Erythrocytes induce vascular dysfunction in COVID-19

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Background: Vascular injury has been implicated as a major cause of clinical complications in patients with coronavirus disease 2019 (COVID-19). Autopsy studies have revealed destruction of the endothelial cell lining, which might explain cardiovascular alterations arising from the infection. However, data demonstrating endothelial dysfunction during ongoing infection are sparse, and the underlying mechanisms are still largely unknown. Red blood cells (RBCs) are affected by COVID-19 with alterations in their structure and function, possibly contributing to vascular injury via increased oxidative stress.

Purpose: To determine the presence of endothelial dysfunction in patients with COVID-19 and to explore the RBC as a possible mediator of such dysfunction.

Methods: The study was performed on 17 patients hospitalized for moderate COVID-19 infection and age- and sex-matched healthy subjects. Inclusion criteria of the COVID-19 patients were PCR-verified SARS-CoV2 infection, pulmonary infiltrates on x-ray, oxygen demand during hospital stay and $\leq$ one cardiovascular co-morbidity. Microvascular endothelial function in vivo was assessed with a pulse amplitude tonometry device on each index finger at baseline and during reactive hyperemia and expressed as reactive hyperemia index (RHI). RBCs from COVID-19 patients (C19-RBCs) and healthy subjects (H-RBCs) were incubated with isolated rat aortic segments for evaluation of endothelium-dependent and -independent relaxation.

Results: COVID-19 patients displayed profound impairment in endothelial function in vivo with RHI 1.56 (1.30–1.81, median and interquartile range) compared to healthy subjects 2.36 (1.97–2.79, $p<0.001$). C19-RBCs induced severe impairment in both endothelium-dependent (27% maximal relaxation) and -independent relaxations (54%) compared to H-RBCs (67% and 95% relaxation, respectively). Further, C19-RBCs induced upregulation of vascular arginase 1 ($\sim$2 fold increase compared to H-RBCs) and markers of oxidative stress ($\sim$6 fold). Consequently, inhibition of vascular arginase or superoxide attenuated the impairment in endothelial function induced by C19-RBCs. C19-RBCs were characterized by increased production of reactive oxygen species ($\sim$1.4 fold) and reduced export of the nitric oxide metabolite nitrate. Following pre-incubation with interferon-γ, but not interleukin-6 or tumor necrosis factor-α, H-RBCs induced impairment in endothelial function.

Conclusions: This study demonstrates the presence of marked endothelial dysfunction in an otherwise mainly healthy patient group hospitalized for COVID-19, and clearly implicates a central role of the RBC as a mediator of endothelial injury through enhancement of reactive oxygen species and arginase. These data shed light on a new pathological mechanism underlying vascular dysfunction in COVID-19 patients and may lay the foundation for future therapeutic developments.

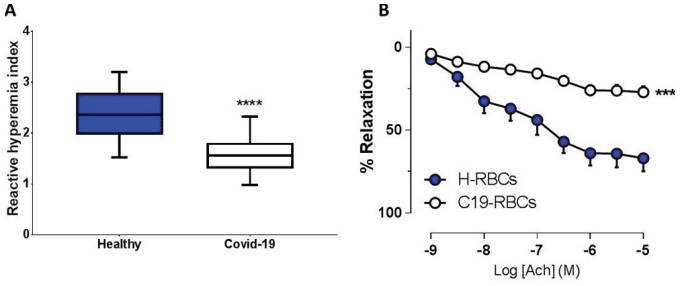

Figure. Microvascular digital endothelial function expressed as reactive hyperemia index (RHI) in healthy subjects and patients with COVID-19 (A, n=14-15 in each group). Endothelium-dependent relaxation (B, n=8-14) evoked by acetylcholine (ACh) in rat aorta following 18h of incubation with red blood cells from either healthy subjects (H-RBCs) or patients with COVID-19 (C19-RBCs). ***p<0.001 vs. Healthy or H-RBCs. Values are expressed as median and IQR (A) or as mean ± SEM (B).