Commentary

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2019 CORONAVIRUS: What are the implications for cardiology?

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It is the third time, in recent decades, that a zoonotic coronavirus has crossed species to infect human beings. Seventeen years ago, an outbreak of a virus whose RNA sequences closely resemble those of a virus that silently circulates in bats – the so-called "SARS-CoV" – caused severe acute respiratory syndrome with a fatality rate of 9 to 11%. A few years later (2012), the Middle East respiratory syndrome coronavirus – the so-called "MERS-CoV" – had a fatality rate of 34%. For both viruses, age and coexisting conditions such as diabetes or heart disease were independent predictors of adverse outcome.[1]

The same is probably true for the new coronavirus, designated as 2019-nCoV, as it emerged in Wuhan, China, at the end of 2019.[2,3] The virus has since been officially named "*Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)*" by the World Health Organisation (WHO). SARS-CoV-2 infects host cells through angiotensin-converting enzyme 2 (ACE_2) receptors, leading to coronavirus-related pneumonia (COVID-19). So, the same virus can be named 2019-nCoV, SARS-CoV-2 or COVID-19.[4] In the present report, we use the term "COVID-19" as it is now the most common wording.

It has been suggested that COVID-19, in addition to damaging the lungs, may also damage the cardiovascular system.[4] Therefore, it is important to explore the possible damage of COVID-19 to the heart, the role of cardiologists and cardiovascular drugs in the current epidemic (*or pandemic*). This is the aim of the present short report.

Where are we today in relation to COVID-19?

It is impossible to provide any up-to-date data as these change as we are writing. There are breaking news stories every hour, to the point that journals such as "*The New England Journal of Medicine*" have set in place a new series of practices to be applied to all submitted manuscripts describing the COVID-19 outbreak.[5] The only certainty is that the spread is enormous: it has reached more than 100 countries or territories – up from 50 a week earlier.

The *good* news is that COVID-19 appears to be less pathogenic than MERS-CoV and SARS-CoV.[1] The majority of illnesses and deaths are (*were*) in Hubei province, where the city of Wuhan is located, with a rate of death between 0.5 and 2%, which is significantly lower than that of the previous corona infections. Elsewhere, the death rate seems to be higher – around 4–6% – but the rate depends on the number of infected people, which is unknown. Countries that have identified just tens of cases will likely have hundreds more undetected circulating cases. This will lower the death rate. And this, in a way, is *bad* news.

The major SARS-CoV and MERS-CoV casualties were by nosocomial transition in hospital, linked to the use of aerosol procedures in patients with respiratory disease.[6] Nosocomial spread and higher mortality allow effective containment of the virus through syndromic (*fever*) surveillance and contact reduction. On the contrary, a lack of severe disease manifestations, as for COVID-19, reduces the possibility of containing the spread. If infected people remain asymptomatic or mildly symptomatic, they will not end up in healthcare centres or hospitals. Instead, they will continue to go to work, to play sport and to travel, thereby spreading the virus to their contacts, even internationally. This is most likely what has happened with COVID-19, favoured by the global interconnection we have created in our crowded world of 7.8 billion people. The lower pathogeny of a virus, the higher its transmission, particularly when combined with super-spreader events. Ironically, it seems that globalisation induces improvements in commercial and social practices, but it also

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provides ideal environments and opportunities for the zoonotic pathogens to infect human beings.

What is the relation of COVID-19 to cardiovascular disease?

An early report on 99 patients hospitalised from 1 to 20 January 2020 at Jinyntan Hospital, Wuhan, China, for COVID-19 pneumonia, shows that 40% of patients had a previous cardiovascular disease.[7] A second report from the same period on 138 patients hospitalised at Zhongnan University Hospital of Wuhan shows that 26% of the patients required cardiologic intensive care. Of these, 16.7% developed arrhythmias and 7.2% experienced acute coronary syndrome.[8] Some patients with pneumonia due to COVID-19 infection at Wuhan also had an increase in high-sensitivity cardiac troponin I levels, suggesting myocardial injury.[9] In other cases testing positive for COVID-19, cardiac symptoms (*palpitations and chest pain*) were the first manifestations.[4] Other published and anecdotal reports indicate presence of myocarditis, cardiac arrest and acute heart failure. It is not clear whether these cardiac conditions are provoked by COVID-19 or are unspecific complications, typical of any other pathology with higher cardio-metabolic demand. Previous epidemiological studies conducted during the flu epidemic in USA in 1900 show that influenza and its secondary pneumonia may cause myocardial infarction due to inflammation-induced destabilisation of coronary artery plaques.[10] This, in turn, is due to multiple mechanisms such as tachycardia, hypoxia, increased wall stress and thrombophilia or release of inflammatory cytokines.[11] Therefore, a possible causal link cannot be excluded. A similar link with myocardial infarction and acute heart failure was shown for the more recent epidemic of SARS and MERS-n-CoV.[12]

