

CONTINUING EDUCATION

Coagulation and Platelet Function During Cardiopulmonary Bypass Surgery

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Bachmann and coworkers in Chicago have performed a careful study of coagulation parameters after cardiopulmonary bypass surgery.¹ In 512 patients, they found a 4% incidence of postoperative bleeding. More than half of these cases were due to surgically correctable causes. About 2% of the population were considered to be bleeding because of an acquired coagulation disorder. One half of these cases, or approximately 1% of the total population, had an acquired defect in the enzymatic coagulation system, and the remaining 1% had an acquired platelet defect. Twenty-nine patients, or 6% of the total population, were identified by having markedly abnormal coagulation tests. Only four of these bled. Two patients had pre-existing severe congestive heart failure with liver dysfunction. The liver dysfunction was thought to contribute significantly to the postoperative coagulation disorder and bleeding problem. One patient was thought to suffer from heparin rebound, and one patient was thought to have Disseminated Intravascular Coagulation. In general, it was thought that most abnormal coagulation tests were due to heparin rebound. Of interest was the frequent mild-to-moderate abnormality of the prothrombin time, which was not due to specific factor deficiencies. It was speculated that the prolonged prothrombin time was due to an unidentified inhibitor in the prothrombin system, which did not affect the partial thromboplastin time.

Another 1% of the population was thought to be oozing and bleeding from an acquired platelet disorder. The platelet disorder was, however, difficult to define. The authors went on, in a different study, to evaluate 13 consecutive patients undergoing cardiopulmonary bypass surgery.² In particular, they found that the template bleeding time was prolonged in 10 of 13 patients, and that there were platelet aggregation abnormalities. In a preliminary exploration of the problem, we confirmed their observation.³ The Harker template bleeding time was unduly prolonged in 77% of patients, collagen aggregation altered in 69%, and the second wave of aggregation in response to 5 μ M ADP and 2 μ M epinephrine decreased in 54% of patients. Although these observations confirmed that platelet function may be altered during cardiopulmonary bypass, they do not pinpoint the mechanism of the platelet dysfunction. The platelet abnormalities observed could be due either to a drug or an anesthesia effect on platelets, due to the hypothermia or due to an acquired platelet defect. That platelet abnormalities occur during and after cardiopulmonary bypass surgery was recognized early on by Dr. Salzman.⁴ Abnormalities in bleeding times and platelet aggregation confirm his observations, but do not elucidate the mechanism of the platelet abnormality.

The physiologic response of platelets to an injury is first to adhere to the injury site. They then undergo a secretory phase, called the release reaction. The platelets secrete free ADP which in turn make other nearby platelets stick to the platelets which

originally adhered to the injury site. Platelets sticking to each other is called "platelet aggregation" and leads to the formation of the hemostatic platelet plug at the site of injury. The methods presently available for defining specific platelet abnormalities are few. We do not yet have a good *in vitro* assay for platelet adhesion. We do, however, have laboratory techniques for observing platelet aggregation, but these are not sufficiently sensitive to pick up all abnormalities, nor are they able to define what specific aspect of platelet function is altered. In research laboratories, we are able to measure products of the release reaction, such as ADP and ATP. This provides us with an opportunity to test platelets pre- and post-operatively to see whether any change has occurred in the ability of platelets to release ADP, the specific chemical which makes platelets sticky and promotes the formation of the hemostatic plug. It used to be assumed that once platelets had undergone a partial or a full release reaction, they were spent and no longer functional. Work done in our laboratory⁵ and Dr. Mustard's laboratory,^{6,7} has shown that these platelets are functional, but appropriately less capable of releasing any more ADP. Dr. Mustard has also shown that platelets which have undergone the release reaction have a normal life span in rabbits.⁷ These observations encouraged us to study the platelets of cardiopulmonary bypass patients before and immediately after surgery.³ It is unlikely that a 30% depletion of the platelet releasable nucleotide pool would be sufficient to cause any observable spontaneous bleeding diathesis. Under the stress of major surgery, however, increased post-operative bleeding may well result. Both the nature of the surgery and the extensive exposure of platelets to foreign surfaces in the pump, afford plentiful opportunity for platelet activation and possible recirculation of platelets that have undergone the release reaction. An additional attractive feature of cardiopulmonary bypass patients is that post-operative bleeding can be semi-quantitatively assessed via chest tube drainage.

A total of 78 patients were studied pre- and post-operatively. At chart review, it was found that a total of 12 patients had received platelets in the operating room because of bleeding and oozing. These patients were excluded from the study. It is interesting to note that this patient group actually had a lower mean chest tube drainage than the non-transfused group. Patients undergoing repeat thoracotomy were likewise excluded from assessment of post-operative bleeding since these patients are thought to bleed more from dissection of old adhesions.

