Platelet Survival Time in Patients with Hypoxemia and Pulmonary Hypertension

PETER STEELE, M.D., JAMES H. ELLIS, JR., M.D., HUGH S. WEILY, M.D.,
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SUMMARY Platelet survival time (autologous labeling with 51chromium) was measured in 63 patients in order to evaluate the role of platelets in the thromboembolic complications of patients with hypoxemia and pulmonary hypertension. Thirty-eight of these patients had chronic obstructive airways disease; 13, primary pulmonary hypertension; seven, recurrent pulmonary embolism; four, the Eisenmenger syndrome; and one, multiple pulmonary arteriovenous fistulae. Forty-three patients were hypoxemic and 41 (95%) had shortened platelet survival. Platelet survival was weakly associated with arterial oxygen tension (r = 0.50), but not with the arterial carbon dioxide tension or the level of pulmonary artery pressure. Sulfinpyrazone lengthened platelet survival in 12 of 24 (50%) treated patients but this drug did not alter either arterial oxygen tension, arterial carbon dioxide tension, or pulmonary artery pressure. Our results suggest that hypoxemia is associated with shortened platelet survival time and that platelets may, therefore, be involved in the thromboembolic complications that develop in patients with hypoxemia.

PLATELETS play a major role in thrombosis and, of available platelet tests, platelet survival time has offered the greatest promise for correlation with thrombosis and for identifying which patients may be prone to thrombosis. Drugs which modify shortened platelet survival time may be of therapeutic value in these patients.

We measured platelet survival time in patients with hypoxemia and pulmonary hypertension, disease states often associated with development of thrombosis. Recurrent pulmonary embolism can produce pulmonary hypertension and autopsy evidence of thrombosis within the pulmonary vasculature has been noted in patients with the Eisenmenger syndrome and primary pulmonary hypertension. Cerebral thrombosis is a serious complication in patients with the tetralogy of Fallot. Pulmonary thromboembolism frequently complicates the course of patients with chronic obstructive airways disease. Mitchell and associates observed pulmonary thromboembolism in 36 of 128 autopsied patients with chronic airway obstruction.

Patients

Platelet survival time was measured in 63 patients (54 men, 9 women). Forty-three patients were hypoxemic (arterial oxygen tension < 60 mm Hg on room air) and 19 had normal arterial oxygen. Of the hypoxemic patients 31 had chronic obstructive airways disease, four had congenital heart disease with the Eisenmenger syndrome, seven had primary pulmonary hypertension (with hypoxemia presumably due to right-to-left atrial shunting through a patent foramen ovale), and one patient had multiple pulmonary arteriovenous fistulae. Nonhypoxemic patients included seven with chronic obstructive airways disease, six with primary pulmonary hypertension, and seven with pulmonary hypertension (confirmed at cardiac catheterization) in association with clinically established deep venous thrombosis and multiple pulmonary emboli.

Deep venous thrombosis of the ilio-femoral veins (venographically confirmed) had occurred at least once in four patients with chronic obstructive airways disease and an additional five patients with chronic obstructive airways disease have had recurrent venous thromboses.

Clinical data are presented in table 1. Seventeen patients had congestive heart failure and required diuretics. Fifteen of these had chronic obstructive airways disease and two had recurrent pulmonary embolism. All patients had a normal arterial blood pH.

Patients were studied while in a stable clinical state and at least three months following an episode of venous thrombosis. Twenty-six of the patients with chronic obstructive airways disease have been previously reported. All patients gave their informed consent to performance of these studies and none were taking any drug known to alter platelet reactivity.

Methods

Platelet survival time was measured by labeling the platelets from about 450 ml of the patient's venous blood. Platelet-rich plasma that had been treated with a citrate was incubated with 100-500 μCi of radioactive chromium (51Cr) and reinfused. Platelets concentrated from samples of blood obtained at two to three hours and daily for seven days were counted, and by computer-assisted least-squares analysis, a single exponential was fitted to the count-rate data for determination of platelet survival half-time. In 18 normal subjects platelet survival half-time averaged 3.7 days, with a range of 3.3 to 4.2 days. None of the normal subjects had a platelet survival half-time of less than 3.3 days.

