Impairment in Platelet Aggregation in Congenital Heart Disease

By Harold M. Maurer, Carolyn M. McCue, Joyce Caul, and W. J. S. Still

Platelet function and coagulation studies were performed on 65 children with congenital heart disease (CHD) and five with acquired heart disease, varying in age from 2 wk to 17 yr. Approximately 11% of the children with CHD had mild bleeding symptoms, and 9% had prolonged bleeding times, despite normal platelet counts. In 14 of 37 children (37.8%) with cyanotic CHD and four of 28 (14.3%) with the acyanotic variety, platelet aggregation by adenosine diphosphate (ADP), noradrenalin, and connective tissue suspension was impaired. The possibility of a platelet inhibitory factor in plasma was unlikely. Platelet content of ADP was normal, and high concentrations of exogenous ADP produced an improvement in aggregation, suggesting that the disturbance may be due to defective release of intrinsic ADP from the platelets. Impairment in aggregation was correlated with the severity of hypoxemia and polycythemia in cyanotic patients. Coagulation data did not support the concept that disseminated intravascular coagulation is a frequently associated finding in cyanotic CHD. Our findings reveal a disturbance in platelet function, until now, not commonly associated with CHD.

It is well recognized that children with cyanotic congenital heart disease (CHD) and secondary polycythemia are prone to cerebral thromboses, bruising, and excessive hemorrhage after trauma or corrective surgery. Less well recognized is the fact that children with acyanotic CHD may also have a bleeding disorder, which is usually mild and characterized by a prolonged bleeding time and normal platelet count.1,2,5,8 These disturbances in hemostasis have been difficult to explain and, at times, difficult to manage.

A recent summary of the literature indicates that a variety of hemostatic abnormalities have been found in some patients with cyanotic CHD.4 The abnormalities described include: thrombocytopenia; prolongation of bleeding times, prothrombin times, partial thromboplastin times, and thromboplastin generation times; hypofibrinogenemia; low values for factors V, VII, and VIII; accelerated fibrinolysis;5 and the presence of split products of fibrin. Except for a prolonged bleeding time, no similar abnormalities have been reported in acyanotic CHD.2

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Two recent reports\textsuperscript{6,7} present data that suggest that disseminated intravascular coagulation (DIC) may be the underlying mechanism responsible for abnormal hemostasis in cyanotic patients. On the other hand, several other investigators have found no such evidence in their patients.\textsuperscript{2,4,8-11}

Because of the absence of available investigative techniques, little attention has been paid to the possibility of disturbances in platelet function in children with CHD. The lack of correlation between a prolonged bleeding time and normal platelet count in some of the reported patients\textsuperscript{1-4,25} is highly suggestive of defective platelet function. In a series of 50 patients reported in 1958 by Alagille et al.,\textsuperscript{1} it was shown that the commonest disturbance in CHD, whether cyanotic or not, was a qualitative abnormality of the platelets without thrombocytopenia. Prolongation of the bleeding time, and defective prothrombin consumption and thromboplastin generation were found in these patients.

More recently, Hardisty and Hutton described a 13-yr-old boy with ventricular septal defect, mild bleeding tendency, prolonged bleeding time, and normal platelet count, whose platelets failed to aggregate normally in vitro.\textsuperscript{3} Similar hemostatic abnormalities were described by Hathaway in a child with pulmonic stenosis.\textsuperscript{26}

Our purpose was to investigate platelet function in patients with cyanotic and acyanotic CHD and to correlate the findings with the clinical status. Coagulation studies were also performed with the aim of determining the frequency of laboratory and clinical evidence of DIC.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Total</th>
<th>Surgical Status</th>
<th>Bleeding Symptoms</th>
<th>Bleeding Time</th>
<th>Platelet Aggregation Impaired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetralogy of Fallot</td>
<td>16</td>
<td>No Surgery</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Palliative</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tricuspid atresia</td>
<td>7</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Transposition of great vessels</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Truncus arteriosus</td>
<td>3</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ventricular septal defect and pulmonary hypertension</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cor biloculare, splenic syndrome</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Corrected transposition of great vessels, ventricular septal defect, pulmonic stenosis</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mitral Atresia</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
| Total                                      | 37    | 13              | 21                | 3             | 4                             | 14 (10.8\%) (8.8\%) (37.8\%)
Table 2. Relation Between Clinical Status and Platelet Aggregation Findings in Acyanotic Congenital Heart Disease

