EDITORIAL

Editorial

The COVID-19 Pandemic: A Challenge for the Cardiovascular Health

Antonio Crisafulli[1,*] and Pasquale Pagliaro[2]

[1]Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy; [2]Department of Clinical and Biological Science, University of Torino, Torino, Italy

INTRODUCTION

It was on April the 24th, 2020, when, together with my past advisor and friend Pasquale Pagliaro, we decided to write this editorial.

The novel aggressive pandemic coronavirus disease (COVID-19), caused by the SARS-CoV-2 virus, first presented as an outbreak in Wuhan (China) on December 12th, 2019 [1], has spread globally and it reached by now to Europe and U.S.A. Its impact on health and economy is unprecedented and unpredictable.

Our country, Italy, was the first among western countries to be interested in this new pandemic. On April 26th, the Italian National Institute of Health [Istituto Superiore di Sanità (ISS), https://www.iss.it/coronavirus] reported 26,644 deaths caused by COVID-19. The median age of deceased people was 79 years, with a prevalence of males (63.3%). Of note, 60.9% patients were with three or more pre-existent pathologies, especially cardiovascular and metabolic diseases. This is in accordance with the findings reporting that, whereas COVID-19 is primarily a respiratory infection, patients with pre-existing cardiovascular and metabolic pathologies experience worse outcomes [2, 3].

Epidemiological studies show that COVID-19 can infect people of all ages, although symptomatic infections are uncommon in the ages between 0-19 years [4]. Moreover, for young individuals, the admission in intensive care units appears to be very rare [5, 6]. The Italian ISS reports 2 dead individuals among under 18 years old COVID-19 patients.

It also appears evident that aging *per se* is a risk factor, with the elderly at higher risk of being infected and of having poor clinical outcomes and prognosis than younger individuals. We still know neither the reason why children are protected from the SARS-CoV-2 invasion nor why elderly are more prone to be invaded by the SARS-CoV-2 and have poorer prognosis.

The main vehicle of the contagion is human droplets with ~5μm diameter generated while talking, breathing, coughing, and sneezing [7]. Droplets spread can be significantly reduced by surgical face masks, which can efficiently reduce the emission of virus particles into the environment [8]. This has important implications for COVID-19 control, suggesting that surgical face masks should be used to counteract the contagion.

One concerning point is that about 25%-50% of infections seem asymptomatic. Asymptomatic transmission of SARS-CoV-2 is actually the Achilles' heel of COVID-19 pandemic control [9]. Therefore, monitoring symptoms alone can not be a good option as a contain measure. Until an effective vaccine or drugs against SARS-CoV-2 become available, the only strategy appears to be the combination of contact tracing, rapid diagnosis, widespread use of surgical masks when outside home, and social isolation [10]. "Lockdown" measures work to decongest hospitals, which otherwise may be deluged with cases of pneumonia, as testified by Chinese and Italian experiences [11]. Fig. (**1**) shows how the total number of COVID-19 cases needing intensive care dropped after the Italian government decided to adopt severe measures to contain the contagion.

The SARS-CoV-2 and the Cardiovascular Apparatus

While it is ascertained that COVID-19 is primarily a respiratory infection, its progression exerts systemic effects and involves several organs and systems, including the immune system, the coagulation, the kidney, and the cardiovascular apparatus. Furthermore, the pathologic process can cause an exaggerated pro-inflammatory cytokine response, thereby triggering a sort of "storm" that is accompanied by high mortality.

COVID-19-induced cardiovascular complications include heart failure, pericarditis, myocarditis, vasculitis, and cardiac arrhythmias [3]. Of note, the combination of vasculitis and prothrombotic state can cause pulmonary embolism [12, 13]. But it is still unknown whether cardiac damage is due to direct viral injury or due to an immunological response, or a combination of both phenomena. It is also still not clear whether the SARS-CoV-2 can directly invade the heart. Indeed, SARS-CoV was found in 33% of human autopsy hearts, with a concomitant marked reduction in cellular Angiotensin Converting Enzyme (ACE2) [14]. Whether the cardiac dysfunction is in part due to the ACE2 reduction is still a matter of intense discussion.

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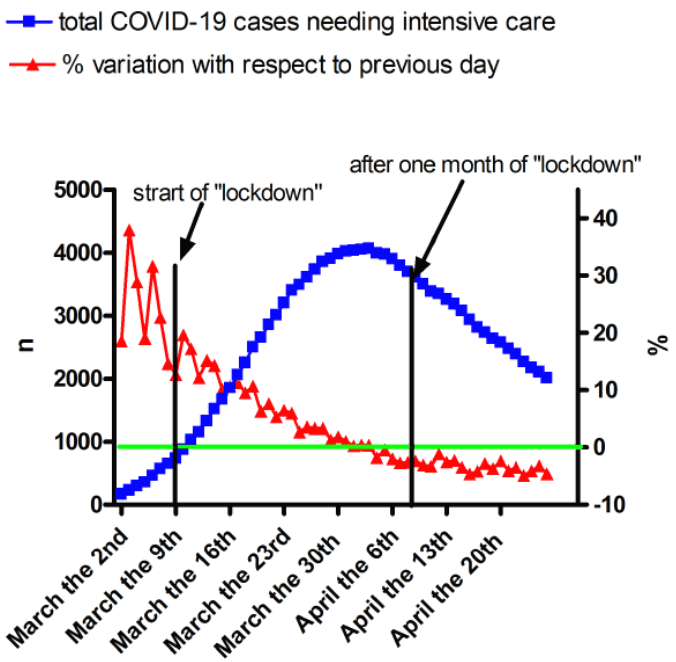

