Coated-Platelet Levels Are Low in Patients With Spontaneous Intracerebral Hemorrhage

Calin I. Prodan, MD; Andrea S. Vincent, PhD; Rajiv Padmanabhan, MD; George L. Dale, PhD

Background and Purpose—Coated-platelets are a subset of platelets with high procoagulant potential observed on dual agonist stimulation with collagen and thrombin. Failure to produce coated-platelets in animals results in a bleeding diathesis. With this background, we undertook a pilot study to investigate coated-platelet production in patients with spontaneous intracerebral hemorrhage (SICH).

Methods—Coated-platelet levels were determined in 26 patients with a diagnosis of SICH and 52 controls.

Results—The patient population had significantly lower coated-platelet levels than the controls (mean±SD, 24.8±9.7% versus 32.9±12.6%, \(P=0.0035\)).

Conclusions—Decreased coated-platelet synthesis may be linked to the mechanisms involved in the events leading to SICH. (Stroke. 2009;40:2578-2580.)

Key Words: platelets ■ hemorrhage ■ intracerebral

Coated-platelets are a subpopulation of platelets observed on dual stimulation with collagen and thrombin. In contrast to single-agonist activated platelets, coated-platelets support a robust prothrombinase activity and retain high levels of several procoagulant proteins on the cell surface, including factor V, fibrinogen, and von Willebrand factor. Our previous research in ischemic stroke demonstrated that coated-platelet levels are elevated in nonlacunar stroke patients compared to controls, an observation compatible with the thrombotic nature of these events. At the other end of the spectrum, a potentially life-threatening bleeding diathesis in dogs results from a deficiency in coated-platelet production. Because these findings suggest that extremes in coated-platelet synthesis may be linked to either thrombosis or bleeding, we undertook a pilot study to investigate coated-platelet production in patients with spontaneous intracerebral hemorrhage (SICH).

Materials and Methods
Twenty-six consecutive patients with a diagnosis of SICH were recruited from the Neurology service at the University of Oklahoma Health Sciences Center (OUHSC) and the Veterans Affairs Medical Center. All patients were diagnosed with SICH by a board-certified neurologist and underwent brain CT or MRI studies at presentation. A neuroradiologist provided a definitive reading for every CT/MRI scan. Race, sex, and medication use were recorded for each patient. The neurologists establishing the diagnosis of SICH were not aware of the coated-platelet levels.

The control population consisted of 52 individuals who were frequency-matched with the patient population for race, sex, current smoking, and use of medications that may alter coated-platelet levels: selective serotonin reuptake inhibitors (SSRIs), HMG-CoA reductase inhibitors (statins), or antiplatelet agents. Exclusion criteria for controls consisted of use of anticoagulation, prior stroke/TIA, myocardial infarction, dementia, or bleeding diathesis. The larger percentage of men in our study is the result of the composition of the United States armed forces during the time these veterans served.

After obtaining informed consent in accordance with the OUHSC regulations, 5 mL of blood was drawn from each subject into acid citrate dextrose, and coated-platelet levels were determined as previously described. Results are reported as percent of cells converted into coated-platelets. The individuals performing the coated-platelet assay were not aware of the coated-platelet levels.

Conclusions—Decreased coated-platelet synthesis may be linked to the mechanisms involved in the events leading to SICH. (Stroke. 2009;40:2578-2580.)

Key Words: platelets ■ hemorrhage ■ intracerebral
Coated-Platelets in Intracerebral Hemorrhage

Results

The Table lists demographics, relevant medications, and coated-platelet levels of patients and controls (Corresponding Percentages in Parentheses).

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Patients (n=26)</th>
<th>Controls (n=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (mean±1SD)</td>
<td>65.0±16.8</td>
<td>64.9±7.6</td>
</tr>
<tr>
<td>Sex, female/male</td>
<td>7/19 (27%/73%)</td>
<td>14/38 (27%/73%)</td>
</tr>
<tr>
<td>Race, black/white</td>
<td>7/19 (27%/73%)</td>
<td>14/38 (27%/73%)</td>
</tr>
<tr>
<td>Current smoking, smoker/nonsmoker</td>
<td>6/20 (23%/77%)</td>
<td>12/40 (23%/77%)</td>
</tr>
<tr>
<td>Pertinent medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins, yes/no</td>
<td>6/20 (23%/77%)</td>
<td>12/40 (23%/77%)</td>
</tr>
<tr>
<td>SSRIs, yes/no</td>
<td>2/24 (8%/92%)</td>
<td>4/48 (8%/92%)</td>
</tr>
<tr>
<td>Antiplatelets, yes/no</td>
<td>10/16 (38%/62%)</td>
<td>20/32 (38%/62%)</td>
</tr>
<tr>
<td>Coated-platelet levels, %</td>
<td>(mean±1SD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24.8±9.7</td>
<td>32.9±12.6</td>
</tr>
</tbody>
</table>

Discussion

This first investigation of coated-platelet synthesis in SICH indicates that SICH patients have significantly lower coated-platelet levels shortly after the hemorrhagic event as compared to normal controls. These pilot data suggest that altered coated-platelet synthesis may be linked to the mechanisms involved in the sequence of events leading to intracerebral hemorrhage.