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Surgical Status</th>
<th>Bleeding Symptoms</th>
<th>Bleeding Time</th>
<th>Platelet Aggregation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>No Surgery</td>
<td>Palliative</td>
<td>Corrective</td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>14</td>
<td>11</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonic stenosis</td>
<td>6</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonic stenosis, atrial septal defect</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Coarctation of the aorta</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>A-V Canal, partial</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>22</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(10.7%)</td>
<td>(10.7%)</td>
<td>(14.3%)</td>
</tr>
</tbody>
</table>

* Von Willebrand's disease.

CLINICAL MATERIAL

Thirty-seven cyanotic and 28 acyanotic children with CHD, four children with rheumatic valvular disease, and one child with hyperthyroid heart disease were studied. The cyanotic group consisted of 17 males and 20 females varying in age from 2 wk to 16 yr, with a median age of 4 yr. Their cardiac lesions are as shown in Table 1. Arterial oxygen saturation in 26 of the cyanotic children ranged from 50% to 89% with a median of 78%. Oxygen saturation values of 90% or greater were present in seven other children with cyanotic cardiac lesions, four of whom had had prior corrective or palliative surgery. No such data were available in four children.

In the acyanotic CHD group, there were 12 males and 16 females varying in age from 2 to 17 yr, with a median age of 9 yr. The cardiac lesions present in these children are shown in Table 2.

The group with acyanotic acquired heart disease consisted of four males and one female, ages 9-17 yr, with a median age of 12 yr. Their cardiac lesions are shown in Table 3.

Ten of the study patients were on one or more medications at the time of evaluation.
These drugs were digoxin, phenobarbital, quinidine, propranolol, and penicillin. None of the patients had received aspirin or any other drug known to alter platelet function, for at least 10 days prior to study.

MATERIALS AND METHODS

Venous blood for coagulation and platelet function studies, platelet electron microscopy, and platelet adenosine diphosphate (ADP) measurement was collected with a disposable needle and plastic syringe and mixed with one-tenth volume of 4% sodium citrate solution in a plastic tube. For determination of platelet adhesiveness to connective tissue, blood was collected in 1% EDTA in 0.9% saline. Anticoagulant was adjusted proportionally to the packed cell volume (PCV) in polycythemic subjects with PCVs above 45%, using the following formula: X = 100–PCV (patient)/55 where: X = volume of anticoagulant (ml) to which whole blood is added to a final value of 10 ml. At the same time, a sample of blood was obtained for determination of platelet count, clot retraction, and split products of fibrin. Platelet-rich plasma, plasma for coagulation tests, and platelet-poor plasma were obtained by centrifugation as previously described. Platelet counts in platelet-rich plasma were adjusted to approximately 300,000/cu mm by dilution with platelet-poor plasma. Bleeding time was determined by the Duke method. The Ivy method was not used, as we found it difficult to perform reliably in infants and younger children.

The following studies were performed within 3 hr of blood collection: platelet aggregation using an “aggregometer” (Chrono-Log, Broomall, Pa.) attached to a recorder (Model EU-20 V, Heath, Benton Harbor, Mich.), platelet adhesion to connective tissue, adenosine diphosphate (ADP) content of platelets, kaolin-induced platelet factor 3 activity, electron microscopy of platelets, one-stage prothrombin time, partial thromboplastin time with celite, plasma fibrinogen, and split products of fibrin detectable in thrombin-treated sera (microcapillary tube precipitin method using rabbit antiserum to human fibrinogen) (Hyland Laboratories, Costa Mesa, Calif.). All studies were performed at least in duplicate.

Agents used to induce platelet aggregation were adenosine 5'-diphosphate (Sigma Chemical, St. Louis, Mo.), aqueous noradrenalin (Winthrop Laboratories, N.Y.), and connective tissue suspension prepared from human subcutaneous fat, as previously described. "Per cent platelet aggregation" was defined as the per cent change in light transmission of plate-rich plasma 5 min after the addition of aggregating agent, and was calculated as follows:

\[
\frac{T_{5\text{ min}} - T_{PRP}}{T_{PPP} - T_{PRP}} \times 100
\]

Where: \(T_{5\text{ min}}\) = transmission at 5 min after addition of aggregating agent; \(T_{PRP}\) = transmission of platelet-rich plasma; and \(T_{PPP}\) = transmission of platelet-poor plasma.

