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Arrhythmogenic mechanisms in inherited and acquired cardiac diseases

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COVID-19 DOES NOT ONLY DISTURB OUR SOCIAL RHYTHM

A.A.M. Wilde, J.A. Offerhaus

With 10 vaccines currently approved and another 81 potentially to be approved in the coming months, the focus on the coronavirus disease 2019 (COVID-19) pandemic has changed from confinement to elimination. However, it is a known viral law that when the going gets tough, the tough get going, with natural selection bringing forth the most favorable mutations. Among these, the most worrying were found in South Africa, Brazil, and the United Kingdom, of which the latter initially has been designated as a “variant of concern.” Early research shows that mutations in these variants might (partly) escape the immune response.¹ Whether this will prevent vaccine-induced immunity remains to be seen, but at least one vaccine has already shown a large drop in efficacy (total efficacy 49.4%) in a South African population of which >90% was infected with the new variant.² Together with an expected increase in “variants of concern,” this finding indicates that the end of the current pandemic might be further away than initially thought, further justifying cardiac research in the COVID-19 population.

Since the beginning of the pandemic, there has been concern that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection could also affect the heart. This was mainly fed by the fact that angiotensin-converting enzyme 2 (ACE2), the receptor to which SARS-CoV-2 binds in order to infect human cells, is expressed on the cardiomyocyte’s surface, with expression possibly increased in patients with cardiovascular disease. This scenario was further supported by initial studies reporting increased levels of troponin I, which was associated with mortality in COVID-19 patients.³

COVID-19 patients potentially have an increased arrhythmic burden. Apart from direct viral effects, administered therapeutics such as, in the early days, (hydroxy)chloroquine, could contain a potential proarrhythmic risk.⁴ These risks are potentially further increased in patients with a pre-existing genetic burden.⁵ Regarding arrhythmias in COVID-19, early cohort studies reported a high percentage in these patients.⁶ However, these initial cohorts were of relatively small size, often did not specify the type of arrhythmia, and were underpowered to test the effect on hard outcomes, thus increasing the need for larger studies.

In a study reported in this issue of *Heart Rhythm Journal*, Mountantonakis et al⁷ focused on atrial fibrillation (AF) in 9564 polymerase chain reaction test–confirmed COVID-19 patients from 13 hospitals. The total incidence of AF during hospitalization was 17.6%. Interestingly, the majority of these patients (65.7%) was not known to have a previous history of AF. The authors investigated the effect of AF on in-hospital mortality using propensity score matching (PSM) analysis. PSM matches cases and controls to avoid potential confounders, where one obviously can only adjust for the measured confounders. Among a total of 2476 matched patients, in-hospital mortality was more prevalent in patients with AF than in those without (54.3% vs 37.2%; $P < .0001$), resulting in a relative risk (RR) of 1.46. The effect was more pronounced in the subgroup of patients with new-onset AF (56.1% vs 36.0%; RR 1.56; $P < .0001$) and remained significant when comparing patients with new-onset AF to those with a past history of AF (55.2% vs 46.8%; RR 1.18; $P = .009$).

In light of what we know about AF in COVID-19, the reported incidence of AF in the current study seems high compared to previously reported incidences between 3.6% and 16.8% (weighted mean incidence 11.6%).^{8, 9, 10, 11} This is presumably due to the severity of systemic illness in the studied population, illustrated by the fact that one-fifth of the patients received mechanical ventilation,

which was higher than reported in most of aforementioned studies. When compared only to publications with a similar percentage of intensive care unit admittance or mechanical ventilation (22.3%–60.0%), the reported incidences of AF are in the same range (15.7%–16.8% total AF; 7.2%–13.0% new-onset AF).^{8,9,11} Of these studies, 2 also analyzed the effect on mortality. One reported a similar association with AF and new-onset AF,⁹ whereas the other study did not.¹⁰ Again, disease severity may explain the difference, and it raises the question whether the found association reflects any direct causality at all, or AF is merely a marker of disease severity and/or a result of administered proarrhythmic therapeutics. Specifications on the cause of death or the incidence of stroke would have provided greater insight into this matter.

Moving further along the COVID-19 path, we have arrived at a new era in which the long-term effects of infection are increasingly recognized. With fatigue as the main complaint,¹² one wonders what role the heart plays in these so-called “long haulers.” A study investigating cardiovascular magnetic resonance images from 145 nonhospitalized student athletes recovering from COVID-19 reported cardiac abnormalities in only 2.8% of the students, with 2 cases of myocarditis.¹³ However, several smaller cohorts of post-hospitalized COVID-19 patients have reported a much higher prevalence of cardiac abnormalities (45%–74%) weeks after recovery.^{14,15}

Complete heart block has already been reported as an example of a possible long-term effect on the heart.¹⁶ In this issue of *HRJ*, Goldstein¹⁷ discusses the mechanisms of postural tachycardia syndrome (POTS) in patients who recovered from COVID-19. POTS is characterized by tachycardia after standing or head-tilt testing and is caused by autonomic dysregulation. Increased sympathetic activity as a result of renin–angiotensin–aldosterone activation due to reduced ACE2 activity by SARS-CoV-2 binding could very well be involved. Literature reporting POTS in COVID-19 patients is few. However, given that infection and vaccination together trigger POTS in half of the cases,¹⁸ it would be of no surprise if this number were to increase in the (near) future. Indeed, in the Heart Rhythm member open forum (<https://communities.hrsonline.org/communities>), individual researchers recently reported an increased prevalence of POTS in young patients post COVID-19.

Although perhaps less pronounced than initially thought, whether the heart takes part in COVID-19 symptomatology is no longer the question. The pandemic not only is disturbing our daily rhythm but, in a significant number of cases, the rhythm of the heart as well. With the substantial number of “long haulers,” the knowledge that SARS-CoV-2 can infect the heart, and the possibility of long-term cardiac abnormalities noted on imaging, it will be interesting to see whether other “rhythmic variants of concern” are to be expected in the future.

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