The complete spectrum of physiological functions of coated-platelets is still under investigation. One of the most intriguing findings to date concerning coated-platelets is that the potential to produce these cells varies greatly among donors. Normal donors generate on average approximately 30% coated platelets. However, the range of coated-platelet values for normal subjects extends between 10% to 50%. This wide range implies that elevated levels may be related to prothrombotic conditions, whereas low levels may be related to greater risk for hemorrhage.

Our previous research showed elevated coated platelets in patients with nonlacunar stroke compared to controls and patients with lacunar stroke. Furthermore, the coated-platelet levels previously noted in patients with lacunar stroke were significantly lower than in controls, and similar to the levels we report here in SICH patients. Similarities in the location and the size of the blood vessels affected between patients with lacunar infarcts and deep intracerebral hemorrhages, the association between cerebral microbleeds and lacunar stroke, and prior research reporting an increased risk of intracerebral hemorrhage after an initial lacunar infarct may all suggest that decreased coated-platelet synthesis in SICH and lacunar syndrome is a reflection of a pathological pathway that is, at least to a point, common for both conditions.

The explanation for these disparities in coated-platelet potential between controls and SICH patients is not yet known; equally important, it is not yet clear whether the difference in these patients existed before hospital admission. Larger prospective studies are needed to better establish the potential connection between altered coated-platelet synthesis and intracerebral hemorrhage. Further investigation of the role of coated-platelets in SICH is warranted to aid our understanding of the pathological mechanisms that contribute to SICH, which in turn may lead to more effective strategies for predicting prognosis and recurrence risk, and potentially treatment and prevention.

Acknowledgments

The authors are indebted to Robert Cox, Paul Friese, Erin Nagode, Elliott Ross, and Linda Cowan for their assistance with this project.

Sources of Funding

This work was supported by the Department of Veterans Affairs and grants from Oklahoma Center for Advancement of Science and Technology (Dr Prodan) and the American Heart Association (Dr Dale).

Table. Demographics, Selected Medications, and Coated-Platelet Levels of Patients and Controls (Corresponding Percentages in Parentheses)

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Patients (n=26)</th>
<th>Controls (n=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (mean±1SD)</td>
<td>65.0±16.8</td>
<td>64.9±7.6</td>
</tr>
<tr>
<td>Sex, female/male</td>
<td>7/19 (27%/73%)</td>
<td>14/38 (27%/73%)</td>
</tr>
<tr>
<td>Race, black/white</td>
<td>7/19 (27%/73%)</td>
<td>14/38 (27%/73%)</td>
</tr>
<tr>
<td>Current smoking, smoker/nonsmoker</td>
<td>6/20 (23%/77%)</td>
<td>12/40 (23%/77%)</td>
</tr>
<tr>
<td>Pertinent medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins, yes/no</td>
<td>6/20 (23%/77%)</td>
<td>12/40 (23%/77%)</td>
</tr>
<tr>
<td>SSRIs, yes/no</td>
<td>2/24 (8%/92%)</td>
<td>4/48 (8%/92%)</td>
</tr>
<tr>
<td>Antiplatelets, yes/no</td>
<td>10/16 (38%/62%)</td>
<td>20/32 (38%/62%)</td>
</tr>
<tr>
<td>Coated-platelet levels, %</td>
<td>(mean±1SD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24.8±9.7</td>
<td>32.9±12.6</td>
</tr>
</tbody>
</table>

Figure. Distribution of coated-platelet levels among patients and controls. Coated-platelet levels in increments of 10% points are presented on the horizontal axis, and the percentage of individuals in each group (SICH and controls) is presented on the vertical axis.
Disclosures

None.

References
Coated-Platelet Levels Are Low in Patients With Spontaneous Intracerebral Hemorrhage
Calin I. Prodan, Andrea S. Vincent, Rajiv Padmanabhan and George L. Dale

*Stroke.* 2009;40:2578-2580; originally published online April 30, 2009;
doi: 10.1161/STROKEAHA.109.549014
*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/40/7/2578

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org//subscriptions/