Heritability, Platelet Function, and Aspirin
A Link Established but Cause Unknown

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Platelets play a critical role in the pathophysiology of atherothrombotic disease. A pivotal event contributing to the understanding of platelet-dependent clot formation was the development of the platelet aggregometer in 1962. An aggregometer specifically measures the ability of platelets to adhere via glycoprotein IIb/IIIa (integrin αIIbβ3), and thousands of articles using this technique have been published, characterizing platelet function; however, the usefulness of these measurements remains unclear. Whereas the aggregometer and related techniques that measure platelet aggregation or glycoprotein expression have led to large amounts of data characterizing platelet function in various settings, the clinical importance of measurable differences in platelet function is still debated. The use of platelet function testing is established in rarer platelet abnormalities, such as the autosomal recessive bleeding disorder Glanzmann thrombasthenia, but no clear consensus has been reached on its usefulness for highly prevalent diseases caused by platelet-dependent thrombosis, such as myocardial infarction. A major factor for this discrepancy is that many of the platelet function defects that lead to bleeding are known to be caused by a single defect, whereas thrombosis in the setting of cardiovascular disease is presumed to be multifactorial.

The evolution of platelet function studies in various clinical settings has led to the realization that wide interindividual variability exists in the platelet activation response. What accounts for this variability? Only a few studies have systematically examined this question. Platelet function has been established as markedly dependent on the type of agonist used, the agonist concentration, and the concomitant use of antiplatelet therapy. In addition, in the large population-based Framingham Heart Study, O’Donnell and colleagues have demonstrated that heritable factors play a major role in determining platelet aggregation, as opposed to measured covariates. Less clear from the current literature is the direct contribution of known genetic variants to platelet function, with both positive and negative studies being reported. Although the findings from the Framingham Heart Study were published >5 years ago, no definitive genetic factor has come through as a strong determinant for the differences in platelet function. However, despite a lack of clear genetic determinants for platelet-dependent thrombosis in cardiovascular disease—as demonstrated by Glanzmann disease (an autosomal recessive disorder) and Bernard–Soulier syndrome—platelet dysfunction can be inherited.

Also presumed to be partially genetically determined is the interindividual variability in platelet function response to aspirin. A profound interest exists in platelet function testing to better define and understand the effect and failure of aspirin in cardiovascular disease and prevention. Clinical trials have demonstrated the efficacy of aspirin in both primary and secondary prevention of myocardial infarction, stroke, and cardiovascular death. Despite this proven benefit, the absolute risk of recurrent vascular events among patients taking aspirin remains relatively high. Platelet function testing has led to the concept of aspirin resistance, on the basis of the detected variability in platelet response. Although formal diagnostic criteria and a validated method of measurement are lacking, aspirin resistance (or treatment failure while taking aspirin) may affect between 5% and 45% of the population. Given the prevalence of cardiovascular disease, the potential impact of aspirin resistance is large.

Currently, many questions remain unanswered on the biological mechanism, diagnosis, and clinical relevance for the observed individual variability in platelet function testing. One possible explanation is that, as with other diseases, each individual has an inherent risk of thrombosis and/or bleeding, and this is reflected in the individual’s level of platelet activation as measured by platelet function testing. This leaves us with several questions. What accounts for the observed differences in platelet-dependent thrombosis? Can this variability be inherited? Does treatment with an antiplatelet therapy modify these differences?

In the current issue of Circulation, Faraday and colleagues address some of these questions and extend the observations from the Framingham Heart Study by asking whether measurable or inherited conditions contribute to interindividual variability in platelet function in the presence or absence of aspirin treatment. In this study, the authors examined platelet function in 1908 subjects from 309 white and 208 black families. The findings were grouped as cyclooxygenase 1 (COX-1) dependent if arachidonic acid was the platelet stimuli or if a thromboxane metabolite was measured. All other measures of platelet function testing were deemed (indirect) COX-1 independent. A clear strength of this study is that the measurements were made both before and after aspirin dosing, allowing for characterization of platelet variability both at baseline and after platelet inhibition. The basic
findings demonstrate an inherited basis for both platelet function and aspirin response.