Fig. (1). Number of cases needing intensive care (blue line) in Italy between March, the 2nd and April, the 26th. The red line identifies the % variation of cases with respect to the previous day; the horizontal green line identifies the 0% variation. Two black vertical lines identify the period between the start and one month after the lockdown. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

The SARS-CoV-2 infection has the particularity of being correlated with the Renin Angiotensin System (RAS), which is pivotal in the regulation of saline homeostasis and blood pressure regulation [15]. The classical angiotensin converting enzyme (ACE), and the more recently discovered ACE2, are two important enzymes of the RAS. ACE converts angiotensin I (Ang I) to angiotensin II (Ang II), which is a potent vasoconstrictor, while ACE2 starting from various substrates, leads to the formation of angiotensin 1-7 (Ang 1-7), which exerts a potent vasodilator effect. Thus, ACE and ACE2 products act balancing each other to finely regulate vascular tone and blood pressure homeostasis. Ang II also induces sympathetic nervous activation, reactive oxygen species generation, and endothelial dysfunction. Moreover, it induces inflammation, thrombotic, proliferative, and fibrotic processes. Differently, Ang 1-7 mediates anti-inflammatory, anti-proliferative and anti-oxidative effects [15, 16].

These different effects explain their opposite role in various pathological conditions, such as hypertension, diabetes, and cardiovascular diseases [15, 16]. SARS-CoV-2 uses ACE2 as a cellular receptor to invade target cells. In particular, the spike protein of SARS-CoV-2 virus is processed by transmembrane protease-serine 2 (TMPRSS2), favoring the binding of the spike protein to ACE2 [17]. ACE2 is importantly expressed and active in different tissues such as lungs, intestine, brain, testes, kidneys, and heart and their endothelium [18]. In particular, within the heart ACE2 is expressed by cardiomyocytes, macrophages, fibroblasts, endothelial cells, and pericytes [19]. Therefore, ACE2 plays a role in the mechanisms of acute myocardial and vascular injury caused by SARS-CoV-2.

Of note, sex hormones affect the homeostasis of RAS: both estrogens and androgens, which decrement with aging, have shown to up-regulate ACE2 expression; however, estrogen shifts the system towards the ACE2/Ang 1-7 formation [20, 21]. Although, the ACE/ACE2 activity ratio in the females is lower than that in the male serum, males may have higher expression of ACE2 in the lungs in comparison with females [22].

Contentious results have been obtained in children and teenagers, in whom the expression and activity of ACE2 are unclear [23]. Some evidence suggests that the increased concentration of ACE2 receptors in lung pneumocytes in children may have a protective effect on severe clinical manifestations due to SARS-CoV-2 invasion. This supports a negative correlation between ACE2 expression and SARS-CoV-2 severe outcomes [24]. However, this result is in contrast with recent findings indicating that high expression of ACE2 increased the expression of genes involved in viral replication, and this may enhance the ability of the virus to enter the host cells [25].

Of note, all the pathological conditions that are accompanied by an increase in ACE/ACE2 ratio are comorbidities that exacerbate the Covid-19 outcomes. These include hypertension, ischemic heart disease, and chronic renal failure [4, 26]. Therefore, it is likely that ACE2 down-regulation is a deleterious condition predisposing to Covid-19 exacerbation.

Of particular concern is the use of ACE inhibitors and AT1R Blockers (ARB). These drugs up-regulate the expression of ACE2 [27], thereby theoretically enhancing the chance of virus binding. While it is well ascertained that ACE2 exerts beneficial effects on cardiovascular functions in patients with cardiovascular disease, it is still unknown whether high expression of ACE2 may transform into a sort of “Trojan horse” [28]. However, very recent findings reported that these drugs are not associ-

ated with a poor outcome in hospitalized patients with COVID-19 [29]. Thus, the current recommendation for patients is not to discontinue these medications. Furthermore, it should be considered that the severity of COVID-19 is not related to viremia, but seems more related to the inflammation and cytokine storm.

From the therapeutic point of view, since the COVID-19 depletes ACE2, a potential therapy may be the administration of drugs that activate ACE2, which has anti-inflammatory effects. Potential candidates are diminazene aceturate, resorcinolnaphthalein, and xanthenone [30]. Also, recombinant ACE2 has been proposed in pneumonia [31]. It has also been suggested that a soluble ACE2 could quench the coronavirus by limiting its attachment to cellular ACE2 [32].

The SARS-CoV-2 Pandemic, Physical Activity and ACE2

Cardiovascular consequences of physical activity/inactivity and cardioprotection acquired through exercise are in our field of research and expertise. Therefore, we were particularly attracted by the possible consequences of physical inactivity due to this pandemic.

