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Opinion

Erythrocyte a Target for Covid-19 Infected Patients

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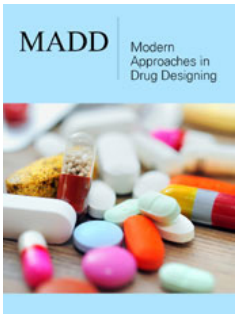

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Abstract

The questions about the Covid-2 and the discussion of the answers are the aim of the present opinion. Facing the great amount of knowledge centered in the field of red blood cells (RBC) or erythrocyte arise the principle for a diagnostic test with efficiency, accuracy, fast and cheap in order to differentiate the infected Covid-19 patients from those that are asymptomatic but with or without the Covid-19. Different results may be obtained and will be here discussed. The signal transduction mechanisms of nitric oxide in the RBC have key points that are therapeutic targets for compounds to apply in infected Covid-19 patients.

Keywords: Blood smears; Erythrocyte membrane band3 protein; Nitric oxide; Microcirculation; Systemic circulation

New Questions and Answers

A pandemic infection among humans appeared through contamination with the SARS-CoV2 Virus (Covid-19) around the world and the majority of dead`s occurs by acute respiratory syndrome followed by irreversible failure in all the organs [1]. Beyond the nose and mouth the eyes are targets for the Covid-19 entrance on the human been [2]. The variety of therapeutic drugs for ocular diseases treatment are used in eye drops formula. Besides its local application and its dimension those enter into the eyes microcirculation and rapidly appear in systemic blood circulation or macrocirculation [3]. The dimension of Covid-19 is lower than the eye drops formula composition known [4].

Recently erythrocyte membrane Band3 protein was identified as the entrance channel for SARS-CoV2 Virus (Covid-19) to inside the RBC [5]. Consequently, arise the question to know if the microscope observation of the human blood smears be the accurate, efficient, fast and cheaper test to identify with confidence the Covid-19 infected people and screening them from those asymptomatic but with the virus from those that have not ? What is the type of interactions occurring inside the RBC between hemoglobin (Hb) molecules or any other the internal biomolecules with each one components of the Corvid-19? These continue to be open questions yet without answer. However, they are also outside of the present opinion. The presence of the Covid-19 inside the erythrocytes increase its internal viscosity which decrease the RBC deformability allow vascular erythrocyte deposition, impair the efflux of oxygen to the endothelial cell wall originating tissue hypoxia installation and decrease of the blood perfusion compromising the blood flow in post capillaries venules [6].

The deoxygenated erythrocytes permanence in microvascular network will develop reactive oxygen and nitrogen species (ROS, NOS) formation with initiation of the acute phase of inflammatory response [7]. If there are a general inflammatory situation in all tissues and organs dead occurs [8]. We have verified in the last century that patients with arterial hypertension, well known as a typical inflammatory disease of blood macrocirculation, also showed microcirculation disturbances in the eyes [9]. The spread of the inflammation process in the systemic circulatory network gathers nowadays consent [10]. The first reported cases of dead with the pandemic disease mention that patients with SARS-CoV2 Virus present lungs destruction [11]. Otherwise in some symptomatic patients disseminated coagulation

was evidenced while others were affected in kidney or in liver and others were infected in nervous system starting suffering with neurological diseases [12]. Those data need to be explained in due time, but all pathophysiological situations have in common the presence of the Covid-19 transported by blood flow inside RBC.

So, taking into account all described above and knowing that the eyes are able to receive the Covid-19 which pass to microcirculation where enter into erythrocyte through membrane band 3 protein comes up the question to know if the microscope observation of the human blood smears may be the accurate, efficient, fast and cheaper test to identify with confidence the presence of Covid-19 in infected people separating them from those asymptomatic where the virus is observed and certificate the absence in those not contaminated? The microscopic observation of blood smears must take into account the viral charge of the patients. So, some could show inside discocyte RBC clearly Covid-19 virus visualization. Otherwise different RBC shapes could be adopted like macrocytes, echinocytes, stomatocytes, spherocytes and acantocytes. Those abnormal RBC shapes have lower ability to reversible deform in order to travel in the capillaries. So, intravascular hemolysis if occurs exposed to the blood flow the RBC internal molecules influent to the disseminated coagulation mechanism observed in some Covid -19 patients [12]. Exovesiculation is a natural occurring process in RBC eryptosis but also can be induced [13,14]. It could be expected to observe in some blood smears RBC with decreased dimensions resulting from exovesicles liberation induced by the presence either of the virus or its own components meanwhile obtained by the action of internal degradative enzymes. Also, it can be observed the presence of reticulocytes as a result of a fast erythropoiesis to null the massive RBC destruction by the advance state of infection of patients without feeling symptoms [15]. If no change erythrocyte shape or neither Covid-19 virus molecules are observed inside RBC in blood smears, a fluorescence label for RNA must be add to the blood samples for fluorescence microscopic observation [16].

