Working Group on Perinatal and Paediatric Microcirculation—WGPPM

Lectures

Blood Cell Deformability—Why Does it Matter in Microcirculation?

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The function of microcirculation is to achieve the exchange of gases, fluids and substances between blood and tissues. By decreasing the diameter of the capillaries and the spacing between them the transport processes are made more efficient for two reasons: 1. The same blood volume will have an increased area of contact with the tissue and 2. the transport distance within the capillaries and in the tissues will be minimized (1). However, the smallest calibre of capillaries must still permit the passage of erythrocytes and other blood cells. Red cells with resting diameters of 8µm are able to enter capillaries with diameters of 3µm because of their unique ability to assume various shapes in a very short time. Thus, red cell deformability is an important prerequisite for narrow and closely arrayed capillaries. The time for marked extensional deformation, for the passage of a red cell through a capillary and for deoxygenation is approximately 0.1 s (2, 3). Moreover, red cell deformation accelerates deoxygenation of red cells (2). This may be explained by closer contact of red cells and vessel wall, by a smaller stagnant layer on the cell surface and by mixing of the hemoglobin during cellular deformation.

Red cell deformability also affects platelet aggregation and platelet adherence to the vessel wall (5). Platelet adherence may be increased as a result of decreased red cell deformability, increased red cell size and increased hematocrit. Platelet aggregation at high shear is enhanced by increased red cell deformability and by increased hematocrit.

Cellular deformability determines the ability of the red cell to survive in the microcirculation (3). Rigid cells (e.g., spherocytes, aged red cells) are destroyed in the spleen. In most types of hemolytic anemias, the final destruction of red cells in the spleen is due to impaired cellular deformability.

Which pediatric disorders are associated with both decreased red cell deformability and disturbed microcirculation? The best known example is sickle cell anemia. Irreversible sickled red cells cannot deform at all and, therefore, plug narrow capillaries. Subsequent red cells are blocked, they release their oxygen, become sickled and plug adjoining vessels, thereby initiating a sickle crisis.

Red cells from preterm and term neonates and adults show similar deformability when studies under defined shear conditions (4). Decreased filterability of neonatal red cells is probably due to their larger volume. In neonates, decreased red cell deformability has been observed in septicemia and necrotizing enterocolitis. This may contribute to impaired circulation in these disorders. Moreover, red cells in infants of diabetic mothers are moderately less deformable than in normal neonates.

In children, red cells may be less deformable because of iron deficiency. This may be hazardous if the hematocrit is increased as in patients with cyanotic congenital heart disease. These patients are highly susceptible to cerebrovascular accidents when polycythemia is associated with iron deficiency. Moreover, red cell deformability may be diminished in children with diabetes, hypertension and M. Raynaud and contribute to the long-term vascular complications in these diseases.

Little is known about the meaning of leukocyte deformability (6) for microcirculation. Neonatal leukocytes are less deformable than adult leukocytes when studied by means of micropipettes and filter techniques. There is also evidence that leukocytes become more rigid in neonatal septicemia. Moreover, leukocytes may be involved in the pathogenesis of vascular complication in diabetes and peripheral vascular diseases. In children with leukemia, circulatory problems have been observed when the leukocyte count exceeds 50.000/µl.

Therapeutic approaches to improve disturbed red cell deformability include simple removal of rigid red cells by exchange transfusion. Leukocytes can be removed by leukopheresis or exchange transfusion. Pentoxifilline is the only drug known to decrease the deformability of red cells. At high concentration, it also decreases the rigidity of leukocyte by up to 50% (6). In spite of extensive use of pentoxifilline in adults, no experience appears to exist for pediatric patients.

References

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Refractory Early Anaemia of Prematurity—Recognition, Physiological Basis and Management

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The refractory anaemia of prematurity (REAP) is one of the multiple non-physiological complications of preterm delivery and reflects the inadequacies of the blood oxygen transport system for physiological needs ex utero. These infants depend for a prolonged period on predominantly fetal red cells of poor viability and high oxygen affinity so that haemoglobin concentration and P50 are low (3). This results in low values of 'available oxygen' (2), during the first three or so months after birth. During this period oxygen requirements for growth, notably of the brain, are high and are intensified by cardio-respiratory and infective complications. The inadequacy of the erythropoietic response to hypoxia is partly explained by inappropriately low erythropoietin concentrations, perhaps also a feature of immaturity (1). This haematinic-refractory anaemia would be compounded by hypoxia from other causes and by spontaneous and iatrogenic blood losses in the early weeks of life. The resulting hypoxia is clinically recognisable by increased respiratory and heart rates at rest or on slight exertion, raised oxygen consumption and poor feeding and growth. These symptoms and signs respond to red cell transfusion, the immunological and infective hazards of which are incompletely understood. The longterm clinical effects of impaired oxygen availability in the first months are unknown, for example, on the individual's ultimate intellectual potential.

Objectives in optimising management of REAP

(1) Define adequate 'available oxygen' values by appropriate clinical investigations in preterm infants during the first few months of life, e.g. until one year post-conception.
(2) Seek means of making 'available oxygen' adequate to prevent short-term and any long-term adverse clinical effects. Preferably avoid donor red cell transfusion.
(3) When red cell transfusion is required, e.g. for replacement of investigational blood losses and/or for the prevention and correction of anaemia, avoid hazards of donor red cell transfusion, e.g. immunological and infective.

Possible means of achieving optimal management of REAP (assuming minimal blood losses and optimal haematinic supplies)

(1) Define and secure optimal placento-fetal transfusion on delivery, avoiding circulatory overload!
(2) Collect and store placental blood for autologous replacement of blood losses.
(3) Optimise the newborn's whole-blood and red cell rheological properties to minimise haemolysis and so jaundice, perhaps circulatory stagnation in vivo and certainly anaemia.
(4) Optimise fetal haemoglobin function for oxygen transport.
(5) Study control of timing and rate of fetal to adult erythropoietic switch and of resumption of erythropoiesis after its post-natal shutdown: bring forward adult erythropoiesis in preterm infants. (Drugs may be developed to achieve some of these goals).

Pertinent investigations:

(1) Laboratory and clinical assessment of adequacy of oxygen supply from blood. 'Available oxygen' calculation; erythropoietin assay. Infant's oxygen consumption at rest and under stress, e.g. in a cool environment. Estimation of cardiac output and calculation of mixed venous oxygen tension.
(2) Placental blood. Placento-fetal transfusion - assess blood volume at birth in relation to subsequent anaemia. Placental blood - collect, store and assess usefulness in autologous transfusion to replace investigational blood losses.
(3) Infant's blood's Hb-O_2 dissociation - may be pharmacologically modifiable.
(4) Infant's red cell deformability - assess at birth and prospectively in relation to later rate of fall of Hb concentration and development of jaundice.
(5) Fetal-adult erythropoietic switch. Assess fetal/adult erythropoetic balance at birth and the changes across period of REAP.
(6) Ultimate assessments - long-term studies needed of red cell transfusion and its complications, e.g. immunological and infective, and of the pathological significance of the REAP in influencing the development of the individual's ultimate intellectual potential.

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