SARS-CoV-2 and myocardial injury: a role for Nox2?

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Received: 3 April 2020 / Accepted: 15 April 2020 / Published online: 12 May 2020
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Abstract
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may be complicated by myocardial injury but at-risk patients as well as mechanism of disease are unclear. We gathered data regarding troponin levels in the so far reported SARS-CoV-2 patients and found a large variability in terms of troponin levels, patients with more severe disease, as those treated by ICU, presenting with higher percentage of troponin elevation. However, lack of prospective studies hampers adequate analysis of risk factors of myocardial damage. Previous study demonstrated that Nox2 is up-regulated in pneumonia and closely associated with troponin elevation suggesting Nox2 activation as mechanism eliciting myocardial damage; data in SARS-CoV-2 are still lacking. We hypothesize that SARS-Cov-2 may induce myocardial injury via Nox2-related ROS production and that analysis and eventually targeting Nox2 may be a novel approach to manage SARS-CoV-2.

The outbreak of pneumonia in Eastern and now in Europe and USA by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a serious social issue for the high number of pulmonary complications needing intensive care units (ICU) treatment and for the mortality risk, which is particularly elevated in north Italy. Even if severe respiratory disease is a key factor precipitating poor outcome, other factors could also play a role. Previous study reported that community-acquired pneumonia (CAP) was associated with cardiovascular disease such as heart failure, myocardial infarction and atrial fibrillation and that myocardial damage, as depicted by elevated high-sensitivity cardiac troponin (hs-cTn) T, was detectable in > 50% of CAP patients; CAP severity was among the factors favoring myocardial injury [1]. As troponin elevation is associated with poor prognosis, we reviewed the data so far reported regarding the behavior of troponins in SARS-CoV-2 patients in relation to the disease severity.

We searched the PubMed database without language restriction for studies in human patients published between 2019 and present time, with a combination of text words and Medical Subject Headings, including “troponin”, “troponins”, “myocardial injury”, “laboratory”, “Coronavirus”, “Covid-19”, “2019-nCOV”, “SARS-COV-2”. Initially, 111 documents were evaluated. After excluding papers that did not report data on troponin levels, reviews, commentaries and letters, seven papers were selected, of which one was excluded because data about the prevalence of patients with troponin elevation were not expressly reported.

Of the six selected studies, five were set in China and one in USA and included a total number of 337 patients (Table 1). Myocardial injury was evaluated by cardiac troponin I (cTnI) in all but two, which measured hs-cTnI [2, 3]. Myocardial injury (i.e., troponin levels exceeding the 99th percentile of the upper reference limit) was observed with a prevalence ranging from a minimum 2% to a maximum 44%. In two studies, the prevalence of myocardial injury was compared between patients with severe conditions requiring ICU and patients not-requiring ICU, finding a significantly higher prevalence of troponin elevation in ICU patients. In particular, Wang et al. [4], in a population of 138 hospitalized patients for Covid-19-associated pneumonia, found that myocardial injury was present in 22% of ICU vs. 2% of non-ICU patients ($p < 0.001$); similarly, Huang C et al. [5], in a cohort of 41 patients, found a myocardial injury prevalence of 31% in ICU vs. 4% of non-ICU patients ($p = 0.017$). In three studies that reported data of ICU patients only [6, 7], prevalence of myocardial injury ranged between 14 and 44%; while Liu et al. [2], in a cohort of 30 hospital infected workers, most of them without a severe pneumonia, showed a
prevalence of myocardial injury of 16.7%. Such large difference in terms of troponin elevation may depend on the time of analysis as troponin levels tend to increase by time after admission; accordingly, in patients needed ICU treatment, Arentz et al. [3] reported troponin elevation at admission in 14% of patients, while the occurrence of cardiomyopathies was seen in a larger number (33%) suggesting an even higher incidence of troponin elevation during the ICU treatment.

In ICU patients, myocardial injury may have an important impact on the prognosis of Covid-19-associated pneumonia: Yang et al. [6] found that mortality was 75% in patients with myocardial injury and 42% in patients without; He XW et al. [7] reported an in-hospital mortality significantly higher in patients with myocardial injury than in patients without (61% vs. 26%, respectively, \( p = 0.013 \)). Together these data indicate that myocardial injury is often detectable in SARS-CoV-2 patients with an impact much more evident according with disease severity; thus, the highest percentage of troponin elevation has been reported in patients needed ICU treatment. It is also of interest that patients with troponin elevation were at higher risk of mortality, but this potentially relevant association is biased by small sample size and lack of confounders analysis. Finally, the mechanisms accounting for myocardial injury in SARS-CoV-2 was not investigated and, therefore, it is still unclear.