Mohandas [17] write that "erythrocyte is more red that dead. At lungs oxygen (O2) enters RBC concomitantly with nitric oxide (NO) and both are delivery from the capillaries at surrounding tissues with lower partial pressure of oxygen [18]. In inflammatory situation vascular endothelial cell are dysfunctional generating reactive oxygen species (ROS) because inducible NO synthase enzyme form substitutes the native constitutive and increasing the NO amount produced [19]. To avoid the oxidative environment, it is necessary to increase the NO scavenger ability of the RBC by reducing or maintaining normal the NO efflux from erythrocyte [20]. So is mandatory to quantify in the first blood samples taken from the Covid -19 patients the NO efflux from RBC using the amperometric method described for the first time, by us [21]. Making those measurements during the patients stay at intensive care units (ICU) help their prognostic evaluation, which could be reinforced by quantification of the blood hemodynamic parameters obtained with a sublingual microcirculatory device [22].

We have observed in patents with amyotrophic lateral sclerosis (ALS) an inverse association between lower levels of NO efflux from erythrocytes and the amelioration of their respiratory function [23]. High plasma fibrinogen (Fib) and high acetylcholine (ACh) concentrations are among other biomarkers of systemic acute phase of inflammation [24,25]. When in ex-vivo studies were performed ACh increase NO efflux from erythrocyte while higher [Fib] did not change it [26,27]. The values of NO efflux maintain in normal range when both Fib and ACh are present at high concentrations [28]. Others in ex-vivo studies showing that ditiotreitol (DTT) and velnacrine maleate both used as therapeutic drugs are able per se to decrease the NO liberation. efflux from RBC reinforcing its scavenger ability [26,29]. In case of high levels of NO efflux from RBC, DTT is better than velnacrine when Covid-19 patients are submitted to the ventilator's machines at ICU. Velnacrine maleate is a strong acetylcholinesterase inhibitor which affect the human cognitive power [30].

Once inside the erythrocyte NO interacts with Hb and becomes able to regulate the uptake and delivery of O2 in function of the tissue oxygen partial pressure [31]. The studies done to modulate the RBC availability in NO, for example when the scavenger of NO is need in inflammatory situations, activators of adenylated cyclase such as forsfokolin (used in obesity and glaucoma treatment) and inhibitors of phosphodiesterase 3 (PDE3) such as phosphoinositol 3 kinase(PI3K) inhibitor wortmannin (WORT) are used [32,33].

NO enter and sort through RBC membrane band 3 protein known as anionic channel bicarbonate and chloride exchange in dependence for example of the of Heinz body formation which close it binding to the cytoplasmic domain of band 3 protein [34]. There are other lipophilic antioxidative drugs like malatonine and others to block the erythrocyte membrane band 3 protein contributing for new views for treatment of the patients infected with SARS-CoV2 Virus [35,36].

Conclusion

In this opinion erythrocyte is present as target for fast test the presence or absence of SARS-CoV2 Virus through observation of the blood smears. Also was suggest the follow-up of the infection progress at IUC looking to the microcirculation hemodynamic parameters using sublingual device in concomitance with the values of nitric oxide efflux from RBC. Some therapeutic drugs acting in the NO signal transduction mechanism erythrocytes by activation of the adenylyl cyclase or inhibition of the phosphodiesterase 3 were suggested. Also compounds that close the dimeric or tetrameric structural forms of membrane protein band 3 have also indicated. Some news scientific contributions are left to which want to forward.

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