The notion that physical activity is protective for the cardiovascular apparatus is supported by a great deal of scientific evidence and has become a sort of cornerstone in the history of Medicine.

Regular physical activity has been associated with a significant reduction in total mortality and specifically in cardiac mortality rate [33, 34]. Conversely, an inactive lifestyle is an established risk [35]. To support the concept that regular exercise is a good practice to stay healthy, there is past evidence that physical capacity is a good predictor of increased risk of death from any cause in healthy subjects as well as in patients suffering from cardiovascular diseases [36, 37].

Actually, regular physical activity reduces several risk factors, such as high blood pressure and cholesterol, and improves insulin sensitivity, vascular endothelium functions, and autonomic activity. Moreover, it induces beneficial structural adaptations in the coronary tree [38 - 43]. Exercise probably confers cardioprotection against infarction, with cellular and molecular mechanisms which are still elusive and to be discovered [44 - 46].

In an attempt to hinder the spread of the COVID-19, the Chinese and the Italian governors have been the first to issue decrees that required all citizens to stay home unless they have valid reasons to go to work or markets for food or other documented valid reasons. It is a sort of "quarantine". More and more governments around the world have taken similar measures which have an innumerable series of consequences in everyone's life.

A direct consequence of these life restrictions is their impact on the possibility of being physically active. Several years ago, it was pointed out that cardiovascular diseases would have become the major cause of death in the world as a whole by the year 2020, this also considering sedentary lifestyle as a potential leading cause [47]. The COVID-19 outbreak will probably worsen this forecast because of the reduction in physical activity due to mandatory homestay. The current World Health Organization recommendations on physical activity for health promotion suggest that "Adults aged 18–64 should do at least 150 minutes of moderate-intensity aerobic physical activity throughout the week or do at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week or an equivalent combination of moderate- and vigorous-intensity activity." (https://www.who.int/dietphysicalactivity/factsheet_adults/en/, accessed on April the 26th 2020). It appears evident that it is very difficult to suit these recommendations for citizens in lockdown areas.

Thus, on one hand, the limitation of physical activities is required to counteract the COVID-19 outbreak, and on the other hand, this certainly entails problems related to the interruption or limitation of physical activities. Considering all the proof demonstrating the positive effects of physical activity on the general and cardiovascular health state, it is advisable that during the SARS-CoV-2 pandemic quarantine people keep exercising at home [48]. Good tools to be utilized are stationary bikes, treadmills, arm cranks, rowing machine and any other tool mimicking real outdoor exercise. The use of elastic band and weights allows to preserve muscle tropism, strength and tone. Also useful can be online-driven exercise sessions or the use of videos which avoids the loneliness of exercising alone. Even going up and down the stairs may be a good solution to keep the fitness level at its minimum.

Among other measures, there was the restriction of some outdoor activities, such as running. It is to be highlighted that, during the effort, hyperventilation increases the possibility to spread the virus more than the suggested social distancing of 1.5 m [49], thus to limit outside exercise has a solid rationale. Moreover, in our opinion, the use of masks specifically adapted to high ventilation rates is advisable. In this regard, a study investigating the distance reached by droplets during hard efforts and how masks reduce this distance is warranted. To the best of our knowledge, none has investigated this topic.

An important consideration is related to the fact that regular physical activity affects RAS functioning. Exercise training can shift the balance of the RAS towards the protective arm ACE2/Ang1-7 [50-52]. Since the virus binds to ACE2, the potential over-expression of ACE2 in highly trained athletes may lead to assume that athletes have an increased chance of virus infection. Furthermore, once the body is infected, the SARS-CoV-2 has the capacity to deplete the ACE2. It is then possible that subjects with high expression of ACE2 may be particularly sensitive to RAS perturbation caused by the COVID-19. Although this may result counterintuitive, it is similar to the controversy regarding the ACE inhibitors or angiotensin receptor blockers. Although there are some indications that beneficial effects of ACE2 over-expression may prevail on the putative deleterious effects, these are just hypotheses that deserve attention and require further investigation.

Finally, it would be worth studying in the near future the impact of the "quarantine" on the classical cardiovascular risks factor which is counteracted by physical activity.

CONCLUSION

At the end of this editorial, we are left with few answers and many questions.

This pandemic is a real challenge for all the scientific community. We have to gather together as much scientific information as possible to fight this common enemy. So, it is essential to share information to rapidly find out solutions.

It will probably take months or years to win against the COVID-19.

We are only at the beginning of this battle.

Tonight (April 26th, 2020), the Italian prime minister announced that from May 4th we will be allowed to do physical activities outside the home and in public parks keeping a minimum social distance of 2 meters, so we suggest jogging when the pandemic conditions are improving. We are confident that countless beneficial effects of exercise outweigh all other possible risks.

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Antonio Crisafulli
(*Editor-in-Chief*)
Department of Medical Sciences
Sports Physiology Lab.
University of Cagliari
09124 Cagliari
Italy
E-mail*:* crisaful@unica.it