Relation of COVID-19 with renin–angiotensin system inhibitors and anti-inflammatory agents

The COVID-19 infection is triggered by binding of the virus spike protein to *ACE_2*, which allows the penetration of the virus into the epithelial cells of the lungs and, to a lesser extent, the heart. ACE_2 is a homologue of ACE_1, which converts angiotensin I to angiotensin II. An increase of both the endothelial and circulating ACE_1 has deleterious consequences on the cardiovascular system, such as increased blood pressure, progression of coronary atherosclerosis and heart failure. Reduction of ACE_1 with ACE_1 inhibitor is a therapeutic target in hypertension, coronary artery disease and heart failure. The role of ACE_2 in the cardiovascular system is not so clear. It is thought that it plays an antagonist role in the adverse effect of ACE_1, thus exerting a beneficial action. At present, there are no specific therapies involving ACE_2. Considering the importance of ACE_2 in the penetration of COVID-19, a negative link with drugs that may indirectly increase ACE_2 activity has been hypothesised. These drugs are inhibitors of angiotensin II receptors, which are commonly used to treat hypertension. In favour of this hypothesis, there is the fact that hypertension increases the severity of COVID-19 infection. However, against the hypothesis, there is the finding that ACE_2 expression is reduced in hypertension models and that hypertension does not affect other coronavirus infections. Therefore, at present, all the suggestions related to angiotensin receptor blockers and/or ACE inhibitors in the COVID-19 epidemic are not supported by any evidence-based data.[13]

Several anti-inflammatory agents have been proposed to treat COVID-19 infection and, recently, the National Health Commission of the people's Republic of China has added to the fifth edition of the guidelines related to treatment of COVID-19 Tocilizumab, a drug that inhibits interleukin 6 and it is used for rheumatoid arthritis.[14] Again, there are no certainties here, but there is, of course, some hope, and clinical trials are just starting.

What lessons does COVID-19 provide to cardiologists?

Cardiac patients should not avoid, in case of recurrences or any real worsening of their health status, referring to a cardiac centre for fear that the infection will be discovered. The majority, if not all, of hospitals have put in place a safe, separate pathway.

Specific protocols should be developed for the management of acute myocardial infarction in the context of the COVID-19 outbreak. Taking a careful epidemiological anamnesis, measuring the fever and searching for pulmonary lesions before starting primary angioplasty is mandatory. This will drive enhanced personal protection and ensure post-procedural sufficient sterilisation and adequate follow-up of patients who may need isolation. Similar information should also be acquired by telephone before admitting patients for elective procedures. The current coronavirus outbreak could also offer the stimulus for the implementation of telehealth programs for the care of cardiac patients. Most hospitals will be unprepared to manage the intense and sudden request of beds dedicated to the treatment of severe respiratory failure and will, if necessary, try to convert other wards for the treatment of those infected. This emergence might involve all

Table 1. Effects of the COVID-19 pandemic in the cardiologic community.

Organisational aspects	Emotional/psychological aspects	Clinical/scientific aspects
■ Changing professional priorities ■ Reorganisation of cardiologic wards to areas dedicated to critically ill patients ■ Reorientation of daily activities towards COVID-19 patients	■ Sense of unpreparedness and inadequacy ■ Fear and anxiety ■ Feeling of "suspended time" ■ Changing personal/familiar priorities	■ Awareness of cardiologic complications during and after infection ■ Contribution to scientific research on new antiviral/anti-inflammatory drugs

cardiologic intensive care units, not to manage cardiovascular complications of the viral infection, but to offer beds for treatment of the severe respiratory failure caused by viral interstitial pneumonia. The net effect of this reorganisation is that elective cardiothoracic surgeries and interventional procedures will be postponed. Thus, this viral emergency could have detrimental effects on the entire health system.

