

Coated-platelets in Ischemic Stroke

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Abstract

While platelets are acknowledged as critical components of ischemic stroke pathophysiology, little is known about the role of platelet reactivity or platelet subclasses in stroke. Coated-platelets are a pro-thrombotic subclass of platelets, levels of which can vary substantially among individuals. Recently, coated-platelets were observed to be elevated in cortical stroke patients and decreased in lacunar stroke patients, thereby providing for the first time a biochemical marker distinguishing these two stroke subtypes. This article reviews the primary observation as well as the clinical and epidemiological implications of this finding.

Keywords

Stroke, lacunar, cortical, hemorrhagic, platelet, coated-platelet

Disclosure: The authors have no conflicts of interest to declare.

Received: February 26, 2009 **Accepted:** June 15, 2009 **DOI:** 10.17925/USN.2010.05.02.55

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Stroke is the third leading cause of death and the number one cause of disability in the US, with an estimated incidence of 780,000 strokes/year.¹ Approximately 10% of all strokes are hemorrhagic, with the remainder being ischemic. Within the ischemic category, two major sub-classes are recognized. Ischemic strokes occurring within large blood vessels of the brain account for approximately 80% of the total and are thought to be the result of thromboembolic events originating in the heart or diseased large arteries. Lacunar strokes are the second major classification of ischemic stroke, occurring in small (200–300µm) penetrating arteries of the brain. The etiology of lacunar strokes is not considered to be embolic but rather represents endogenously generated clots, perhaps as a result of endothelial abnormalities. Large-vessel strokes, subsequently referred to as cortical (or non-lacunar) strokes, have a worse prognosis for 30-day mortality, residual disability, and recurrence than do lacunar strokes.^{2,3} Modifiable risk factors for ischemic stroke include hypertension, diabetes, smoking, and hyperlipidemia,¹ all factors that similarly contribute to atherosclerotic disease. While platelet participation is recognized as integral to the thrombotic process associated with ischemic strokes, there has been limited evidence to suggest that variations in platelet reactivity may also be a risk factor. This paucity of data is at least partially due to technical limitations in quantitating platelet reactivity, and also possibly due to the numerous platelet parameters that could affect thrombotic potential.

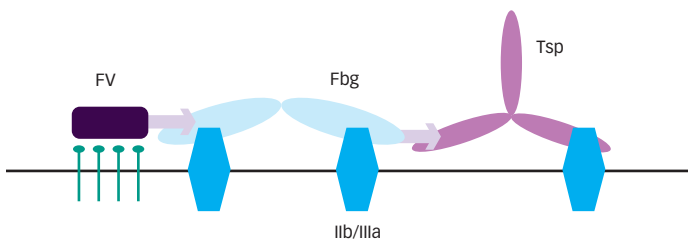
Coated-platelets

Our interest in the platelet's role in ischemic stroke resulted from studies with coated-platelets, a subset of activated platelets with

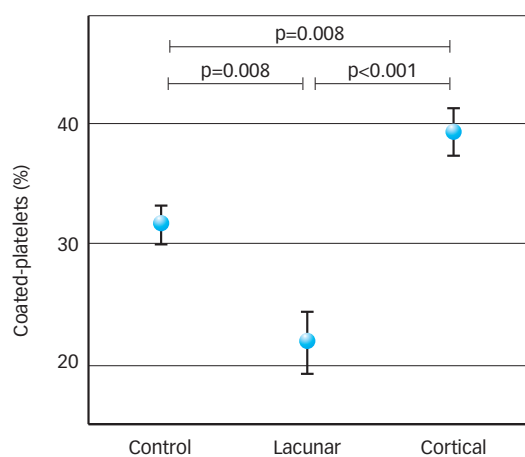
pro-thrombotic characteristics first described in 2000 by Alberio et al.⁴ The initial observation was that dual agonist activation with both thrombin and collagen resulted in enhanced prothrombinase activity and retention of coagulation factor V (FV) on the surface of a subgroup of activated platelets. Subsequently, Dale et al.⁵ demonstrated that several additional procoagulant proteins, including fibrinogen, von Willebrand factor, and thrombospondin, were also retained on the surface of these dual activated cells.

Dissection of the synthetic processes associated with coated-platelet formation indicated that serotonin was covalently attached to platelet pro-coagulant proteins via a transglutaminase reaction⁵ and that serotonin derivatization was responsible for the tight binding of these proteins to the coated-platelet surface.⁶ A proposed model for the structure of coated-platelets is shown in *Figure 1*.⁷

A recent study examining 70 normal controls found the average coated-platelet level was 31.6±13.2% (mean ± SD); however, the range was 7–59%.⁸ This is an exceptionally large range for a potential pro-thrombotic marker. We therefore sought to determine factors affecting coated-platelet levels and observed several relevant medications and behaviors.⁸ For example, individuals who smoke have elevated coated-platelet levels, while individuals on aspirin have lower coated-platelet levels.⁸ Patients using selective serotonin re-uptake inhibitors (SSRIs) also had decreased levels of coated-platelets,⁸ an observation likely associated with the role of serotonin in coated-platelet formation.⁵ In addition, inflammation appears to regulate coated-platelet levels, as

