Acquired Decrease in Platelet Secretory ADP Associated With Increased Postoperative Bleeding in Post-Cardiopulmonary Bypass Patients and in Patients With Severe Valvular Heart Disease

By Christina Beurling-Harbury and Carol A. Galvan

The purpose of this study was to assess (1) whether or not cardiopulmonary bypass surgery would decrease platelet secretory ADP, (2) whether or not patients with severe valvular disease have a decrease in platelet secretory ADP, and (3) whether or not such a decrease in secretory ADP is associated with surgical bleeding. Total and releasable platelet ADP and ATP were measured by the luciferase method. Platelet size was measured on a Coulter H4 system. Postoperative bleeding was assessed by volume of chest tube drainage. Pre- versus postoperative assessment of releasable and total ADP and ATP in 66 patients revealed a significant decrease in both (paired t test, p < 0.001). The decrease in secretory ADP was significantly correlated with postoperative bleeding and with duration of bypass. Duration of bypass alone did not correlate with postoperative bleeding. Pre- versus postoperative platelet size did not change significantly; thus large granule-rich platelets were not selectively removed. Forty-three valve patients with disease severe enough to require surgery were compared with 22 concurrent controls; patients had significantly less releasable ADP and ATP, as well as significantly less total ADP (non-paired t test p < 0.01), and total ATP was lower but not significantly different. Thus patients with severe valvular disease also had a decrease in secretory ADP, and this decrease was correlated with surgical and postsurgical bleeding.

It has long been realized that platelet function may be altered during cardiopulmonary bypass surgery. In a preliminary exploration of this problem, we performed Harker bleeding times and aggregation studies on 13 cardiopulmonary bypass patients. Our findings confirmed those of McKenna et al. The bleeding time was unduly prolonged in 77% of patients and collagen aggregation altered in 69%, and the second wave of aggregation in response to 5 μM ADP and 2 μM epinephrine decreased 54%, in each case.

Although these observations confirmed that platelet function may be altered during cardiopulmonary bypass, they do not pinpoint the mechanism of the platelet dysfunction. The abnormalities observed could be due to drugs, anesthesia, hypothermia, or an acquired platelet defect.

Cardiopulmonary bypass surgery subjects circulating platelets to stimulation by the large foreign surfaces in the oxygenator, to stimulation by thrombin potentially formed either in the pump or at the surgical site, and to stimulation by altered intravascular surfaces created by the vascular surgery itself. All of these are potent stimulators of the platelet release reaction. We therefore...
chose to study whether or not there was an intraoperative change in platelet secretory ADP and whether or not such a change, if it existed, correlated with observed postoperative blood loss. Fortunately, the cardiopulmonary bypass patients offered a unique opportunity to assess postoperative blood loss via measurement of chest tube drainage.

Our rationale for determining if an intraoperative decrease in platelet releasable ADP occurred was that platelets as secretory cells secrete the content of their storage granules when stimulated. One of the important release products is ADP, which initiates platelet aggregation and promotes the formation of the hemostatic plug. A decrease in the number of storage granules or a defect in the mechanism that releases the granules can be congenital, acquired in myeloproliferative disorders, or induced by drug ingestion. The defect will usually not produce a severe spontaneous bleeding diathesis but may result in bruising. Bleeding after trauma or surgery is, however, often how these patients are identified. Drugs such as acetylsalicylic acid are known to produce a partial temporary defect in the platelet release reaction. This defect does not produce spontaneous hemorrhage in the normal individual but does statistically increase the amount of bleeding observed after the trauma of surgery. Hemostatically compromised individuals, such as hemophiliacs and, probably, patients receiving coumadin anticoagulants, are thought to have an increased rate of spontaneous bleeding while taking aspirin. It thus appears that a moderate defect in the ability of the platelets to release ADP when stimulated can contribute to postsurgical bleeding in the normal individual and spontaneous bleeding in the hemostatically compromised individual.

