 mM); levels chosen to give >90% aggregation in platelets from normal subjects, not taking aspirin. This is more stringent than the criteria recently proposed by Gum et al. (11) who defined ‘aspirin resistance’ as <20% aggregation with a 10 fold lower concentration of AA (0.5 mM).

At the start of surgery, all patients had <25% aggregation to 5 mM AA. By the end of the operation every patient showed an increase in the response to AA that ranged between 150% and 3900% of the pre-operative response. The majority (75%) of patients had a post-operative response of >25% aggregation. The patients, whose response did not rise above 25% following the operation, all had a pre-operative response that was also in the lowest quartile of the range, but all showed a rise in the response to AA during the operation. The post-operative samples were taken between 1 and 2.5 hours after the start of the operation depending on the length of the procedure and this may, at least in part, account for the variation in the extent of the increase in the response to AA.

For the 10 patients studied during the operation, samples were all collected within 30 minutes of the start of the procedure, after anaesthesia and heparin administration. In these samples the aggregation in response to AA rose above 25% in all patients. In addition, all patients showed a fall in the AA response at the end of the operation suggesting a reversal of the apparent bypass of the effects of aspirin.

A number of intra-operative factors could account for this transient form of ‘aspirin resistance’. Firstly, platelet activation is well known to increase during surgery, including CEA (19), largely due to the release of known platelet agonists such as thrombin (20). Spontaneous aggregation, an ex vivo marker of platelet activation, increased by a small but significant amount at the end of surgery, but not to anywhere near the magnitude of the increase seen in the response to AA. Previous studies have also reported increased responsiveness to other physiological platelet agonists during surgery (19, 21). Whilst an increase in response to ADP, collagen and TRAP in vitro was seen in the present study the average increase was less than 40%, as compared to the large (>500%) increase in the response to AA. Added to this, the concomitant addition of apyrase or hirudin to the blood, to neutralise ADP or inhibit thrombin, either alone or in combination, had no effect on the increased platelet aggregation in response to AA seen at the end of surgery. It is therefore unlikely that release of ADP or generation of thrombin in vivo, either singly or together, would account for the transient increase in the ex vivo platelet response to AA.

Levels of the adrenergic stress hormones epinephrine and norepinephrine can be elevated during surgery and can increase the platelet response to other agonists in vivo and in vitro (22, 23). This effect has been implicated in the sudden reversal of the effects of aspirin (24). However, the in vitro addition of the alpha-2 receptor antagonist yohimbine did not reduce the increase in AA-induced aggregation in the samples taken at the end of surgery. Furthermore, the addition of a high physiological level of epinephrine in vitro did not potentiate AA-induced aggregation in the pre-operative PRP samples. To exclude the possibility that the effect was caused by the general anaesthetic, a control group, taking aspirin, who were undergoing leg angioplasty under local anaesthetic, was studied. These patients were found to exhibit a similar, albeit slightly smaller, rise in AA-induced and spontaneous aggregation. They underwent a less invasive procedure but did receive unfractionated heparin (2500-3500 u) prior to blood sampling.

Unfractionated heparin is known to activate platelets and potentiate the effects of physiological agonists in vitro and in vivo (25, 26). In this study, the addition of heparin in vitro to pre-operative samples at an equivalent in vivo dose, produced a small but non-significant increase in AA-induced platelet aggregation, which would not account for the large increase in response to AA seen intra-operatively.

Heparin may, however, be having an effect in vivo through a number of potential routes. Unfractionated heparin is known to release hepatic lipase from liver sinusoids and lipoprotein lipase from endothelial cells (27), resulting in release of arachidonic acid from plasma lipoproteins (28) thus increasing the available amount of arachidonic acid, which might overcome the inhibitory effects of 150 mg aspirin and result in the transient apparent “aspirin resistance”. However, preliminary experiments indicate that increased levels of AA in vivo would not account for the observed increases in aggregation in response to AA in vitro since it could not be overcome by the addition of further aspirin to the PRP (data not shown).