How relevant are vaccinations for patients and cardiologists in the era of COVID-19?

The absence of the – *tremendously needed* – vaccine for COVID-19 offers the opportunity of becoming aware of the waste that patients and doctors make when they remain vaccine-free for influenza and/or pneumococcus, despite these vaccines being readily available. It is compulsory for patients with cardiovascular disease to remain up-to-date with vaccination, given the increased risk of secondary bacterial infections on top of the COVID-19 infection. The benefits of vaccination in patients with heart failure and acute ischaemic syndromes are well documented.[15-17] Vaccination can be safely performed, even during hospitalisation for an acute coronary syndrome, and it will still be efficacious to reduce further coronary events.[16] Patient vaccination is highly recommended by the guidelines for coronary syndromes and heart failure. However, this recommended action is not always followed. In the context of COVID-19 infection, if patients without vaccination develop fever for a simple flu, they will or may enter into the psychosis of having contracted COVID-19. Vaccinations are of paramount importance for healthcare providers as well and, especially, for cardiologists and health personnel working in intensive care rooms, cath labs and electrophysiological labs, as well as in wards. In several nations, the level of anti-influenza vaccination among doctors is around 30–40%, which is clearly not enough. Cardiologist vaccination is a duty for patient protection, as a respiratory complication in a cardiopathic patient has serious consequences per se, and particularly so in the current context.

How relevant are clean hands?

For years, the first contact with a cardiac patient has been by *taking their pulse*. This is fine… but with washed hands? WHO considers that one of the most useful measures for COVID-19 containment is (*properly*) washing hands, and often.[18] The standard consumption of specific hand-washing gel should be $\geq$20 litres for 1000 days of hospitalisation, a level far beyond that reached in the majority of hospitals.[17] Equally, it is essential to decontaminate surfaces, including stethoscopes, probes and any device. Of course, these are general rules that should be applied at any time, but the era of COVID-19 is strongly reminding all of us to do so. In an update bulletin of 6 March 2020, the American College of Cardiology recommends encouraging additional, reasonable precautions in all cardiovascular patients because of their increased risk related to COVID-19 infection. These are obvious considerations, but there are other, more subtle, consequences of the present situation.

The switch from fear to anxiety

COVID-19 is a unique, strange fight that several countries are facing all at the same time. It is unique as human beings have never experienced such a global fight and it is strange as there is no tangible enemy. The enemy is invisible. The fight does not mean dropping bombs somewhere by someone. It is a fight everybody is asked to combat by a drastic change in his/her social life. Basically, people have to isolate themselves, although to different degrees, depending on whether they are symptomatic or not. This is one of the most difficult changes to impose and accept, but it is a necessary measure; if left to itself, the COVID-19 pandemic doubles every five to six days, at best.

Containing and mitigating the virus involves more than doctors and paramedics. It causes a drastic slowdown of the economy. It is estimated that the Gross Domestic Product in America and Europe will be 2% lower than it would have been in the absence of the pandemic, and even as much as 8% lower if the spread cannot be controlled and the mortality rate is higher. Several people will lose their jobs. In fact, many

people do not have health coverage or sick pay as this depends on the national health system policies of different countries.

There is tension for both an individual's economic status and health. This may be true for every fight but, for the present one, everybody is in first line and, yet, there is no visual enemy. Psychologically, this is relevant. When there is an objective danger, there is fear of the danger and the subtle reaction is to escape from it. This is an instinctive protective reaction. But when the danger is invisible, escaping from it is impossible. The fear is transformed into anxiety and anxiety will increase cardiovascular diseases by different mechanisms: increased sympathetic tone, blood pressure, heart rate, etc. Cardiologists should be aware of this, considering that the psychologic switch from fear to anxiety will cause more panic attacks, more need to reassure patients and, unfortunately, more acute coronary syndromes.

Conclusions

It is a difficult time. Table 1 underlines the effects of the COVID-19 pandemic in the cardiologic community. In general, health policy aims to preserve hospitals by lowering the epidemic's peak, which means to isolate people. Economic policy aims to reduce factories shutting down and the absence of staff. Governments will aim to strike a balance. Cardiologists will have to "*wash their hands and roll up their sleeves*" to try to manage this difficult time.

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