As expected,10 treatment with aspirin reduced arachidonic acid aggregations and thromboxane metabolite measurements. Measured covariates (primarily age and sex) were only modestly related to postaspirin treatment by COX-1-dependent platelet function. However, these covariates were more strongly related to non- (indirect) COX-1 function testing. Because hardly any interindividual variability exists for the direct COX-1 effects after aspirin ingestion, the contribution of heritability or any other measurable factor cannot be estimated with these tests. Therefore, when aspirin is correctly dosed and adequate compliance exists, no heritability of COX-1-dependent effects is detected. The authors also report that the baseline platelet function directly related to COX-1 pathways does not predict the postaspirin response. Because little interindividual variability existed for the COX-1-dependent tests’ postaspirin response, this is to be expected.

More revealing were the results from the testing deemed to be non- (indirectly) COX-1 dependent. These phenotypes (both pre- and postaspirin) were more strongly and consistently heritable in both whites and blacks, whereas measured covariates accounted for relatively little of the variability in aspirin responsiveness. Many previous studies have characterized platelet responsiveness to aspirin by a myriad of platelet function tests, but this is the first study to determine the contribution of cardiac risk factors and polygenic heritability to variability in platelet function at baseline and in response to aspirin. In addition, these observations confirm the in vitro findings of Frelinger et al4 demonstrating that residual platelet activation after aspirin treatment reflects the baseline platelet function. Cardiac risk factors have been shown to be associated with platelet responsiveness to aspirin,6,11 but the current study suggests that the contribution is small, with heritable factors contributing more to platelet reactivity. In addition, the baseline platelet phenotype was a substantial contributor to the heritability of postaspirin phenotypes indirectly related to COX-1.

Another interesting finding was the difference between demographic heritability. Although some differences in heritability were observed between black and white subjects, the overall pattern was inconsistent. Also reported was less platelet suppression after aspirin therapy, associated with female sex for indirect COX-1 phenotypes. Recent data suggest that women may not accrue the same cardioprotective benefits as men do from low-dose aspirin therapy used in primary prevention.12 Consistent with the current study is a report where women retained modestly more platelet reactivity than did men after aspirin therapy.13 These findings are also consistent with a study demonstrating increased platelet reactivity associated with female sex.2 An association between genetic variations in platelet glycoprotein Ibα and VI and the risk of coronary heart disease events in postmenopausal women taking hormone therapy has been reported in the Heart and Estrogen/Progestin Replacement Study.14 These observations are intriguing, both as an explanation for aspirin resistance and as a potential cause for the failure of aspirin in primary prevention for women.

A limitation of this study is that it did not prospectively examine platelet function and clinical outcomes. Another related limitation is that, despite large numbers of reported studies using platelet function testing, standardization and reproducibility have been lacking. If an individual is found to have “reactive” platelets, is the observation consistent over time? Although traditional aggregometry, the “gold standard”9 of platelet function testing, has recently been maligned as poorly reproducible, expensive, and not as easy as point-of-care testing, it has provided some of the best information for defining platelet reactivity in individuals. In a recent study by Yee et al,2 the reproducibility of platelet aggregation was characterized in healthy subjects. Whereas subjects demonstrated considerable interindividual variability in aggregation response to agonists, reproducibility was demonstrated for up to 3 years with a specific agonist. Although reproducible, the clinical relevance of platelet function testing is still not clear. Aggregometer and point-of-care testing measure specific markers of platelet function, but these measurements may not correlate with better outcomes. This limitation is illustrated by the clinical failure of the oral glycoprotein IIb/IIIa inhibitors, which are known to effectively inhibit platelet aggregation.15

In summary, Faraday and colleagues6 report the heritability of the platelet function response to aspirin therapy for non-COX-1 platelet function tests. The findings suggest that the variability seen in baseline platelet function and with the non–COX-1-dependent tests after aspirin ingestion have a genetic basis. The findings show that although aspirin inhibits COX-1, one’s predisposition to atherothrombotic events after taking aspirin may be inherited. Despite these interesting and valuable observations, questions remain. Is defining an individual’s inherent platelet variability by platelet function testing clinically useful for predicting disease? Can information about heritability and platelet function testing assist in deciding which patient populations would benefit from selective platelet inhibitors or combinations of platelet inhibitors? Lastly, what is the genetic basis for this variability? In summary, as with bleeding, the platelet thrombotic response seems to be inherited, and further information should assist us in determining the cause, effect, and clinical utility of this variability.

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