MATERIALS AND METHODS

The patient population consisted of all sequential adults going to cardiopulmonary bypass surgery. Patients undergoing reoperations were avoided because adhesions could potentially cause increased bleeding. Routine preoperative coagulation screens consisting of partial thromboplastin times (PTT) and prothrombin times (PT) were normal in all patients. Postoperatively, in the patients with chest tube drainage above and below 400 ml the PTT was 36 and 33 sec, respectively (normal 25-39 sec, control 32 seconds), the PT 37", and 35", respectively, and the prothrombin and proconvertin time 52"", and 55"", respectively. There were no statistically significant differences between the two groups, nor were there any outstanding individual differences. Patients who received platelet transfusions prior to leaving the operating room were excluded because transfused platelets would make the postoperative platelet observations invalid. Studied were 66 patients: 16 with valve replacements, 43 with coronary artery bypass grafts (CABG), and 7 with other miscellaneous procedures. There were 9 aortic valve, 5 mitral valve, and 2 mitral-aortic valve replacements. Of these, one was a reoperation, and that patient was excluded from all assessments of bleeding. The miscellaneous group consisted of patients with a sinus of valsalva aneurysm (1), subaortic muscular stenosis (1), atrial septal defect (1), combined CABG-valve (1), and aortic aneurysms (3). The aortic aneurysm patients were excluded from the evaluation of bleeding, since they sometimes bleed excessively through the graft. An additional 12 patients were studied but were found to have received platelets at the time of chart review. These consisted of 10 valve patients and 2 with CABG. The preoperative samples on an additional 17 valve patients were assessed, yielding preoperative values for 43 valve patients. Assessment of drugs given immediately pre-, intra-, or postoperatively showed no significant correlation with chest tube drainage above and below 400 ml. Twenty-two normal men and women were studied as concurrent controls.

Bypass characteristics. The Bentley and Harvey oxygenators were used during cardiopulmonary bypass. Priming solution was at room temperature, 18°C, at the beginning of the
bypass. Oxygenator blood was not temperature controlled until the latter part of bypass, when warming was started. Mean patient core temperature fell to 32°±2°C. Mean perfusion pressure was 40 mm Hg, and mean flow rate was 2.8 liters/min. There was no filter on the arterial line. At the end of the bypass procedure, heparin was neutralized by protamine using the activated clotting time as a guide.

Blood collection. Nine milliliters of blood were collected into 1 ml of 0.11 M trisodium citrate at room temperature; the tubes were corked and the contents mixed well. The blood was centrifuged at 220 g for 10 min at 22°C. The platelets-rich plasma (PRP) was then taken off using a siliconized Pasteur pipette and mixed well. One blood sample was collected preoperatively and one at 3.25±1.7 hr after the bypass procedure. All samples were processed immediately.

Platelet counting and sizing. Phase and Coulter platelet counts were performed. Instruments included a ZBI Coulter counter with a 5060 aperture (50 μM). 1/amplification = ½, 1/aperture current = ½ (1 ma), lower threshold 10, upper threshold 100; a model H4 signal processor, aperture select 50 μM, exclusion threshold 10, concentration index kept at or below 10⁻⁵; a model H4 data processor with an XY recorder and Data Entry/Recall Terminal. The Coulter Counter H4 system was calibrated using 2.02-μM-diameter latex particles obtained from Coulter Electronics. PRP was immediately diluted into Coulter Isoton for counting and sizing. Three separate dilutions were made of each specimen, and three counts were made on each dilution. The mean SD of this set of observations was 1.5%, of the mean platelet count. Paired Coulter platelet counts on 30 different specimens yielded a mean Coulter platelet count of 242,000/μl and a mean phase platelet count of 238,000/μl. A paired t test showed no significant differences between the Coulter and the phase counts (t = 0.42). The platelet counts ranged from 60,000 to 500,000/μl. In 50 normal controls, the mean platelet volume was 7.22±0.84 cu μM. When 30 separate dilutions were made on single donor PRP and the platelets sized within 15 min, the SD of the mean volume measured was 2.8%. When platelet volume in 16 individuals was assessed on separate specimens over a 7-mo period the percentage deviation from the respective mean platelet volumes was 1.45%, ± 1% (n = 75).

Platelet release and nucleotide extractions. These methods, with minor modification, were as described by Holmsen and co-workers.8,19,20 The release reaction was induced with the most potent agent known, thrombin, to minimize any potential drug effects. Parke-Davis thrombin was used at a final concentration of 20 U/ml. The potential effects of plasma ADPase and ATPase were assessed by incubating samples for 0.5, 1, 2, and 3 min with thrombin. No difference in released ADP and ATP was observed.

