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Editorial

Platelets and RBCS Changes Underlie Cardiovascular Diseases, in the COVID-19 Era

Bahram Alamdary Badlou

PhD Hematology and Drs. Medical Biology, Cardiology, BBAdvies and Research, Research and Development Dept. Zeist, The Netherlands

***Correspondence to:** Dr. Bahram Alamdary Badlou, PhD Hematology and Drs. Medical Biology, Cardiology, BBAdvies and Research, Research and Development Dept. Zeist, The Netherlands.

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Worldwide all countries are distressed from COVID-19 outbreaks, causing more than 260 million infections, and 5.3 million deaths (and counting). Globally compared, the US, Russia, and European countries have less than 20% population but are suffering from more than 50% death cases (Dec-2021). Different unspecific drugs and (in-)effective vaccines cause extraordinary increased morbidity and mortality rates, of which the exact mechanisms are not elucidated yet.

Platelets (PLTs) play a pivotal role not only in Thrombosis and Haemostasis (T&H), blood clotting, cancerogenic metastatic processes but also in mortal consequences of abused anticoagulants. Nonetheless, PLTs are affected by COVID-19 variants(-vaccines), which is resulting in different uncontrolled and severe clinical episodes, and an increase in morbidity and mortality rates [1].

Pro-atherogenic, (pro-)thrombosis and (pro-)inflammatory processes play a vital role in cardiovascular diseases (CVD), Coronary Artery Diseases (CAD), of which the exact mechanisms are not fully elucidated. Apparently, we are arriving in a COVID-19 era, where Basic scientists and Clinicians have to fully be updated concerning modern and complex diseases separately or occurring simultaneously. Moreover, understanding novel combined processes i.e. Hematoimmunology, Hematooncology function of PLTs and leakage of PLTs factor 4 (PF4), in combination with COVID-19 mutations is not so easy.

Recent studies revealed that antibody epitopes in vaccine-induced immune thrombotic thrombocytopaenia (VITT) [1] and PF4 leakage [2] are occurring due to both COVID-19 variants and associated vaccines.

Important Science-based know-how is focusing on perceptive and rare pathophysiologic processes viz. thromboinflammation, microthromboinflammation, microthromboinfections and heme-microparticles. One might speculate that general knowledge has stopped with microscopic analysis, however; especially concerning PLTs metabolism and rare mutations, while aforementioned PLTs membrane-based disorders, and the VITT processes are changing at nanoscale modifications.

Besides, RBCs play a pivotal role not only in the oxygen transport metabolism, regeneration of tissues, iron metabolism but also in the exacerbation of COVID-19 cardiopulmonary failure (3,4). The main important changes in the RBCs could occur in 1. shape 2. size 3. Proteins and heavy metals contents/composition i.e. Iron, Hb, and 4. their colors. Moreover, Sickle Cell Disease (SCD) is one of the most common hereditary hemoglobinopathies worldwide, affecting almost 400,000 newborns globally each year. It is characterized by chronic hemolytic anemia and endothelial dysfunction, resulting in a constant state of disruption of the vascular system and leading to recurrent episodes of ischemia-reperfusion injury (I/RI) to multiple organ systems [3]. Ansari and Gavins 2019 suggested that the I/RI is a fundamental vascular pathobiological paradigm, and contributes to morbidity and mortality in a wide range of conditions, including myocardial infarction, stroke, acute kidney injury, and posttransplantation. A possible mechanism is that I/RI is characterized by an initial restriction of blood supply to an organ, which can lead to low-flow and/or no-flow ischemia, followed by the subsequent restoration of perfusion and concomitant re-oxygenation [3].

The clinical hallmark of SCD is episodes of acute pain and other common manifestations, including cerebrovascular events, such as transient ischemic attacks, ischemic strokes including silent cerebral infarcts, intracerebral hemorrhages, acute chest syndrome, pulmonary hypertension, bacterial infections, splenic infarcts, and progressive multiorgan's dysfunction syndrome [3-5]. Recall, PLTs and RBCs are very important a- and enucleated blood cells, which both play pivotal roles during COVID-19 infection and its progression, on one hand. On the other hand, people are suffering from combined CVD/ CAD, and newly generated diseases, mainly are suffering from PLTs and RBCs pathophysiologic changes.

Recent (un-)published studies are reporting an atypical decrease in PLTs count in infected COVID-19 patients (a remarkable decrease toward 140000-155000 per microliter), and astonishing mutations in Neutrophils production from the Bone marrow up to matured variants (data under investigation).

