Anatomy & Physiology

Zaets, Anatom Physiol 2013, 3:1
http://dx.doi.org/10.4172/2161-0940.1000e122

Editorial Open Access

Do We have Enough Direct Evidence to Postulate that Abnormally Shaped Red Blood Cells Impair Microvascular Blood Flow in Critical Conditions?

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Red blood cells (RBCs) play a key role in microcirculation and oxygen delivery to organ and tissues. This role is determined by their ability to deform and to pass through the vessels that are even smaller than RBC size. There is a close relationship between RBC deformability and its unique disc shape. Under different circumstances, RBC may change their shape and undergo echinocyte, stomatocyte or spherocyte transformation. Echinocytes or stomatocytes are potentially capable to restore the disc shape if they are put in favorable environment (e.g. fresh normal plasma), whereas the spherocyte transformation is considered to be irreversible [1]. *In-vitro* studies using micropore filtration technique demonstrated that normal RBCs (discocytes) have an optimum shape for the flow in microvessels. In contrast to discocytes, stomatocytes and echinocytes produced by adding chlorpromazine or sodium salicylate, respectively, to normal RBCs demonstrated altered passage through circulation [2]. Mechanisms of microcirculatory disorders in critical conditions such as trauma-hemorhagic shock, sepsis or burn have been under investigation for decades. Numerous experimental and clinical studies have proven that these insults cause a significant decrease in RBC deformability [3-11]. Smaller number of publications report RBC shape changes as a result of critical conditions [5,11,12-15]. Experimental studies demonstrated that the number of abnormal (reversibly and irreversibly changed) RBCs after hemorrhagic shock was increased more than five times compared to control values and their proportion to normal discocytes exceeded 30% [5,13]. The similar phenomenon was observed in patients with severe trauma [14]. Linear regression analysis revealed a tight correlation between the percentage of abnormally shaped RBCs and their elongation index, the measure of deformability, in rats subjected to trauma-hemorrhagic shock [5]. The question comes if we have enough direct evidence to postulate that abnormally shaped RBCs impair microvascular blood flow in critical conditions?

Several studies demonstrated that RBCs artificially hardened by various chemicals can cause microcirculatory blockade. Simchon et al. performed exchange transfusions in rats with RBCs with reduced deformability or with sham RBCs [16]. Lowered RBC deformability was achieved by incubation with glutaraldehyde and confirmed by micropore filtration technique. Labeling of RBCs with isotopes made possible their detection in organs and tissues. Experiments showed that poorly deformed RBCs were trapped in spleen, lung, and liver. The degree of flow reduction in these organ compared to control animals (rats subjected to sham RBC transfusion) measured using radioactive microspheres was 77%, 69%, and 54%, respectively and correlated with the amount of trapped RBCs. However, the authors did not investigate the shape of transfused RBCs. Betticher et al. perfused isolated rabbit lungs with stiffened and abnormally shaped RBCs (stomatocytes) [17]. RBC transformation was achieved by adding chlorpromazine. Reduced deformability of RBCs and their shape abnormalities were confirmed by micropore filtration technique and light microscopy, respectively. The authors demonstrated a decrease in pulmonary oxygen diffusion capacity and an increase in the mean pulmonary arterial circulating pressure (both by 18%) as a result of perfusion with abnormal RBCs. It should be stated that in these two aforementioned experiments, abnormal RBCs were produced *in-vitro* but not as a result of a real critical condition. The conclusions received in these two studies were confirmed in "pure" *in-vivo* experiments by Machiedo et al. [18]. The authors performed exchange transfusion in rats with blood obtained animals rats subjected to trauma-hemorrhagic shock or to sham shock. The reduced RBC deformability in rats that experienced trauma-hemorrhagic shock and normal RBC deformability in those who were subjected to sham shock was confirmed by laser ektacytometry. However, the authors did not investigate RBC shape in transfused blood. It was demonstrated that microvascular blood flow in the lungs, spleen, and intestine measured by radioactive microsphere technique was significantly lower in rats subjected to the infusion of trauma-hemorrhagic shock blood than in those that were infused with sham blood.

Our current knowledge suggests that the hypothesis of the important role of critical insult-induced RBC shape changes in the development of microcirculatory disorders in organ and tissues is most likely true. However, there is only indirect evidence. Experimental studies that prove this hypothesis have certain limitations. In some of them, RBCs altered *in-vitro* but not RBCs that became abnormal as a result of a real critical condition modulated *in-vivo* were used to cause a decrease in microvascular blood flow. Other experiments, where blood from animals subjected to trauma-hemorrhagic shock was transfused to recipient animals to induce microcirculatory disorders, did not evaluate RBC morphology in infused blood. Thus additional experiments are still needed to prove direct contribution of RBC shape alterations caused by critical conditions to the development of post-insult microcirculatory disorders. If this hypothesis is confirmed, the next step should be determination of the proportion between reversibly and irreversibly changed RBCs that may cause clinically relevant microvascular blood flow abnormalities.

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Received August 02, 2013; **Accepted** August 05, 2013; **Published** August 08, 2013

Citation: Zaets SB (2013) Do We have Enough Direct Evidence to Postulate that Abnormally Shaped Red Blood Cells Impair Microvascular Blood Flow in Critical Conditions? Anatom Physiol 3: e122. doi: 10.4172/2161-0940.1000e122

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