Ethanol reagent. 200-proof Rossville Gold Shield alcohol (Commercial Solvent Corp., Agnew, California) was cooled at 0°C; 94.5 ml ethanol was added to a cold 100-ml volumetric flask. Distilled water at 0°C was added to make 100 ml after mixing well at 4°C. This mixture was stored at 4°C for no more than 1 mo.

EDTA reagent (0.1 M) was adjusted to pH 7.4 and stored at 4°C for no more than 1 mo. Immediately prior to the final step in the extraction, nine parts ethanol was mixed with one part EDTA and kept in an ice bath. Glass pipettes were used to measure the desired volume.

Distilled low-fluorescent water was prepared from distilled deionized water redistilled on a double Brinkman glass B1 distiller.

Processing. Aliquots (1 ml) of PRP and PPP were pipetted using Eppendorf pipettes into Eppendorf-Brinkman 1.5-ml plastic test tubes. The test tubes were warmed for 30 sec at 37°C. Then 20 μl of 1000 U/ml thrombin was added to the appropriate test tubes and incubated for 90 sec at 37°C in a shaking water bath. They were then cooled on ice for 5 min. In the thrombin tubes, the clot was reamed. The tubes were centrifuged at 8000 g for 4 min. After EDTA-ethanol extraction, the supernatant was aliquoted into 400-μl Brinkman centrifuge tubes and stored in duplicates at −80°C until assay. The PRP tube, intended for extraction of total platelet ADP and ATP, remained at 22°C until the 0°C EDTA-ethanol was added. It remained on ice for 10 min and was centrifuged and stored in the same manner as the other specimens.

Luciferase assay for ADP and ATP was performed as described by Holmsen and co-workers8,19,20 with no alterations on a DuPont Luminescence Biometer. Luciferase was obtained from DuPont. Pyruvate kinase and phosphoenolpyruvate were bought from Sigma. The ATP
Table 1. Patient Data

<table>
<thead>
<tr>
<th>Population</th>
<th>n</th>
<th>OREBL</th>
<th>RBCTx</th>
<th>CTD</th>
<th>CPBT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABG</td>
<td>43</td>
<td>734 ± 385°</td>
<td>6.5 ± 2.4†</td>
<td>453 ± 398</td>
<td>113 ± 47</td>
</tr>
<tr>
<td>Valve</td>
<td>16</td>
<td>1556 ± 918°</td>
<td>8.5 ± 3.2†</td>
<td>526 ± 264</td>
<td>95 ± 18</td>
</tr>
<tr>
<td>Plot Tx</td>
<td>12</td>
<td>1631 ± 1022</td>
<td>7.1 ± 2.9</td>
<td>411 ± 210</td>
<td>111 ± 27</td>
</tr>
</tbody>
</table>

CABG, coronary artery bypass graft; Valve, valve patients; Plot Tx, platelet-transfused patients; OREBL, operating room estimated blood loss; RBCTx, units of red blood cells transfused; CTD, chest tube drainage (cc)/6 hr; CPBT, cardiopulmonary bypass time (min).

°Nonpaired t test, p < 0.001.
†Nonpaired t test, p < 0.01.

standard was crystalline adenosine 5'-triphosphate disodium salt (Boehringer and Mannheim). It was made up to 10 μM in isotonic NaCl and then extracted with EDTA-ethanol in the manner described. The standard was made into aliquots and stored at −80°C.

Statistical analysis was performed using the χ² test and paired and nonpaired t tests. Deviations are expressed as ± 1 SD.

RESULTS

Assessment of Bleeding

As may be seen in Table 1, operating room estimated blood loss (OREBL) and units of red cells transfused (RBCTx) were notably and significantly greater in valve patients as compared to CABG patients (nonpaired t test, p < 0.0001 and p = 0.01, respectively). This may, in part, reflect the different surgical techniques and the saline used to rinse valves as well as the variable use of red cells to prime the pump and to maintain intravascular volume. Mean chest tube drainage (CTD), on the other hand, was not significantly different in CABG versus valve patients and was used as a gauge of postoperative bleeding in all patients. Bypass time (CPBT) was not significantly different in the two groups. For the total group of 66, CTD was 464 ± 358 cc for the first 6 hr, CPBT was 104 ± 41 min, and RBCTx was 7 ± 2.7 units.