Pre- and post-operative blood samples were obtained, usually within three hours of the bypass procedure. Platelets were counted by phase microscopy and by a Coulter counter. Platelet volume was determined by a Coulter H-4 system. The release reaction was induced by 20 units/cc of thrombin to insure a maximal stimulus and a maximal release reaction, despite potential prior release reaction. ADP and ATP were measured by the luciferase assay as described by Holmsen. Post-operative blood loss was measured in ml of chest tube drainage over the first six hours. The final patient population consisted of 16 with valvular heart disease, 43 with coronary bypass grafts and seven with congenital lesions, making a total of 66. None of these patients had received platelet transfusions and none could be described as severe bleeders. As has been previously documented, there was a significant fall in the platelet count pre- vs post-cardiopulmonary bypass. The mean pre-operative platelet rich plasma platelet count was 386,000/ μ l, the mean post-operative platelet count was 214,000/ μ l.

One current understanding of platelet physiology considers the young platelet to be large, granule rich and hemostatically active. During a major challenge such as

cardiopulmonary bypass, we would therefore expect this platelet population to become activated. If the activated platelets are removed from the circulation, then we would expect a decrease in the mean platelet volume. We measured mean platelet volume pre- and post-operatively and found no significant change using the paired t test. The mean pre-operative platelet volume was $7.03\mu^3$ and the mean post-operative platelet volume was $7.06\mu^3$. Small individual changes occurred but these consisted of either an increase or a decrease. We can, therefore, not conclude that platelets of a particular volume or size have been removed from the circulation.

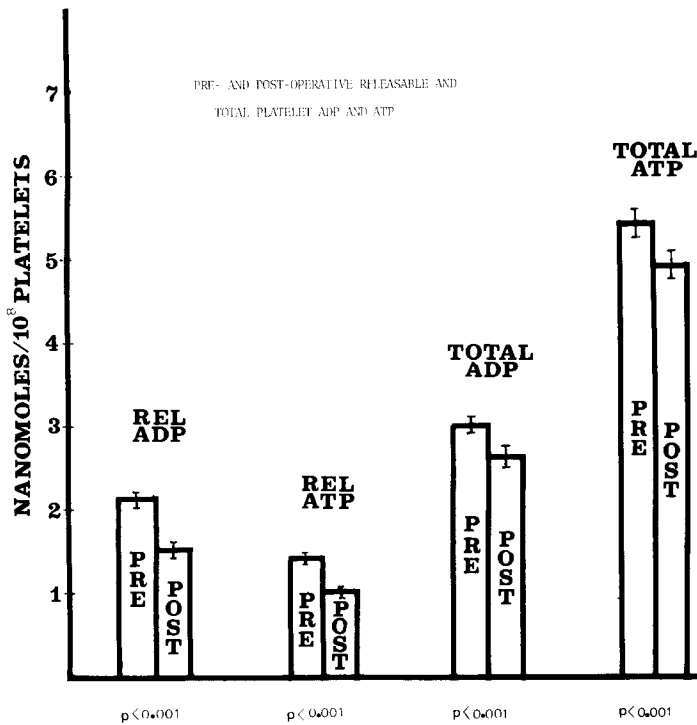


Figure 1

Bars indicate releasable and total platelet ADP and ATP pre- and post-cardiopulmonary bypass surgery in 64 patients. Means \pm 1 standard error are shown. There is a significant drop in all post-operative nucleotide levels (paired t test, $p < 0.001$).

Both releasable and total platelet ADP and ATP (Figure 1) showed a significant decrease pre- versus post-operatively (paired t test $p < .001$). There was a 30% decrease in releasable ADP and ATP post-operatively. This decrease could be due to intraoperative release of ADP and ATP from the platelets. Alternatively, if one postulates that there are granule rich young platelets of all sizes, then the observed decrease could be due to selective removal of young, granule rich platelets. In either case, the remaining platelets are less able to release ADP and induce the formation of a hemostatic platelet plug.

Of interest is whether the decrease in releasable ADP correlates with the degree of post-operative chest tube drainage. The patients were divided into two groups, those who bled more than 400 cc's for the first six hours, those who bled less. Using a X^2 test, we found that blood loss above 400 cc's was significantly correlated with a decrease in releasable ADP of 0.5 nanomoles or more $X^2 = 5.79$ ($p < 0.02$).

Patients with a platelet count below $100,000/\mu^3$ might be expected to bleed more than the average patient on that basis alone. When these patients were excluded from analysis, $X^2 = 8.2$ ($p < 0.01$) (Figure 2). Thus, there was a positive correlation between platelet ADP depletion and amount of post-operative bleeding. We did not find a significant correlation between pre- or intra-operative drugs and bleeding, duration of bypass and bleeding, nor type of oxygenator and bleeding. There was, however, a significant correlation between duration of bypass and ADP depletion of 1 nanomole or more. If bypass procedures above and below 90 minutes are compared, X^2 was 7.97 ($p < 0.01$) and if 105 minutes is used for a cut-off, $X^2 = 9.05$ (Figure 3).