Figure 1: Proposed Model of Coated-platelets

Procoagulant proteins, including factor V (FV), fibrinogen (Fbg), and thrombospondin (Tsp), are immobilized onto the surface of coated-platelets by multivalent interactions. These interactions include traditional receptors (e.g. fibrinogen receptor, IIb/IIIa) as well as contacts with derivatized serotonin (pink arrows). Reprinted with permission from Dale, 2005.⁷

Figure 2: Coated-platelets in Ischemic Stroke

Forty patients with cortical stroke and 20 patients with lacunar stroke were analyzed for coated-platelet levels. Control values for coated platelets are also indicated. Reprinted with permission from Prodan et al., 2008.¹¹

shown in a recent study of end-stage renal disease (ESRD) patients.⁹ These patients had elevated coated-platelets that were positively correlated with serum C-reactive protein (CRP) levels.⁹

Considering the pro-thrombotic potential of coated-platelets and the range of levels found within a normal population, we considered the possibility that variation in coated-platelet levels might contribute to the risk for either thrombotic or hemorrhagic events. Specifically, we predicted that elevated levels of coated-platelets would be associated with pro-thrombotic disease while low levels of coated-platelets would result in a bleeding diathesis. The impact of low coated-platelet levels was recently verified with the observation that a genetically determined bleeding diathesis in German Shepherd dogs is due to an absence of coated-platelets.¹⁰ At the other end of the spectrum, the consequence of high coated-platelet levels in pro-thrombotic conditions has been less clear, although our study in ESRD demonstrated increased coated-platelets⁹ in a population with a well-documented risk for thrombosis.

Coated-platelets in Ischemic Stroke

The pro-thrombotic nature of coated-platelets led us to investigate their possible role in ischemic stroke. While our expectation was that elevated levels of coated-platelets would occur in all patients with

ischemic stroke, the actual results were surprising and informative.¹¹ Patients with cortical stroke did have high levels of coated-platelets compared with controls (see Figure 2), in agreement with our hypothesis that the pro-thrombotic nature of these activated platelets would potentially facilitate the thrombotic processes known to be associated with large-vessel strokes. The unexpected observation was that patients with lacunar stroke had significantly lower levels of coated-platelets compared not only with patients with cortical stroke but also with the control population (see Figure 2). Why lacunar strokes, which are considered to result from locally generated thrombi, would be associated with a low level of coated-platelets is not clear at this time.

Most importantly, these data indicate fundamental differences in the etiology of cortical and lacunar strokes with regard to the role of coated-platelets. As stated above, the consensus among stroke experts has been that cortical and lacunar strokes are sufficiently dissimilar that they are likely to be caused by discrete pathophysiological mechanisms; however, to date there has been little biochemical evidence supporting that supposition. Our observation regarding differences in coated-platelet production between cortical and lacunar strokes provides the first biochemical clue supporting this distinction.^{11,12}

Coated-platelets and Hemorrhagic Stroke

A logical extension of our first report on coated-platelets in ischemic stroke¹¹ is whether these activated platelets also have a role in hemorrhagic stroke. While it is accepted that a bleeding diathesis is not the primary cause of hemorrhagic strokes, it is logical that a bleeding tendency might well contribute to the pathophysiology of this stroke subtype. Recently, we observed a marked decrease in coated-platelet levels in patients with spontaneous intracerebral hemorrhage (SICH).¹³ Interestingly, the actual coated-platelet levels in SICH were similar to those previously observed in lacunar strokes, a finding supportive of the hypothesis that SICH and lacunar strokes have similarities in etiology and pathophysiology.¹⁴⁻¹⁸ A recent study lends additional support to this hypothesis by showing that patients with prior lacunar stroke had a significantly higher risk for developing intracerebral hemorrhage compared with patients with prior non-lacunar stroke.^{3,19}

Implications of Coated-platelet Observations

These findings suggest several consequences in addition to revealing differences in pathophysiological pathways for cortical and lacunar strokes. For example, a key question is whether it is appropriate to treat both cortical and lacunar stroke patients with identical antiplatelet regimens, currently the core management strategy for preventing stroke recurrence in both stroke subtypes. If the pro-thrombotic actions of coated-platelets are indeed a contributor to the pathology of cortical strokes, antiplatelet therapy remains a logical course of treatment. However, if low coated-platelet levels contribute to the pathophysiology of both lacunar strokes and SICH, antiplatelet medications may be problematic. This dilemma is aggravated by the paucity of stroke epidemiological data regarding response to medications, in particular antiplatelet agents, for sub-classes of ischemic stroke (i.e. cortical versus lacunar stroke). As a result, it is feasible that the occurrence of high and low coated-platelet levels

within the broad classification of ischemic strokes may partially explain the relatively modest efficacy of antiplatelets in clinical trials for secondary prevention of ischemic stroke.²⁰ This poor performance is particularly noteworthy compared with the success of antiplatelet therapy in secondary prevention of myocardial infarction.

Summary

Stroke remains a major public health challenge. Even though important advances in identifying and treating risk factors for stroke have occurred, the overall rate of stroke remains significant. In this article we have briefly discussed a potential role for coated-platelets in the pathophysiology of ischemic stroke and the implications of these findings for modifying future epidemiological studies of stroke. We suggest that greater attention to stroke subtypes is essential when considering risk factors and medications aimed at preventing stroke recurrence. ■



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