Bypass-induced Platelet Damage

The mean platelet count of PRP preoperatively was 386,000/μl ± 118, postoperatively 214,000/μl ± 87. Using a paired t test, this was a significant drop (p < 0.001, n = 66). As may be seen in Fig. 1, there was a significant decrease in post- versus preoperative total and releasable platelet ADP and ATP. Releasable ADP (nmoles/10⁸ platelets) was 2.15 ± 0.7 preoperatively, 1.51 ± 0.3 postoperatively. Using a paired t test, the intraoperative decrease was significant at p < 0.0001 (t = 8.08). Releasable ATP (nmoles/10⁸ platelets) was 1.38 ± 0.4 preoperatively, 1.0 ± 0.4 postoperatively. Using a paired t test, the intraoperative decrease was significant at p < 0.0001 (t = 7.32). Total platelet ADP (nmoles/10⁸ platelets) was 3.0 ± 0.8 preoperatively, 2.5 ± 0.8 postoperatively. Using a paired t test, the intraoperative decrease was significant at p < 0.0001 (t = 4.39). Total platelet ATP (nmoles/10⁸ platelets) was 5.5 ± 1.3 preoperatively, 4.9 ± 1.1 postoperatively. Using the paired t test, the intraoperative decrease was significant at p < 0.001 (t = 3.52). The ratio of total ATP to ADP was 1.97 ± 0.4 preoperatively, 2.20 ± 0.6 post-
operatively. Using a paired t test, this was a statistically significant change ($p < 0.01$).

Mean platelet volume was measured on 35 patients and was $7.03 \pm 0.5$ cu μm preoperatively, and $7.06 \pm 0.6$ cu μm postoperatively. Using a paired t test, no significant difference in platelet volume could be shown ($t = 0.4$).

**Association of Platelet Damage with Bleeding**

Chest tube drainage was used as a measure of bleeding. Less than 400 cc/6 hr was defined as insignificant bleeding, more than 400cc/ 6 hr as significant bleeding. This cutoff point was chosen because it represented the median chest tube drainage. For the group of 66, the mean for chest tube drainage was $274 \pm 79$ cc below 400 cc, $670 \pm 435$ cc above 400 cc. Nucleotide depletion $\geq 0.5$ nmoles/10⁸ platelets of releasable ADP was significantly associated with
chest tube drainage above 400 cc \( (\chi^2 = 5.79, p < 0.02) \). Since platelet counts below 100,000/\( \mu l \) predispose to bleeding, this population was deleted in order to assess the sole effect of nucleotide depletion. When those patients with postoperative platelet counts above 100,000/\( \mu l \) were analyzed (see Figure 2), \( \chi^2 = 7.92, p < 0.01 \). Thus there was a significant correlation between depletion of releasable ADP and postoperative blood loss. The mean drop in platelet count was not significantly different in those with chest tube drainage above 400 cc as compared to those with chest tube drainage below 400 cc (nonpaired \( t \) test, \( t = 0.81 \)).

**Association of Platelet Damage with Bypass Duration**

A nucleotide depletion \( \geq 1 \text{n mole}/10^8 \text{ platelets} \) of releasable ADP was significantly correlated with duration of bypass (Fig. 3). If the group was divided by bypass times above and below 90 min, \( \chi^2 = 7.97, p < 0.01 \). If the group was divided by bypass times above and below 105 min, \( \chi^2 = 9.05, p < 0.01 \). Bypass time, however, did not correlate with chest tube drainage, OREBL, or RBCTx given.

**Presence of a Platelet Secretory ADP Depletion and a Bleeding Diathesis in Patients with Severe Valvular Disease**

In order to assess whether or not the platelets of patients with sufficiently severe valve disease to require surgery differed from normals, 43 preoperative values of valve patients were compared to those of 22 concurrent normal controls. As may be seen in Fig. 4, mean releasable ADP and ATP were lower in valves as compared to normal controls. Mean releasable ADP for controls was 2.35 \( \pm 0.6 \) and for valve patients was 1.86 \( \pm 0.5 \text{n moles}/10^8 \text{ platelets} \); using a nonpaired \( t \) test, these were significantly different values \( (t = 3.35, p < 0.01) \). Mean releasable ATP for controls was 1.7 \( \pm 0.4 \) and for valve patients was 1.2 \( \pm 0.4 \text{n moles}/10^8 \text{ platelets} \); a nonpaired \( t \) test showed these to be significantly different \( (t = 4.05, p < 0.01) \). Total platelet ADP for controls was
Fig. 4. Bars, releasable and total platelet ADP and ATP in 22 normal controls and 43 preoperative valve patients. There was a significant drop in releasable ADP and ATP and total ADP (nonpaired t test, p < 0.01).

