Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

Troponin elevation in COVID-19 patients: An important stratification biomarker with still some open questions

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection determines a disease predominantly affecting lungs. Its clinical spectrum is wide, including asymptomatic infection, mild upper respiratory tract illness and severe viral pneumonia leading to respiratory failure and death.

However, heart and vessels can represent other targets of the virus. On this level, SARS-CoV-2 has been associated to many CardioVascular (CV) disorders such as myocardial injury, acute coronary syndrome, pulmonary embolism, myocarditis and arrhythmias.

Focusing on myocardial injury, which is defined as a sudden raise in troponin levels over the 99th percentile, its incidence as a COronaVIrus Disease 19 (COVID-19) related complication ranges from 7.2% to 36% [1].

The article published in this issue of the International Journal of Cardiology by Maino et al. entitled "Prevalence and characteristics of myocardial injury during COVID-19 pandemic: a new role for high-sensitive troponin" [2] provides new data about the link between SARS-CoV2 infection and the damage exerted over cardiomyocites.

Designed as a retrospective single-centre study, in this work the authors analysed 189 patients from the emergency room of "Fondazione Policlinico Universitario A. Gemelli IRCCS" in Rome (Italy) with a COVID-19 diagnosis, in which high-sensitive troponin I levels were measured within the first 24 h from admission. Results confirmed a high prevalence of myocardial damage (16%), which is more common among COVID-19 patients reporting more frequently features of frailty (older age, greater burden of CV comorbidities) and presenting a prominent inflammatory state (higher biochemical levels of inflammation). Furthermore, the multivariate analysis confirmed troponin as one of the most significant determinants of disease severity: higher levels of this biomarker appeared to be in connection with higher prevalence of intensive care unit admission, increased need of endotracheal intubation and higher mortality rate, resulting in a worse intercourse of disease and a poorer outcome.

From the present study and the previously published one [3,4] three questions arise. The first one could be easily answered; the second one may be a little less intuitive; while the latter is definitely much more difficult.

The first question is if the presence of myocardial damage could help identifying a group of COVID-19 infected subjects that present a higher risk for short and long term outcomes. The answer is simply yes. In fact, many similar works [3,4] validate the correlation between high levels of myocardial enzymes and worse outcomes, especially in patients with high-risk factors, such as male gender, old-age and CV comorbidities.

Hence, from a clinical point of view, detecting abnormal troponin elevation whilst the acute phase of COVID-19 could help the selection of high-risk patients requiring stricter cardiac monitoring.

Many possible mechanisms underlying heart injury in the course of SARS-CoV-2 disease has been suggested: direct viral damage in cardmiomyocites; massive inflammatory response triggered by the infection (cytokine storm, endothelial disfunction, microvascular damage, hypercoagulability state); oxygen mismatch (raised metabolic demand during infection in face of a reduced supply due to respiratory failure); increased ventricular strain with myocyte trauma; augmented catecholaminergic response (Fig. 1) [5].

This brings to the second question. Whether the damage on myocardial tissue is due to a direct action of the virus over the heart or it is subsequent to the severe generalised impairment during viral sepsis, is still matter of debate.

While, at the beginning of the pandemic, SARS-CoV2 was supposed to impair openly the CV system, some new findings questioned this idea. A study on tissue biopsies from patients deceased for COVID-19 [6] analysed myocardial samples for the presence of myocarditis, defined as the evidence of multiple foci of inflammation associated to cellular injury. The typical histological picture attributable to myocarditis was present only in 14% of the cases, while the remaining ones showed a diffuse inflammatory infiltrate without a direct myocyte involvement, comparable to cardiac resentment due to critical illness.

Another work [7] found myocardial damage to be common in critical COVID-19 patients, suggesting a connection with worse outcomes. In this, the biochemical and clinical follow-up until 15 days from admission showed that troponin levels were strongly related to inflammatory markers values (C-reactive protein and interleukin-6), possibly implying a nonspecific cytokine-mediated cardiotoxicity.

The last worth mentioning study was published by Jirak et al. [8] In this, myocardial involvement observed during COVID-19 infection was compared to the one developed during critical bacterial pneumonias. Prevalence of heart damage emerged to be less frequent in SARS-CoV2 pneumonias than in other aetiologies (78.1 vs 96.4%, $p = 0.004$), with similar rate of in-hospital mortality (38.2 vs. 51.3%, $p = 0.142$).

Taken together, these results enhance the hypothesis that injured cardiomiocytes in SARS-CoV-2 infection are not a pathognomonic item triggered by the virus per se, but depends both on the severe systemic inflammatory state and the multiple factors previously indicated.