Since the aggregation in response to AA was measured in platelet rich plasma, in the absence of leucocytes, any aggregation seen after adding arachidonic acid should be due to the metabolism of AA within platelets and not to TxA2 produced by other cell types. It is therefore proposed that transient ‘aspirin resistance’ seen in the patients during surgery must be primarily mediated through the direct metabolism of arachidonic acid within the platelets. However, since COX-1 was blocked effectively prior to surgery and the apparent bypass of this inhibition seen during surgery was reduced by the end of the operation, without any further aspirin intake, it is assumed that the arachi-
Arachidonic acid must be metabolised through a COX-1 independent pathway.

An alternative route of arachidonic acid metabolism in platelets is via the lipoygenase pathway, resulting in the production of 12-hydroxyicosatetra-enoic acid (12-HETE) (29). There are conflicting data on the role that 12-HETE may play in platelet activation (30, 31), but low levels can prime the effects of sub-threshold concentrations of AA to induce aggregation (32). Lipoygenase metabolism of AA has been previously implicated as a mechanism for long-term ‘aspirin resistance’ (13, 33). Alternatively there are reports of non-enzymatic, oxidation-dependent conversion of AA to proaggregatory isoprostanes (34) that have been implicated in aspirin resistance. In addition ‘aspirin insensitive’ thromboxane synthesis has been described, resulting from the COX-2-mediated generation of PGH₂ by endothelial cells (35), which could bypass the blockade of COX-1 in aspirinated platelets and generate TXA₂, but whether such effects could persist in vitro remains to be established.

At the therapeutic dose used here aspirin acts mainly on COX-1 leaving COX-2 unaffected. Unlike COX-1, COX-2 can be rapidly and transiently up regulated in monocytes/macrophages and endothelial cells. As we have studied the effects of arachidonic directly on platelets, in the absence of other cell types, this precludes the direct involvement of COX-2 from other cells. However, recent observations link ‘aspirin resistance’ to the presence of the inducible enzyme COX-2 in platelets (36) and COX-2 has been shown to be upregulated in platelets from patients undergoing coronary artery bypass (14, 37). However there is conflicting evidence for platelet COX-2 in the literature (38).

Could the transient ‘aspirin resistance’ observed here be due the release of new platelets capable of generating thromboxane, either through COX-2 or COX-1? Given that the cyclo-oxygenase pathway was inhibited immediately before surgery, and the duration of the operation was short (<2 hours) it is unlikely that a significant platelet population would be produced within this timescale. In fact the platelet count fell slightly although remaining above 150 × 10⁹/dl in all but 5 of the patients. In these 5 the pre-operative platelet count was low and the drop in count was comparable to that seen in the rest of the subjects. Taken together these data also argue against heparin induced thrombocytopenia, either Type I (non-immune) or type II (immune) as a likely cause of the transient apparent ‘aspirin resistance’.

In conclusion, despite adequate inhibition of COX-1 prior to surgery patients’ platelets acquire the ability to utilise arachidonic acid during surgery by a process that is subsequently reversed. The increased response to AA cannot be accounted for by elevation of other platelet agonists such as ADP, thrombin or epinephrine, nor by metabolism of AA through COX-1 since the reversal occurs without further intake of aspirin. Possible routes are proposed including the the lipoygenase pathway, the presence of the inducible enzyme COX-2 in platelets or the action of endothelial derived PGH₂, but further studies are needed to determine which if any of these pathways may be operating.

At this stage it is not clear whether this observed phenomenon is clinically relevant. A much larger cohort would need to be studied to determine the relationship between transient ‘aspirin resistance’ during surgery and thromboembolic complications. Whilst none of the patients in this study would be classified as having long-term ‘aspirin resistance’, an examination of the mechanism for this transient phenomenon may give clues as to the underlying mechanisms contributing to long term ‘aspirin resistance’. Further studies are needed to characterise this effect, to explore potential mechanisms and to investigate the clinical significance in the context of surgery. If proved clinically relevant this could argue for alternative antiplatelet therapy to reduce the risk of thromboembolism during surgical procedures.

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References