The platelet suppressant drug, sulfinpyrazone, was administered to 24 of the present patients, all of whom were hypoxemic, with shortened platelet survival time in a dosage
of 800 mg per day for three months and platelet survival time measurements were then repeated.

On two separate days during the time that platelet survival was measured, arterial oxygen tension was determined.

Mean values were statistically compared, using Student's t-test.

Results

Of the 63 patients studied, 12 had normal platelet survival half-time (>3.3 days) and 51 had shortened platelet survival. Of the 43 patients who were hypoxemic, 41 (95%) had shortened platelet survival; ten of the 20 (50%) who were not hypoxemic also had shortened platelet survival times.

Platelet survival times for the various groups of patients are presented in table 2. Platelet survival time was significantly different from normal in each of the patient groups (P < 0.001). In patients with chronic obstructive airways disease and primary pulmonary hypertension, in which hypoxemic and nonhypoxemic patients were studied, platelet survival time was significantly shorter in the hypoxemic patients (table 2). In addition to the results in table 2, platelet survival time was 2.0 days in one hypoxemic patient with multiple pulmonary arterio-venous fistula. This patient did not have pulmonary hypertension.

Platelet survival time correlated with the arterial oxygen tension (r = 0.50; N = 63). Platelet survival did not correlate with patient age, sex, the arterial carbon dioxide tension, level of pulmonary artery pressure, hematocrit or arterial pH. Of the 17 patients with congestive failure, platelet survival was shortened in 15.

Sulfinpyrazone was administered to 24 patients with shortened platelet survival, all of whom were hypoxemic (table 3). Sulfinpyrazone significantly increased platelet survival time (2.3 ± 0.10 to 2.7 ± 0.12 days; P < 0.001). One-half of the treated patients had lengthening of platelet survival and in four more (17%) platelet survival time was brought within the normal range. Six patients had no alteration of platelet survival with sulfinpyrazone. Sulfinpyrazone did not alter either the arterial oxygen tension or the level of pulmonary arterial pressure.

Table 1. Clinical Data on the 63 Patients

<table>
<thead>
<tr>
<th>Condition</th>
<th>N</th>
<th>Hypoxemic</th>
<th>N</th>
<th>PAP* (mm Hg) Mean (range)</th>
<th>aCO2t (mm Hg) Mean (range)</th>
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<tbody>
<tr>
<td>Chronic obstructive airways disease</td>
<td>38</td>
<td>31</td>
<td></td>
<td>38/20 (18–86–66/30)</td>
<td>45</td>
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<tr>
<td>Eisenmenger's syndrome</td>
<td>4</td>
<td>4</td>
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<td>118/43 (105–40–130/50)</td>
<td>35</td>
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<tr>
<td>Primary pulmonary hypertension</td>
<td>13</td>
<td>7</td>
<td></td>
<td>95/52 (78–38–165/72)</td>
<td>36</td>
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<tr>
<td>Recurrent pulmonary embolism</td>
<td>7</td>
<td>0</td>
<td></td>
<td>58/32 (47–27–87/49)</td>
<td>36</td>
</tr>
<tr>
<td>Multiple pulmonary arterio-venous fistulae</td>
<td>1</td>
<td>1</td>
<td></td>
<td>20/6</td>
<td>34</td>
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</table>

*Pulmonary artery pressure, systolic/diastolic.

| Arterial CO2 tension. |

<table>
<thead>
<tr>
<th>Disease</th>
<th>N</th>
<th>Hypoxemic</th>
<th>N</th>
<th>PAP* (mm Hg) Mean (range)</th>
<th>aCO2t (mm Hg) Mean (range)</th>
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<td>7</td>
<td>0</td>
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<td>58/32 (47–27–87/49)</td>
<td>36</td>
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Table 2. Platelet Survival Time