Regardless of its origin, and according also to the results of the work of Maino et al. [2] measurement of serum levels of cardiac enzymes could play a pivotal role in the detection of subjects at high risk of cardiac impairment during the early and the recovery stage of COVID-19, in order to triage (admission to more intensive department), treat

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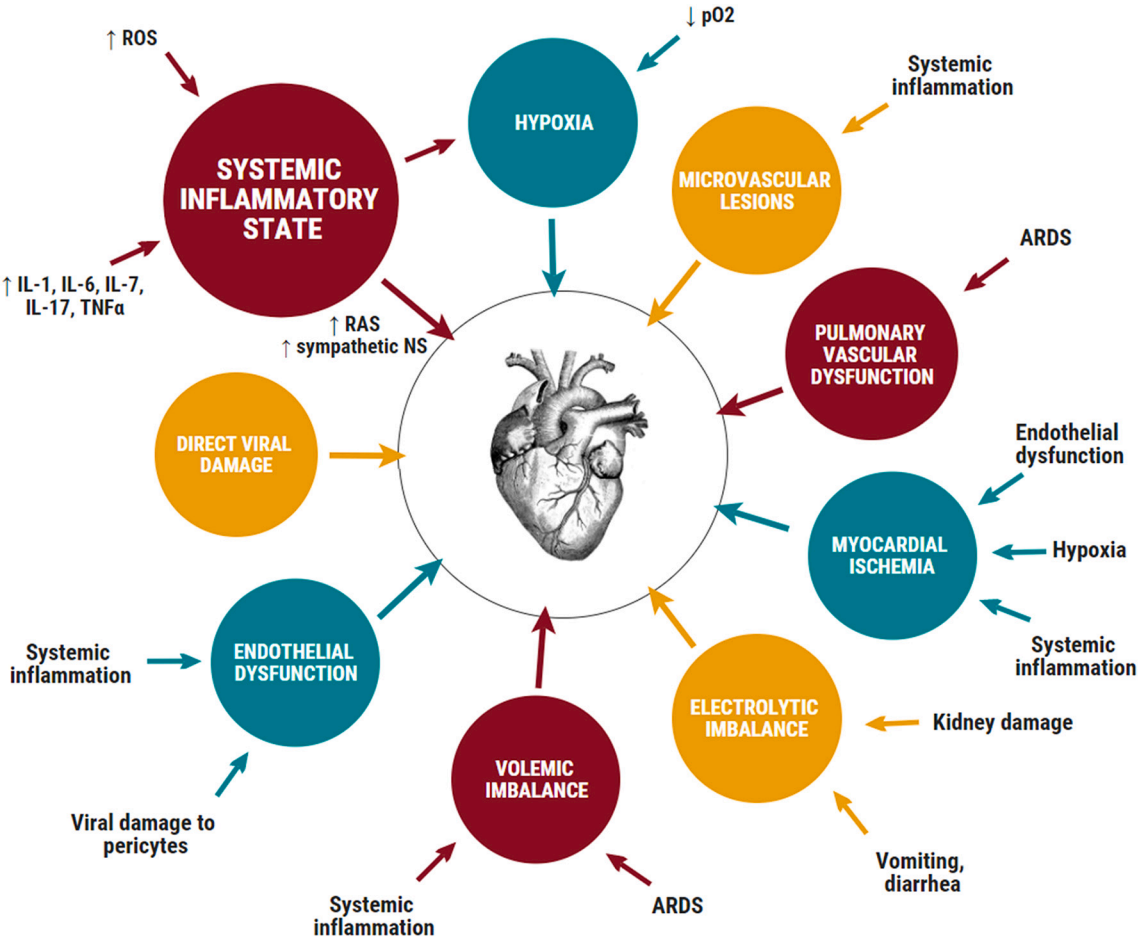

Fig. 1. Possible mechanisms implicated in the myocardial damage during COVID-19 infection. With permission from Ruzzenenti G et al. High Blood Press Cardiovasc Prev. 2021. Epub ahead of print. [5].

and follow-up them properly. Regarding this last point, and the final associated open question, possible long-term consequences of SARS-CoV-2 infection on CV system is something that need to be strongly investigated. Only few papers have been published about vascular and cardiac sequelae of the disease, founding long-term vascular [9] (endothelial dyfunction and arterial stiffning) and cardiac [10] (persistent inflammation at magnetic resonance and diastolic dysfunction at echocardiographic assessment).

However, how long these alterations persist and what is the real clinical value connected with long-term outcomes are still a matter of debate, and definitely require many further studies.

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