The study has limitations and implications. The study focused only in the Chinese population and included a small number of subjects. However, the myocardial injury is almost impressive and its impact with clinical outcomes should be studied prospectively. Due to the potentially already reported interplay between myocardial Nox2, cell injury and heart failure (Fig. 1) targeting Nox2 may be an approach to limit myocardial injury in patients affected by SARS-CoV-2. So far, however, there are not drugs in the market which inhibits Nox2; an alternative possibility is the interruption of the vicious circle Nox2 activation -ROS-Nox2 activation, which perpetuates oxidative stress (Fig. 1). In this context, a simple and cheap approach may be provided by intravenous infusion of Vitamin C that behaves as an antioxidant in vivo only at millimolar concentrations. Intravenous infusion of 1 g ascorbic acid resulted in an antioxidant effect that ultimately down-regulate Nox2 activation without eliciting any side effect [11]. Of note, another drug commonly used for arthritis, i.e. tocilizumab, and now under investigation in SARS-CoV-2 patients, behaves also as an antioxidant and may interrupt the vicious circle Nox2-ROS-Nox2.

In conclusion, the data so far reported indicate that patients with SARS-CoV-2 display signs of myocardial injury, which is more evident in patients with severe disease. Prospective study is needed to assess the impact of myocardial injury on clinical outcomes. Nox2 down-regulation may be an option to limit myocardial injury by SARS-CoV-2.

### Table 1 Studies reporting myocardial injury during SARS-CoV-2 infection

| N   | Clinical characteristics                        | Age        | Male (%) | Myocardial injury (%) | Non-ICU (%) | ICU (%) | Mortality (%) |
|-----|-----------------------------------------------|------------|----------|-----------------------|-------------|---------|---------------|
| Wang et al. [4] | 138 Non-ICU: 102 ICU: 36 | 56 (42–68) | 54.3     | 7.2                   | 2           | 22      | 4.3           |
| Yang et al. [6]  | 52 All critically ill ICU patients | 59.7 ± 13.3 | 67       | 23                    | n.a         | 23      | 61            |
| Huang et al. [5] | 41 Non-ICU:28 ICU: 13 | 49 (41–58) | 73       | 12                    | 4           | 31      | 15            |
| He et al. [7]  | 54 Severe/critical conditions                | 68 (60–74) | n.r      | 44                    | n.a         | 44      | 48            |
| Liu et al. [2] | 30 Medical workers, four with severe conditions | 35 ± 8 | 33       | 16.7                  | n.r         | n.r     | n.r           |
| Arentz et al. [3] | 21 ICU admitted patients                              | 79 (43–92) | 52       | 14                    | n.r         | 14      | 52.4          |

n.a. not applicable, n.r. not reported

An important mechanism of cellular injury in SARS-CoV-2 infection is the down-regulation of Angiotensin converting enzyme 2 (ACE2), the functional receptor for SARS-CoV-2, that triggers lung infection upon binding its spike protein to ACE2 [8]. This interaction may lead to ACE2 down-regulation which is potentially deleterious for the heart as ACE2 serves to degrade angiotensin II to angiotensin 1–7, which counteract the angiotensin’s vasoconstrictive activity [8]. Thus, ACE2 down-regulation by SARS-CoV-2 may be a potential trigger for oxidative stress as impaired angiotensin II degradation could lead to activation of Nox2, which is among the most important enzymes generating reactive oxidant species (ROS) [9](Fig. 1). Of note, Nox2 localizes in the heart and rises during the acute phase of CAP [1], independently correlates with troponin elevation [1] and is associated with experimentally-induced heart failure; furthermore, Nox2 independently correlates with heart failure that often complicates CAP [1, 10]. So far, Nox2 has not been measured in SARS-CoV-2 patients; its evaluation might be useful to investigate the mechanism of disease of myocardial injury.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Statements of human and animal rights Not applicable.

Informed consent Not applicable.

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