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Letter to the Editor

Importance of the evaluation of systemic microvascular flow and reactivity in critically ill patients with coronavirus disease 2019 — COVID-19☆

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ABSTRACT

Amidst the pandemic that has mesmerized the entire world, as it has not spared anyone according to any specific characteristic, some conditions have, in fact, emerged as risk factors for a complicated evolution of COVID-19. Older age, cardiovascular disease including hypertension, diabetes and pulmonary disease, have been associated with more severe presentations and/or adverse prognosis. In this letter to the editor, we propose that the link between cardiovascular and metabolic diseases and the higher incidence and worse prognosis of COVID-19 patients is the (micro) vascular endothelium.

To the Editor

Recent studies suggested the role of cardiovascular and metabolic diseases on the prevalence and impact in COVID-19 patients in China, including an increased risk of developing more severe complications (Li et al., 2020). Some conditions have, in fact, emerged as risk factors for a complicated evolution of COVID-19, such as older age, cardiovascular disease - including hypertension, diabetes and pulmonary disease - and overweight/obesity, which have been associated with more severe presentations and/or adverse prognosis. In this context, we propose the hypothesis according to which there exists a common link between the invasion of the body by SARS-CoV-2 and pre-existing cardiometabolic diseases: the vascular endothelial cells.

SARS-CoV-2 infects the host cells via the transmembrane angiotensin-converting enzyme 2 (ACE2) receptor, which is expressed in several cell types, tissues and organs, including the endothelial cells (Varga et al., 2020). The cytokine release syndrome (also known as “cytokine storm”), which has been considered a major cause of morbidity and mortality in patients with severe COVID-19, is induced by rapid virus replication and excessive pro-inflammatory cytokine release, including IL-1β, IFN-1 and IL-6, and results in vascular endothelial cell apoptosis (Moore and June, 2020). Moreover, pro-inflammatory cytokines increase the process of vascular inflammation and the expression of leukocyte-vascular endothelium adhesion molecules. This results in endothelial activation accompanied by a pro-coagulant and pro-adhesive phenotype, which is characteristic of the dysfunctional endothelium in the microcirculation, ultimately inducing severe changes in the microvascular flow and, consequently, in tissue perfusion.

Microvascular endothelial dysfunction has long been regarded as both cause and consequence of systemic arterial hypertension, and is an important pathway linking obesity to hypertension. Moreover, there is an association between endothelial dysfunction and type 2 diabetes, impaired glucose metabolism and insulin resistance with the increasing risk of cardiovascular events.

In the context of the critically ill patient in the intensive care unit (ICU), the evaluation of microcirculatory flow and reactivity is of paramount importance, because the mismatch between macro- and microcirculations can be misleading and result in inadequate clinical management of these patients. This concept has stimulated the search for new methods to monitor microcirculatory (tissue) perfusion in the ICU. Laser speckle contrast imaging (LSCI) is a newly-developed non-invasive and real-time technique that allows for the continuous recording of skin microvascular blood flow, that has been proven to be an effective technique for the evaluation of systemic microvascular reactivity in patients with cardiovascular and metabolic diseases (Cordovil et al., 2012). LSCI is typically coupled with physiological or pharmacological local cutaneous vasodilator stimuli, to test endothelium-dependent (micro-iontophoresis of acetylcholine or post-occlusive reactive hyperemia) and endothelial-independent (micro-iontophoresis of sodium nitroprusside) microvascular reactivity. The methodology of non-invasive transdermal drug delivery using low-intensity electric current (iontophoresis) has previously been established (Cordovil et al., 2012). Of note, the cutaneous microcirculation has been considered to be an accessible and representative vascular bed for the assessment of mechanisms underlying microvascular alterations in cardiovascular and metabolic diseases.

Laser-based methods - in this case laser Doppler perfusion monitoring - have been successfully employed during cardiac surgery (Salgado et al., 2014), showing the ability to detect acute changes of microvascular flow. Moreover, similar results can be achieved using additional non-invasive methods, including hand-held sidestream dark field imaging and reactive hyperemia-peripheral arterial tonometry. Therefore, the use of such techniques could be extrapolated to the critically ill patient with severe COVID-19, as multiple pathologic stimuli, together with vasoactive drugs, simultaneously act on the systemic microvasculature, whose true status may be difficult to monitor with conventional, available techniques. Of note, it has already been

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demonstrated, using diverse non-invasive techniques for the evaluation of microvascular flow and reactivity, that peripheral endothelial function is a predictor of future cardiovascular events in different clinical situations (Matsuzawa and Lerman, 2014).

The abovementioned methodologies might offer additional, non-invasive, easy-to-perform and repeatable evaluation of tissue perfusion, thus being ideally suited for the severe COVID-19 patient, who often displays rapid and unpredictable clinical and hemodynamic changes, with long ICU permanence and the need for frequent re-evaluations.

Declaration of competing interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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