RESULTS

Four of 37 children (10.8%), from 10 mo to 10 yr, with cyanotic CHD, and three of 28 children (10.7%), ages 3–13 yr, with acyanotic CHD, had symptoms suggesting excessive bleeding (Tables 1 and 2). These symptoms were generally mild and included easy bruising, recurrent petechiae, epistaxis, gingival bleeding, and excessive bleeding after trauma. In one child, blood was found in the pericardial cavity at the time of surgery. In reviewing the records of these patients, as well as those with no bleeding symptoms, no excessive surgical bleeding was noted during either palliative or corrective surgery. In addition, postoperative thrombosis was not a problem.

Duke bleeding times, normally below 5 min in our laboratory, were mildly
Table 4. Relation of Packed Cell Volume and Arterial Oxygen Saturation to Platelet Aggregation in Cyanotic Congenital Heart Disease

<table>
<thead>
<tr>
<th></th>
<th>Normal (23)</th>
<th>Impaired (14)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial O2 saturation (mean±SD)</td>
<td>84.1%±10.3</td>
<td>70.2%±14.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Packed cell volume (mean±SD)</td>
<td>48.5%±9.6</td>
<td>54.0%±8.8</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Number in parentheses indicates number of patients.

Prolonged to up to 6.5 min in one of the symptomatic patients in each of the two groups and in four others, including two cyanotic and two acyanotic patients, with no history of excessive bleeding (Tables 1 and 2).

Packed cell volume ranged from 36 to 71% with a median of 50% in the cyanotic group, and from 29 to 46% with a median of 39% in the acyanotic group. Platelet counts were above 180,000/cu mm in all patients.

Platelet Studies

Forty-seven normal individuals, who had received no medications for at least 10 days, served as controls for platelet aggregation studies. This group consisted of 30 children, between the ages of 2 wk and 13 yr with a median age of 6 yr, and 17 adults. Platelets contained in platelet-rich plasma were aggregated by ADP (final concentration, 4 μM), noradrenalin (final concentration, 20 μM), and connective tissue suspension (1:4 dilution of stock). The mean ± 2 SD for per cent aggregation in normal individuals is shown in Fig. 1.

![Fig. 1. Per cent platelet aggregation 5 min after addition of aggregating agents, adenosine diphosphate (ADP), connective tissue suspension, and noradrenalin, to platelet-rich plasma. Bars represent mean values ± 2 SD in 47 normal individuals. Points represent values found in 70 patients with heart disease.](image-url)
In 18 of 65 patients (27.7%) with CHD, platelets responded poorly to each of the aggregating agents (Fig. 1). The results obtained indicated: (1) a decreased or absent second wave of aggregation with ADP or noradrenalin, following the normal initial wave; and (2) decreased or absent aggregation by connective tissue suspension. Normally, with either ADP or noradrenalin, two waves of aggregation may be observed—the first moderate, and probably due to the direct action of these agents themselves, and the second maximal, and due to the release of endogenous platelet ADP. Aggregation by connective tissue suspension occurs in one wave and is perhaps entirely dependent on the release of platelet ADP.

Impaired aggregation was found in 14 of 37 patients (37.8%) with cyanotic CHD and in four of 28 (14.3%) with the acyanotic variety (Tables 1 and 2). Patients exhibiting this abnormality included all but one (vide infra) of those with bleeding symptoms and/or prolongation of the bleeding time, as well as eight others with normal bleeding times and no history of excessive bleeding. In the cyanotic children, the abnormality was not limited to any single variety of cardiac lesion, but in the acyanotic group two patients had a ventricular septal defect and two had pulmonic stenosis with or without atrial septal defect. The majority (71.4%) of the 14 cyanotic children with impaired aggregation had completed palliative surgery, but none had, at the time of study, been subjected to corrective surgery. With regard to the four children with acyanotic CHD and abnormal platelets, none had undergone any kind of cardiac surgery. In a retrospective review of the hospital records, no operative bleeding or postoperative thrombosis was seen in any of the patients with either normal or abnormal platelet function.