3.3 ± 0.5 and for valve patients was 2.6 ± 0.6 nmoles/10⁸ platelets; a nonpaired t test showed these to be significantly different (t = 4.12, p < 0.01). Total platelet ATP for controls was 5.7 ± 0.8 and for valve patients was 5.3 ± 1.1 nmoles/10⁸ platelets (t = 1.07), not a significantly lower value. Total ATP to ADP ratio for controls was 1.82 ± 0.2 and for valve patients was 2.27 ± 0.6; a nonpaired t test showed these to be significantly different (p < 0.01).

The significant decrease in releasable ADP and ATP and total ADP found in valve patients could potentially put them at greater hazard of bleeding when challenged at surgery. When valve patients were compared to CABG patients and chest tube drainage above and below 400 cc was analyzed by χ² analysis, χ² = 5.12, p < 0.02. Of the 12 patients discovered at chart review to have received platelet transfusion, 10 were valve and 2 were CABG patients. If these were included in the total analysis and considered to be "bleeders," χ² analysis yielded χ² = 11.01, p < 0.001. Units of red cells given and OREBL were also significantly greater in valve patients (p < 0.01; see Table 1). The modest decrease in platelet secretory ADP existing in patients with severe valve lesions may predispose them to bleeding when severely challenged by surgery.

DISCUSSION

Cardiopulmonary bypass exposes platelets to large foreign surfaces, to the potential formation of thrombin in the oxygenator and at the surgical site, and to altered intravascular surfaces created by the surgery itself. This presents major stimuli to the platelets, as evidenced by the well-documented fall in platelet count.¹ The platelets remaining in the circulation are exposed to the same stimuli as those removed. We explored whether or not the platelets remaining in the circulation are less able to undergo the release reaction and release ADP and if such a decrease correlates with the amount of postoperative blood loss. A decrease in the amount of ADP that could be released under maximal thrombin stimulation was indeed found, despite no significant alteration in platelet volume. The decrease in releasable platelet ADP could be hypothesized
as being the selective removal of hemostatically reactive granule-rich platelets of all sizes during cardiopulmonary bypass. This hypothesis presumes that platelets are made in two categories, granule-rich and hemostatically active or granule-poor and less hemostatically active, or, alternatively, that they acquire these characteristics through circulatory stress and strain during their lifespan. Solid evidence to support one or the other of these possibilities does not yet exist. In either case, a platelet containing less secretory ADP would be less hemostatically responsive.

An alternate explanation for the decrease in platelet releasable ADP is that the platelets are stimulated to undergo a partial release reaction during the cardiopulmonary bypass procedure, yet some of them continue to circulate. There is some evidence in vitro and, as yet, little evidence in vivo for the existence of such a mechanism. The study of the function of platelets that have undergone a partial release reaction has been a particular interest of this laboratory and that of Mustard. In vitro the platelets are able to aggregate well, but they are less responsive to stimuli that induce the release reaction. This may therefore make a platelet that has undergone a modest release reaction in vivo less responsive to a repeat physiologic stimulus to secrete ADP. Reimers et al. showed that platelets that underwent a release reaction had a normal life span when reinjected into their animal donors. In thrombocytopenic animals they are less able to shorten the bleeding time than normal platelets, however. These observations indicate that platelets can undergo a release reaction and become partially depleted of secretory ADP yet remain capable of continuing to circulate.

There are two reports of patients thought to have an acquired storage pool deficiency. Zahavi and Marder reported on a patient with an acquired storage pool deficiency in association with circulating platelet antibodies, and Pareti et al. reported on a patient with an acquired storage pool deficiency during disseminated intravascular coagulation.