Besides, is reported that Neutrophils play a pivotal role not only in the antibacterial defense mechanism but also against COVID-19 manipulations, however. Neutrophils adhere and roll along the endothelium through selectins and integrin's interactions in the direction of blood flow; and are activated by chemokines along with the endothelial layer. They also send activation signals to modulate their phenotype (aged neutrophils) that promotes sickle cell vaso-occlusion [3,4]. (In-)dependently, activated PLTs cause neutrophils to release chromatin and granule proteins to form neutrophil extracellular traps, and might capture sickle-formed RBCs [3]. The subsequent responses consist of continuous accumulation of leukocytes, PLTs, and RBCs interactions, with the (re-)activation of the coagulation factors cascade [3-7]. These interactions may

be mediated by the production of various proinflammatory and prothrombotic mediators, and different coagulating factors [3].

Selectins mediate cellular rolling and adhesion to the endothelium. In particular, endothelial cells, as well as platelet-derived P-selectin, might have a key role in the pathogenesis of vaso-occlusive crises, and P-selectin-mediates adhesion of sickle forming RBCs to vessels wall could assist in the formation of Neutrophil-PLTs satellitism and agglutinates/aggregates [3,7]. As more blood cells become further incorporated and recruited into growing thrombi, fibrin scaffolds are formed. Under T&H's condition, Neutrophils generally produce annexin A1, which counteracts proinflammatory responses and enables potentially antibacterial defense and firmness, in the different phases of vascular immunopathology [3].

There are different drugs to prevent the abovementioned PLTs, RBCs, and Neutrophils pathologic (re-) actions and (ant-)agonistic functions i.e. the RBC ion channel blockers, β-blockers, and mitogen- activated protein/extracellular signal-regulated kinase inhibitors, which could be used for management of acute vaso-occlusive episodes [3]. Antiplatelet agents may reduce inflammatory tone, decrease platelet activation and aggregation, and reduce expression of adhesion molecules and selectins [3]. Anticoagulants, will reduce thromboinflammation and decrease circulating leukocytes and reticulocytes [2,3,7]. Although, why patients with combined diseases suffer less or more than healthy subjects is not clarified as well.

Taken together, the correlation between changes of the enucleated blood cells and occurring CAD/CVD in the COVID-19 era, became so complex that One might speculate that most Scientists are doing (almost) nothing to prevent infected CAD/CVD's patient incidents. Obviously, increased morbidity and mortality rate because of the complexity of too many (un-)known signal transductions, prevent them to take any risks. It seems modern personalized medicine here can be a very handy approach to tackle COVID-19 side effects on the CAD/CVD progression and aggravation.

Bibliography

1. Huynh, A., Kelton, J. G., Arnold, D. M., *et al*. (2021). Antibody epitopes in vaccine-induced immune thrombotic thrombocytopaenia. *Nature, 596*(7873), 565-569.

2. Scully, M., Singh, D., Lown, R., Poles, A., Solomon, T., Levi, M., *et al*. (2021). Pathologic antibodies to platelet factor 4 after ChAdOx1 nCoV-19 Vaccination. *N Engl J Med., 384*(23), 2202-2211.

3. Asadifar, M., Bakhti, M., Habibi-Rezaei, M., Moosavi-Movahedi, A. A., Tabatabi, M, R., Ahmadinejad, M. & Badlou, B. A. (2015). Platelet aggregation increased by advanced glycated hemoglobin. *J Blood Disord Transfus., 6*(4).

4. Ansari, J., Felicity N. E. Gavins. (2019). Ischemia-reperfusion injury in sickle cell disease: from basics to therapeutics. *The American Journal of Pathology, 189*(4), 706-718.

5. Bunn, H. F. (1997). Pathogenesis and treatment of sickle cell disease. *N Engl J Med., 337*(11), 762-769.

6. Luzzatto, L. (2012). Sickle cell anaemia and malaria. *Mediterr J Hematol Infect Dis., 4*(1), e2012065.

7. Ansari, J., Moufarrej, Y. E., Pawlinski, R. & Gavins, F. N. E. (2018). Sickle cell disease: a malady beyond a hemoglobin defect in cerebrovascular disease. *Expert Rev Hematol., 11*(1), 45-55.

8. Ataga, K. I., Kutlar, A., Kanter, J., Liles, D., Cancado, R., Friedrisch, J., *et al*. (2017). Crizanlizumab for the prevention of pain crises in sickle cell disease. *N Engl J Med., 376*(5), 429-439.