Of the entire group of 18 patients with defective platelets, 16 were 10 yr of age or less. In the cyanotic CHD patients, the median age of the group with defective platelets (14 patients) was identical to that with normal platelets (23 patients), i.e., 4.5 yr. In the patients with acyanotic CHD, the median age of the group of four patients with defective platelets was 6 yr and that with normal platelets (24 patients) was 9 yr. From these data, no conclusions can be drawn with respect to the age dependency of this abnormality, but careful follow-up studies should resolve the question concerning this relationship. Both sexes were equally affected.

Patients in the cyanotic group with defective aggregation had significantly \( (p < 0.01) \) lower arterial oxygen saturations (mean ± SD, 70.2%±14.2), and significantly \( (p < 0.05) \) greater PCV's (mean ± SD, 54.%±8.8) than those in the group with normal aggregation (84.1%±10.3, 48.5%±9.6, respectively) (Table 3).

In three of the patients with impaired platelet aggregation, more concentrated solutions of ADP (final concentration, 20 \( \mu \)M), noradrenalin (final concentration, 40 \( \mu \)M), and connective tissue suspension (stock suspension) were added to their platelet-rich plasmas, and aggregation was recorded. With ADP, the percent aggregation was greatly increased (1.8- to 2.3-fold) over that at lower concentrations, whereas only minimal increases (0.1–0.4-fold) in per cent aggregation occurred at the higher concentrations of the noradrenalin and connective tissue suspension.
To lessen the possibility of a plasma factor inhibitory to platelet aggregation, cross-mixing experiments were carried out in vitro. These studies showed that plasma (0.4 ml) from each of two abnormal patients (one cyanotic and one acyanotic CHD), when incubated for 1 hr at room temperature with platelets (300,000/cu mm) from normal individuals, did not impair the aggregation of these platelets. Conversely, when defective platelets (300,000/cu mm) were incubated with plasma (0.4 ml) from normal individuals, aggregation remained impaired.

The ability of platelets to adhere to connective tissue fragments was estimated by microscopic examination of specimens of EDTA platelet-rich plasma that had been stirred with connective tissue fragments in the aggregometer. Platelets from normal individuals and patients were tested simultaneously and compared. In seven patients studied, including four (three cyanotic and one acyanotic CHD) with impaired platelet aggregation, platelets were seen sticking normally to connective tissue fragments.

Platelet factor 3 activity was studied in 20 patients, including eight (four cyanotic and four acyanotic CHD) with impaired aggregation. All patients showed normal activity.

Platelet content of ADP was determined in seven cyanotic patients with impaired aggregation and 15 normal individuals. The amount of ADP contained in defective platelets (mean ± SE, 27.6±2.9 μM/10⁹ platelets), was not significantly different (p >0.05) from that of normal platelets (26.7±2.0 μM/10⁹ platelets).

Platelets from four patients (three cyanotic and one acyanotic CHD) with impaired aggregation were examined by electron microscopy and found to be morphologically normal.

No clinical or laboratory abnormalities related to hemostasis were found in any of the five patients with acquired disease (Table 3).

Coagulation Studies

plastin time and a factor VIII level of 25% (normal, 50–200%), no other

Except for a 9-yr-old girl with patient ductus arteriosus, who was thought to have von Willebrand’s disease on the basis of a prolonged partial thrombocytagulopathy was found. Prothrombin times, partial thromboplastin times, and clot retraction tests were normal in all other patients.

Five patients with acyanotic cardiac lesions (15.1%) and the same number with cyanotic lesions (13.5%) had plasma fibrinogen levels of less than 200 mg/100 ml, the lowest being 135 mg/100 ml. Split products of fibrin, normally absent, were detected in the sera of five other patients with cyanotic CHD (13.5%). All other coagulation studies were normal in these patients. There was no correlation between the fibrinogen level, the platelet count, and split products of fibrin. Impairment in platelet function also had no correlation with the presence of split products of fibrin in serum.

