Effect of Profound Hypothermia on Leukocytes and Platelets

S. A. SHENAQ, M.D.*, D. H. YAWN, M.D.†, A. SALEEM, M.D.‡, R. JOSWIAK, CRNA*, and E. S. CRAWFORD, M.D.§

Departments of Anesthesiology, * Pathology, † and Surgery $ Baylor College of Medicine, Houston, TX 77030

ABSTRACT

Seventeen patients who underwent aortic arch replacement were subjected to profound hypothermia and circulatory arrest. At maximum cooling, platelet count dropped from 184 ± 122 to 37 ± 30 thousand per microliter, and the total leukocytic count fell from 6.27 ± 4.0 to 1.47 ± 0.6 thousand per microliter. The thrombocytopenia was partially reversed with rewarming. The total white cell count consistently returned to precooling values or higher (10.5 ± 4.0). The mechanism for this cold induced phenomenon is not well understood.

Introduction

Hypothermia diminishes tissue metabolism and increases the viability of organs under conditions of ischemia. According to the degree of cooling, hypothermia is classified into mild (37° to 32°C), moderate (32° to 26°C), deep (26° to 18°C), and profound (18° to 13°C). Under profound hypothermia, circulation can be interrupted safely up to 45 minutes. Animal studies have shown that profound hypothermia causes reversible leukopenia and thrombocytopenia. This study was undertaken to determine whether or not this phenomenon occurs in patients subjected to profound hypothermia while on cardiopulmonary bypass.

Methods

The study concerns 17 patients who had repair of aneurysm of the transverse aortic arch (segment of aorta from which the brachiocephalic vessels arise). Repair of this type of aneurysm requires clamping of the brachiocephalic arteries and interruption of cerebral circulation. Profound hypothermia was utilized for protection of the brain during the period of circulatory arrest. Patients were anesthetized with Sublimaze® (fentanyl) 50 to 100 mcg per kg and Valium® (diazepam) 0.3 mg per kg. Pavulon® (pancuronium) 0.1 mg per kg was used for muscle relaxation. Patients were monitored for changes in electrocardiogram and tem-
temperature (rectal, esophageal, and nasopharyngeal). Extensive hemodynamic monitoring was performed with a pulmonary artery catheter. Patients were placed supine and a median sternotomy was performed. After exposure of the heart and the arch aneurysm, heparin (4 mg per kg) was administered to the patient. The pump was primed with plasmalyte® solution of 20 ml per kg. The patients were perfused through a cannula in the femoral artery, and the venous blood was brought to the oxygenator from cannulae in superior and inferior vena cavae. Controlled cooling to 15°C rectal temperature was achieved by cardiopulmonary bypass utilizing an ice water bath in the heat exchange circuit. Cooling rate did not exceed 1°C per minute. After cooling to 18°C (rectal), the pump flow was stopped and the aneurysm was repaired during circulatory arrest.

On completion of the repair, circulation was resumed and the patients were rewarmed at a rate of 1°C per three minutes until a rectal temperature of 38°C was reached. Warming was accomplished by using the heat exchanger of the cardiopulmonary bypass machine. Peripheral blood was collected at each 2°C change in temperature during the cooling and rewarming phases. The initial (baseline) value for peripheral blood white cell and platelet counts was taken at the time the patient had been placed on total cardiopulmonary bypass. This normothermic baseline was selected to allow for effects of hemodilution and the effects of cardiopulmonary bypass, per se, on peripheral blood white cell and platelet counts. Smears of the blood sample were prepared for morphologic examination of platelets and differential white cell counting. The counts were performed utilizing a Coulter Plus 2 Cell Counter®. Platelet size distribution curves were made with platelet counts.

After termination of cardiopulmonary bypass, the heparin was reversed with protamine. All the patients required 12 or more units of platelets to achieve adequate hemostasis. All the platelet counts were taken before the infusion of platelets.

Results

A consistent marked drop in the peripheral white cell count and platelet count was noted with cooling to the 18 to 22°C rectal temperature range. Typical hypothermia induced change in circulating platelet and leukocyte counts is shown in figure 1. The marked leukopenia was due primarily to a decrease in circulating neutrophils, but mononuclear cell counts also dropped. Decreased peripheral platelet counts followed a pattern similar to the decline in peripheral blood leukocytes. With rewarming, however, total peripheral white blood cell

![Figure 1. Typical changes in platelet and leukocyte counts during cooling and rewarming in one patient. The platelet count dropped with cooling and increased with rewarming, but did not achieve baseline value. The white cell count showed a marked drop during cooling and returned to precooling values with an overshoot.](image-url)
count and neutrophil count returned to precooling values with an overshoot observed in the majority of patients. The platelet count increased with rewarming but did not achieve baseline values. Changes in peripheral blood leukocyte and platelet counts are summarized in table I. These changes were statistically significantly from baseline values (p < 0.01) according to t test analysis. Platelet size distribution curves taken during the baseline, cooling and warming periods showed no significant change in platelet size during this period. No platelet aggregates were found in the peripheral blood at the point of maximum cooling.

Discussion

This study documents that there is a consistent drop in peripheral blood platelet and leukocytes in humans subjected to profound hypothermia. Cardiopulmonary bypass and hemodialysis can cause leukopenia apparently due to complement activation, leukocyte aggregation and pulmonary leukosequestration. Mild thrombocytopenia is also associated with normothermic cardiopulmonary bypass procedures. This has been attributed to hemodilution and some degree of platelet injury and consumption in the bypass circuit. This study indicates that hypothermia itself causes a further significant drop in circulating leukocytes and platelets. This effect is additive to the effects of cardiopulmonary bypass per se. The hypothermia induced changes are partially reversible with respect to platelets and completely reversible with respect to circulating neutrophils. The reversible nature of this phenomenon suggests sequestration in the microcirculation. These changes could result from cold induced changes within endothelial cells or changes in adhesiveness of leukocytes and platelets.

Studies reported suggest that cold enhances platelet aggregation and decreases in vivo survival. The physiologic mechanism for this phenomenon has not been documented by us. Moreover we could not document pulmonary sequestration as the platelet and leukocyte counts from the blood withdrawn from the distal port of the pulmonary artery catheter were not different from peripheral blood counts. The majority of patients actually showed a higher white blood cell count after rewarming as compared with initial counts (p < 0.01). This may signify (1) release of white blood cells sequestered in microcirculation (2) release from bone marrow or (3) demargination from vessel walls. Consumption of platelets during bypass and decreased reserves (as compared to leukocytes) may help explain the failure of platelet count to reach precooling values. One patient was subjected to a skin biopsy during the period of maximum cooling. The biopsy studied by routine light and a transmission electron microscopy failed to show intravascular platelet or neutrophil aggregates.

Villalobos investigated the mechanism of cold induced thrombocytopenia and leukopenia in dogs. He induced hypothermia with surface cooling without extracorporeal circulation. By tagging platelets with $p^{32}$, he concluded that the platelets were sequestrated in the liver and spleen. However, Villa-
COLD-INDUCED LEUKOPENIA AND THROMBOCYTOPENIA

Iobos stated that the hepatectomized-splenectomized dog still developed some thrombocytopenia and concluded other areas could be sites of sequestration as well. Future studies should attempt to define the mechanism and site of cold induced sequestration of circulating neutrophils and platelets. This phenomenon is of some clinical importance as it may explain the excess bleeding in patients subjected to profound hypothermia.

References


