The Aspirin Resistance Controversy
Clinical Entity or Platelet Heterogeneity?

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In acute coronary syndromes, rupture or fissuring of the atherosclerotic plaque exposes the subendothelium and lipid core, which leads to platelet adhesion and activation. Although the most commonly used inhibitor of this process is aspirin, information about its limitations has grown over the past decade. Because the absolute risk of recurrent vascular events among patients treated with aspirin remains relatively high (8% to 18% after 2 years), a concept known as “aspirin resistance” has flourished. Aspirin resistance has been defined both as a clinical entity (thrombotic event while taking aspirin) and by a myriad of altered biomarkers and enhanced platelet function testing. Although many embrace this concept, others believe that aspirin resistance may reflect treatment failure rather than “resistance” to aspirin.

Aspirin-related compounds are among the oldest known medicinal substances, with stone tablets documenting the use of willow leaf (a source of salicylic acid) dating back to the Sumerian period. Controversy surrounding the use of aspirin can be traced back to the Greek empire, when Hippocrates was a proponent of willow bark for pain, whereas Dioscorides preferred coriander. We will never know whether Dioscorides was merely resistant to the beneficial properties of aspirin because thousands of years later we are still trying to understand and define the individual variability seen with its use.

The antithrombotic properties of aspirin were first reported in the Mississippi Valley Medical Journal in 1953, and, in the half century since, the benefits of aspirin’s platelet inhibitory properties have been documented in thousands of patients. Clinical trials have demonstrated that aspirin is effective for both primary and secondary prevention of myocardial infarction, stroke, and cardiovascular death, as well as in the acute treatment of unstable coronary disease and stroke. However, the potential impact of aspirin resistance is great, because its prevalence has been estimated to be between 5% and 45% of the population. Despite consistency in the observation of aspirin resistance across a wide range of individuals, the exact prevalence remains uncertain, in part owing to the absence of standardized diagnostic criteria or a single validated method of identifying affected individuals. There is well-known variability with regard to platelet function and biomarker testing, and this variability has also been called “resistance.”

Much of the reported variability is due to the large and diverse biomarker and platelet function testing used to define aspirin resistance. Aspirin achieves its primary antithrombotic effects through the inactivation of cyclooxygenase 1 (COX-1), a key enzyme in platelet arachidonate metabolism and the formation of thromboxane A2, a potent activator of platelets. Measurement of thromboxane A2 has been suggested to be the most direct measurement of aspirin resistance; however, the best marker is not known, nor is there consensus on this point. Many of the tests for aspirin resistance reflect its inhibition of COX-1 by studying alterations in platelet activation (aggregometry, flow cytometry, and most point-of-care tests) or indirect plasma or urine measurements of thromboxane formation. However, the assessment of platelet function is complex and multifactorial, and laboratory methods for quantifying the antithrombotic effects of aspirin have primarily focused on measurements that reflect platelet aggregation.

The mechanism for aspirin resistance remains uncertain and is also probably multifactorial. Residual COX activity has been reported. Clinically, compliance, duration of aspirin therapy, and use of nonsteroidal antiinflammatory drugs have all been associated with aspirin resistance. Aspirin resistance has also been attributed to genetic differences in the COX-1 gene, platelet antigen, or the glycoprotein IIb/IIIa receptor complex. The mechanism for this persistence in function may also be a reflection of the redundancy of platelet activation pathways, receptors, and signaling pathways. Pathways that involve nonthromboxane activation, such as thrombin, adenosine diphosphate, or collagen, could circumvent the inhibitory effect of aspirin, leading to activation. Aspirin may also influence hemostasis and vascular disease by COX-1–independent mechanisms. Although less clearly understood, decreased platelet-dependent production of thrombin, inhibition of neutrophil-mediated platelet activation, and antiinflammatory effects have also been described as possible reasons for the beneficial cardiovascular properties of aspirin.

Heterogeneity in the platelet response to aspirin is also present in different clinical populations. In patients receiving aspirin for secondary prevention of cardiovascular events, uninhibited platelet COX activity persists in younger and heavier patients and in those with a previous myocardial infarction. Women’s platelets have also been shown to be significantly more reactive at baseline. Aspirin therapy has
been shown to decrease the percent aggregation to arachidonic acid (the direct COX-1 pathway) more in women than in men.\textsuperscript{15} The laboratory description of sex differences in platelet function has been borne out in a recent large, primary prevention clinical study demonstrating that, as distinct from men, aspirin lowers the risk of stroke in women without affecting the risk of myocardial infarction or death from cardiovascular causes.\textsuperscript{16}

Thus, there is well-known variability between patients and normal subjects in regard to platelet function and biomarker responses to aspirin.\textsuperscript{8} In the current issue of \textit{Circulation}, Frelinger and colleagues\textsuperscript{17} add to our knowledge of the effects of aspirin by studying almost 700 aspirin-treated patients undergoing cardiac catheterization for platelet activation by flow cytometry and COX-1 activity by thromboxane measurements. A strength of this study is its size and carefully executed platelet function testing. Notable limitations are that it is a single-site study, it did not compare the data with aggreometry, and the data were not linked with clinical outcome. On a practical note, although the authors present an exhaustive and highly informative examination of platelet function by flow cytometry, it is unlikely that the average clinical laboratory will ever utilize this challenging technique in the setting of patient care.