<table>
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<th>Condition</th>
<th>PST (days)*</th>
<th>Shortened PST</th>
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<tr>
<td>Chronic Obstructive Airways Disease (N = 38)</td>
<td>2.4 ± 0.12</td>
<td>29 (94%)</td>
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<tr>
<td>Hypoxemic (N = 31)</td>
<td>3.1 ± 0.21*</td>
<td>3 (43%)</td>
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<tr>
<td>Eisenmenger's Syndrome (N = 4)</td>
<td>2.1 ± 0.14</td>
<td>4 (100%)</td>
</tr>
<tr>
<td>Hypoxemic (N = 4)</td>
<td>3.3 ± 0.27**</td>
<td>3 (50%)</td>
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Table 3. Effect of Sulfinpyrazone on Shortened Platelet Survival Time

<table>
<thead>
<tr>
<th>Dx</th>
<th>PAO2 (mm Hg)</th>
<th>PAP (mm Hg)</th>
<th>Het (%)</th>
<th>PST (t-4 days)</th>
<th>Control</th>
<th>SFP</th>
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<td>75</td>
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<td>22</td>
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<tr>
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<tr>
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<td>2.4</td>
<td>3.1</td>
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<tr>
<td>CAO</td>
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<td>66</td>
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<td>3.1</td>
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<tr>
<td>CAO</td>
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<td>48</td>
<td>2.3</td>
<td>3.5</td>
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<td></td>
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<tr>
<td>CAO</td>
<td>48/30</td>
<td>60</td>
<td>3.0</td>
<td>2.1</td>
<td></td>
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<tr>
<td>CAO</td>
<td>54/28</td>
<td>48</td>
<td>2.7</td>
<td>3.1</td>
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<td>49</td>
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<td>3.0</td>
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<td>CAO</td>
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<tr>
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<td>64</td>
<td>0.8</td>
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<tr>
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<tr>
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<td>60</td>
<td>2.0</td>
<td>2.8</td>
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Mean 2.3 2.7

*P < 0.001

Abbreviations: PAO2 = arterial oxygen tension; PAP = pulmonary artery pressure (systolic/diastolic); Het = hematocrit; CAO = chronic airways obstruction; PPH = primary pulmonary hypertension; EIS = Eisenmenger syndrome; SFP = sulfinpyrazone.
Discussion

These data suggest that hypoxemia is associated with shortened platelet survival time. Ninety-five percent of the patients with hypoxemia had shortened platelet survival time. We also found a weak association between platelet survival and arterial oxygen tension. Whether or not pulmonary hypertension is associated with shortened platelet survival time cannot be ascertained from these data. Pulmonary hypertension was present in some degree in every patient studied except the patient with multiple arteriovenous fistulae. Thirteen patients had pulmonary hypertension with normal arterial oxygen tension; seven of them had shortened platelet survival (table 2). These data suggest that non-hypoxemic patients with pulmonary hypertension may frequently have shortened platelet survival, but there are not enough patients in this group to confirm this tendency. Platelet survival time did not correlate with the level of pulmonary arterial pressure for these patients or for the subgroups with or without hypoxemia. Disorders associated with hypoxemia also frequently are associated with an increased pulmonary artery pressure.

The cause of shortened platelet survival time in hypoxemic patients is not clear. Alteration of pulmonary vascular endothelium due to the associated pulmonary hypertension may be responsible for increased platelet adherence. Hypoxemia may produce either platelet injury or, more likely, endothelial injury which could cause increased platelet surface interaction. Other factors that need study include the effect of oxygen administration on platelet survival time in hypoxemic patients with chronic obstructive airways disease, and serial measurement of platelet survival time before and after surgical correction of tetralogy of Fallot, patients who are initially hypoxemic and develop normal oxygen tension after successful surgery. These latter patients have a pulmonary artery pressure which would allow the effects of hypoxemia to be separated from that of pulmonary hypertension.

The finding of shortened platelet survival in hypoxemic patients suggests that the thromboembolic events in these patients may be caused by increased platelet reactivity. Sulfipyrazole lengthens shortened platelet survival time and this drug or another platelet suppressant agent might prevent thrombosis in hypoxemic patients.

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References

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