In patients with a congenital absence of storage granules, there is a large shift in the total ATP to ADP ratio from a normal of 1.93 to approximately 5. This shift is ascribed to the fact that the storage granules concentrate ADP more selectively than ATP, as compared to the platelet as a whole. When normal platelets undergo the release reaction in vitro, their ATP to ADP ratio goes from 1.93 ± 0.4 to 2.91 ± 0.8. Pareti et al. reported a ratio of 2.77 in their patient with disseminated intravascular coagulation. In our patient population, the ratio was 1.97 ± 0.4 preoperatively and 2.20 ± 0.6 postoperatively, a statistically significant increase in the ratio and of a magnitude compatible with the induction of a partial release reaction. The ratio change was, however, also compatible with selective removal of granule-rich platelets of all sizes, if such populations exist.

At present, we have no evidence allowing us to choose between the alternative mechanisms leading to a platelet with fewer secretory granules and less releasable ADP. Whichever is the causative mechanism, the endproduct is a platelet less responsive than the average platelet to a physiologic release stimulus.

The next question is whether or not there is any correlation between platelet
ACQUIRED LOSS OF PLATELET SECRETORY ADP

ADP depletion and observed postoperative bleeding. The patient population studied was weighted against finding such a correlation, since patients with severe hemorrhage had received platelet transfusions and were excluded from the study. After most types of surgery, only extreme degrees of blood loss can be identified, although not quantified. This may well account for the lack of studies showing correlation between postoperative bleeding and platelet function as assessed by the bleeding time and platelet aggregation. Cardiopulmonary bypass patients are unique in that postoperative bleeding is semiquantitatively assessed via the chest tube drainage. This makes it feasible to study if a correlation exists between postoperative bleeding and platelet function. We elected not to study bleeding times, since short bleeding times could be ascribed to peripheral vasoconstriction secondary to hypothermia and long bleeding times could be blamed on potential drug effects and would not define any precise platelet defect. We likewise elected not to study platelet aggregation, since abnormalities, when found, could have many causes. We chose to study quantitatively the amount of ADP the platelet could release under maximal stimulation. This circumvented drug effects and potential effects of hypothermia and pinpointed a single platelet function altered during cardiopulmonary bypass, and it did not exclude the possibility of other associated platelet injuries that could contribute to decreased platelet function. One of these may be a decreased ability to adhere, as was found in a study in vitro by Reimers et al.27

A significant correlation was found between decrease in releasable platelet ADP and chest tube drainage above 400 ml; however, this correlation was not absolute (Fig. 2). Half of the patients with chest tube drainage < 400 ml had ADP depletion, while most but not all of the patients with chest tube drainage > 400 ml had ADP depletion. Thus platelet ADP depletion, and possibly other platelet injuries associated with it, significantly contributed to chest tube drainage above 400 ml in this patient group that excludes patients having received platelet transfusions because of intra- and postoperative hemorrhage. However, these dysfunctions are unlikely to be the sole determinants of bleeding.

Although the 30%, average decrease in releasable ADP appears small when compared to the 70%–100%, decrease seen in congenital storage pool disease, we observed that a 30% decrease was clinically significant in terms of bleeding after major surgical stress. This significance may be interpreted in terms of a densensitized pool of platelets that was either created less responsive to physiologic stimuli with fewer secretory granules or became less responsive with fewer secretory granules during the natural stress of circulation or during cardiopulmonary bypass. Complete depletion of secretory ADP was not observed in this population, nor evidently is it a prerequisite for measurably increasing bleeding after major surgical stress in some patients.

Routine coagulation studies were not significantly different in the patients with chest tube drainage above and below 400 ml. They were similar to those of Bachmann et al. in their study of 512 patients.32

Patients with valvular heart disease severe enough to require surgery had a small but significant decrease in platelet total and releasable ADP when compared to normal controls. This may relate to platelet injury in association with flow over a damaged heart valve and could either represent a depletion of
granule-rich platelets or be the results of a release reaction in vivo with re-circulation of some of the platelets. Harker and Slichter showed that the platelet lifespan in these patients is shortened, confirming that platelet injury and stimulation is occurring. Handin reported increased circulating platelet factor 4, which he interpreted as platelet activation and release in vivo. These valve patients experienced significantly more intra- and postoperative bleeding, which, in part, may have been caused by their modest decrease in platelet secretory ADP and perhaps by other platelet injuries associated with this condition.

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Acquired decrease in platelet secretory ADP associated with increased postoperative bleeding in post-cardiopulmonary bypass patients and in patients with severe valvular heart disease

C Beurling-Harbury and CA Galvan