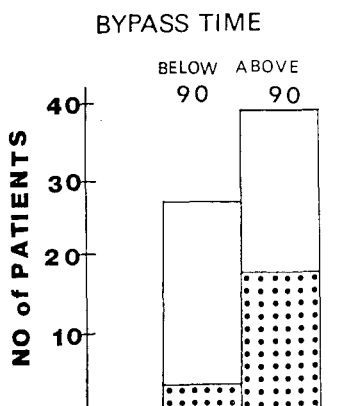


Figure 2

Bars indicate patients with chest tube drainage above and below 400 cc. The dotted area indicates patients with a decrease of 0.5 nanomoles per 10^8 platelets or more of releasable ADP. There is a significant correlation between ADP depletion and chest tube drainage ($X^2 = 7.92$, $p < 0.01$). Patients with postoperative platelet counts below 100,000 level have been excluded.

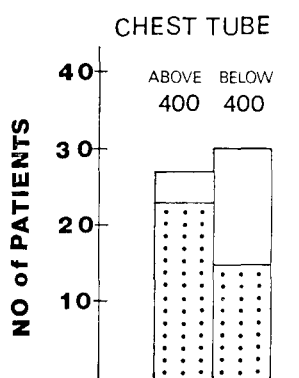


Figure 3

Bars indicate patients with cardiopulmonary bypass time of above and below 90 minutes. The dotted area indicates patients with a decrease of 1 nanomoles per 10^8 platelets or more releasable ADP. There is significant correlation between ADP depletion and bypass duration ($X^2 = 7.97$, $p < 0.01$).

In order to assess whether the platelets of patients with sufficiently severe valve disease to require surgery differ from normals, a total of 43 pre-operative values of valve patients was compared to 22 concurrent normal controls. Flow of platelets over a damaged valve could potentially activate the platelets *in vivo*. As may be seen in Figure 4, mean releasable ADP and ATP are significantly lower in valve patients as compared to normal controls. Total platelet ADP was also lower, but total platelet ATP was not significantly lower in the valve patients.

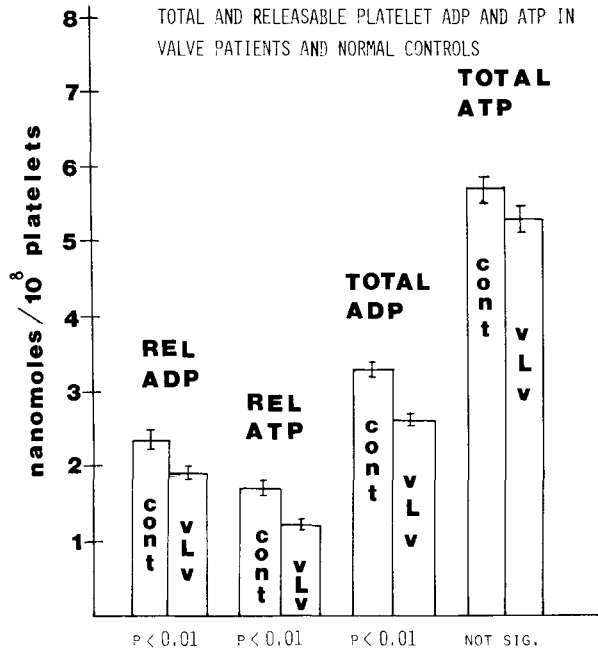


Figure 4

Bars indicate releasable and total platelet ADP and ATP in 22 normal controls and 43 pre-operative valve patients. There is a significant drop in releasable ADP and ATP and total ADP (non-paired t test $p < 0.01$).

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 is analyzed by a X^2 analysis, $X^2 = 5.12$, $p < 0.02$. Of the 12 patients who were discovered at chart review to have received platelet transfusion, 10 were valves and two were CABG. If these are included in the total analysis and are considered to be "bleeders" and X^2 analysis yields a $X^2 = 11.01$, $p < 0.001$. Units of red cells given and OREBL were also significantly greater in valve patients ($p < 0.01$). The modest decrease in platelet secretory ADP existing in patients with severe valve lesions may predispose them to bleeding when severely challenged by surgery.

In summary, pre- versus post-operative 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 post-operative bleeding and with duration of bypass. Duration of bypass alone did not correlate with post-operative bleeding. Pre- versus post-operative platelet size did not change significantly; thus, large granule-rich platelets were not selectively removed. Forty-three valve patients with sufficiently severe disease to require surgery were compared with 22 concurrent controls. There was significantly less releasable ADP and ATP, as well as significantly less total ADP (nonpaired t test, $p < 0.01$). 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 post-surgical bleeding.

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