DISCUSSION

Newly available techniques for investigation of platelet function in hemostasis have shed considerable light on many aspects of platelet behavior and
have resulted in identification of new causes of bleeding. When a vessel is injured and subendothelial basement membrane or connective tissue is exposed, a chain of events is initiated in the flowing blood that leads to thrombus formation. Platelets adhere to exposed basement membrane or collagen. This reaction induces structural and chemical changes in the platelets termed the "release reaction." Platelets swell, and adenine nucleotides, serotonin, catecholamines, hydrolytic enzymes, and platelet factor 4 are released; intracellular organelles disappear, and the rate of platelet glycolysis is increased. Low concentrations of released ADP cause platelets in the vicinity to adhere to one another and, in turn, they release their constituents promoting further platelet aggregation. Thrombin and adrenalin or noradrenalin, like collagen and ADP, can cause aggregation. Aggregation produced by these agents is due almost entirely to the ADP they release from the platelets.

Our survey has revealed the existence of a bleeding disorder, usually mild, in association with cyanotic and acyanotic CHD. Approximately 11% of these patients had mild bleeding symptoms, although, curiously, none appeared to bleed excessively during palliative or corrective surgery. Approximately 9% had slightly prolonged bleeding times despite normal platelet counts. The incidence of prolonged bleeding time in this series is slightly lower than the incidence of 15% in 171 patients with CHD reported by O'Neill and Hutton. Their patients similarly did not appear to have an increased tendency to bleed, either during or after surgery.

Platelet function studies revealed a finding, until now, not commonly associated with CHD: impairment in platelet aggregation in vitro. In 37.8% of patients with cyanotic CHD and 14.5% of those with the acyanotic variety, platelet aggregation by ADP, noradrenalin, and connective tissue suspension was impaired. This abnormality was present in all patients with prolonged bleeding times and in all those with a bleeding tendency (except for the girl with von Willebrand's disease), as well as in some with no history of excessive bleeding or prolongation of the bleeding time. It was associated with a variety of cyanotic cardiac lesions but only with two types of acyanotic cardiac lesions, namely, ventricular septal defect and pulmonic stenosis with and without atrial septal defect. A platelet inhibitory factor in plasma was looked for but was not found. Since platelets must adhere to connective tissue (collagen) before aggregation can occur, a defect in platelet-to-connective tissue adhesion might account for the abnormalities observed. No such defect was observed in any of the patients.

Further studies were carried out in an attempt to clarify the nature of the platelet defect. Defective platelet aggregation in reported patients has been attributed thus far to one of four mechanisms: (1) lack of platelet response to ADP, as is seen in Glanzmann's thrombasthenia; (2) diminished platelet stores of ADP, as is the case in a recently described familial platelet disorder; (3) impairment in release of ADP from the platelet, as is the case following ingestion of large amounts of aspirin; and (4) an unexplained temporary refractory state or decrease in the platelet aggregation response to ADP and collagen, as has recently been noted during major operations.
In our patients, the platelet content of ADP was normal, and high concentrations of exogenous ADP produced an improvement in aggregation; therefore, the disturbance in aggregation may be due to defective release of intrinsic ADP from the platelets. Since our patients were not receiving aspirin or any other kinds of medication known to impair aggregation, we believe that the abnormality is associated with CHD.

Impairment in aggregation was clearly correlated with the severity of hypoxemia and polycythemia in the cyanotic group. Arterial oxygen saturation was significantly lower and PCV higher in those with defective platelets, as compared to those with normal platelets, suggesting that this defect is more commonly associated with severe cyanotic heart disease. Before we can attempt to explain the relation between platelet function and cyanotic CHD, more information is necessary regarding the effect of hypoxemia on platelet production and metabolism. The mechanism for impairment in aggregation in acyanotic CHD also remains unknown.

Coagulation data in our patients, as in other series cited, do not support the concept that DIC is a frequently associated complication of cyanotic CHD. Platelet counts, prothrombin times, and partial thromboplastin times in our patients were normal. Only a few showed either mild hypofibrinogenemia or increased amounts of split products of fibrin in their sera. These scattered abnormalities did not present a meaningful pattern. In our experience, DIC almost regularly produces a pattern of abnormalities consisting of at least thrombocytopenia, hypofibrinogenemia, and detectable levels of split products of fibrin in serum. The prothrombin time and partial thromboplastin time may also be prolonged, due to deficiencies in factors II, V, and VIII.

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