0.4.1 A. Schmidt Memorial lecture: Acquired Platelet Storage Pool Deficiency: Clinical and Experimental Considerations

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The activation of blood platelets during hemostatic or thrombotic processes does not necessarily lead to loss of their cellular integrity. Even upon secretion of their granular constituents activated platelets can return to the resting state and recirculate with normal survival time. However, these "exhausted" platelets are hemostatically defective due to partial or complete loss of granular constituents and/or metabolic alterations.

Circulating degranulated platelets have been identified in various clinical conditions such as extracorporeal circuits (cardiopulmonary bypass, hemodialysis), artificial heart valve, acute myocardial infarction, myeloproliferative disorders, acute leukemia, autoimmune thrombocytopenia, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, renal allograft rejection, systemic lupus erythematosus, and disseminated intravascular coagulation. In some instances the occurrence of circulating "exhausted" platelets is associated with bleeding. However, the presence of degranulated platelets resulting in an acquired storage pool deficiency is not a constant finding in the aforementioned clinical conditions. Probably, a balance between (1) intensity and duration of action of platelet secretion inducers, (2) platelet removal from the circulation, and (3) production of new platelets from the bone marrow determines the number of circulating "exhausted" platelets.

The evaluation of defects of platelet secretion and acquired storage pool deficiency depends on a number of techniques. Electron microscopy allows the morphological assessment of the various types of storage organelles. Measurement of alpha and dense granule constituents by means of biochemical, radioimmunologic, or radiolabeling procedures is quantitative and more specific. Using these techniques, it could be shown that in certain situations such as after cadiopulmonary bypass or hemodialysis a selective depletion of alpha granule proteins occurs. To further evaluate some of the biochemical alterations of "exhausted" platelets we studied their TxA_2 formation after in vitro stimulation with thrombin or collagen. The TxA_2 synthesis of platelets depleted of 50 % of their alpha and dense granular constituents was impaired. This defect may reflect their previous activation in vivo. However, it is impossible to identify the inducer (e.g. thrombin, immune complexes, subendothelial structures) which acted on the circulating platelets. In this situation thrombin-degranulated platelets may serve as an in vitro model for some types of acquired storage pool disease. Using thrombin-pretreated platelets, we were able to show that the reduced TxA_2 formation upon subsequent stimulation with ADP, collagen, or thrombin again is not caused by inhibition of cyclooxygenase activity. In contrast, experimental findings suggest that the reduced capacity of platelet TxA_2 synthesis is due to depletion of their endogenous pool of arachidonic acid. Thus, it could be demonstrated that thrombin-degranulated platelets reveal normal TxA_2 formation upon stimulation with arachidonic acid. However, it appears important to further examine platelets in vitro whether prostaglandin/thromboxane formation from endogenous arachidonic acid pools can recover, as has been observed in other cells after stimulation.