A primary question in this study was, if there is residual platelet activity despite aspirin treatment, how much is COX-dependent versus COX-independent? Significantly, few of the patients had serum thromboxane B\textsubscript{2} levels that were similar to those of non-aspirin-treated patients. In patients taking aspirin, “resistance” (\textasciitilde2%) was only rarely due to noncompliance or underdosing with aspirin therapy (only 2 patients). In addition, differences in serum thromboxane levels were not significantly different overall between patients taking low-dose aspirin and those taking 325 mg of aspirin. In all, only 12 patients had serum thromboxane levels that were 2 SDs above the mean for all patients taking aspirin. In these select patients, a greater number were taking low-dose aspirin, but it is difficult to draw real conclusions because this group was very small.

Despite aspirin treatment, the authors still found significant residual arachidonic acid–dependent platelet activation. In patients and normal volunteers, further inhibition of the COX pathway failed to lead to further inhibition of platelet activation, which suggests that a COX-1– and COX-2–independent pathway was responsible for the platelet variability. However, these studies were performed on an ex vivo basis, so only the effect of COX inhibitors on platelets was assessed. Finally, this study may eliminate COX-dependent pathways as the cause for the residual platelet activation but does not provide another definite mechanism. The data presented in regard to the additional platelet inhibitory effects of clopidogrel are too limited to draw any firm conclusions and are counter to a recent study demonstrating that many aspirin-resistant individuals are also clopidogrel-resistant.\textsuperscript{18}

Most studies of aspirin resistance measure residual platelet function only after the subject or patient has taken aspirin. In the study by Frelinger et al.,\textsuperscript{17} the baseline preaspirin level of platelet activation was compared with the posttreatment level in normal subjects. Oral aspirin reduced arachidonic acid–stimulated (COX-1 dependent) platelet activation; however, platelet activation remained relative to the patient’s own baseline value. The finding that the residual arachidonic acid–induced platelet activation occurs in direct proportion to the degree of baseline platelet activation is interesting and relevant. Perhaps measurements of aspirin resistance merely reflect baseline heterogeneity in platelet response. The assumption that individuals all begin with the same baseline platelet function is a problem that confounds many studies of aspirin resistance. This observation, coupled with the COX-independent nature of the residual platelet function, suggests that additional antithrombotic treatments instead of aspirin substitutes will have the highest likelihood of clinical success in resistant patients. Also, because the authors used flow cytometry, they were able to show that the degree of residual arachidonic acid–induced platelet activation in aspirin-treated patients occurs in proportion to the level of platelet activation in the circulation (distinct from the level that was activated ex vivo). This highlights the laboratory benefits of using flow cytometry compared with standard platelet aggregation or point-of-care testing, ie, nonstimulated platelets can be assessed for activation before stimulation with an agonist ex vivo.

What can we conclude from this new information on “aspirin resistance”? First, heterogeneity is present in the many available studies. Frelinger et al.\textsuperscript{17} did not find aspirin noncompliance, which is supportive of some reports\textsuperscript{19} but contrary to others.\textsuperscript{20} Second, despite the lack of noncompliance or underdosing, arachidonic acid–induced platelet activation persists. The data in the present study suggest that the residual activation is likely COX-1 and COX-2 independent. Third, the aspirin resistance seen in both the normal and patient populations studied may be due to individual heterogeneity in their platelet function and not actual resistance.

Although platelet function heterogeneity may account for aspirin resistance, this does not negate the need to find patients who require further treatment in addition to aspirin or alternative antithrombotics. Although previous research has provided us with outstanding data demonstrating heterogeneity in aspirin response, the study in the current issue of \textit{Circulation} suggests that some of this may reflect the inherent variability in platelet function across individuals. Finally, despite this wealth of data, we are still missing crucial information, specifically with regard to the following: (1) Prospective data demonstrating that aspirin resistance is clinically relevant; (2) proof that treating aspirin resistance with either additional aspirin or another platelet inhibitor will alter the clinical (not biomarker) course of disease; and (3) data demonstrating that a biomarker or specific platelet function test can reliably predict aspirin resistance and that this test is tied to clinical outcome. The interaction between aspirin, COX, and platelet function remains central to our understanding of thrombosis, and the completion of this study will yield great benefit for our patients with cardiovascular disease.

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References


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