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ON MY MIND

Urgent Need for Studies of the Late Effects of SARS-CoV-2 on the Cardiovascular System

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It is challenging to set policy and predict long-term societal fitness challenges from the coronavirus disease 2019 (COVID-19) pandemic at this time. A year after the initial case spikes in Wuhan, China; Lombardy, Italy; New York City; and other areas, we still have limited information on the late effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on the cardiovascular system. Initial reports suggested relatively high rates of cardiovascular complications such as myocarditis, myocardial infarction, strokes, vascular thromboembolism, and a multisystem inflammatory syndrome in children.

Cardiovascular morbidities are critically important to recognize and mitigate during active infection. Reducing these complications, in addition to the primary pulmonary injury, drastically reduces short-term mortality. Beyond the acute phase, however, is a great unknown. What are the late health risks of COVID-19, in particular the cardiovascular complications? Recent publications have begun the process of determining the extent to which SARS-CoV-2 may affect survivor fitness and what was reported was potentially concerning. Puntmann et al[1] concluded that 78% of recovered adult patients (n=100; median age, 49 years) had ongoing cardiac involvement, of whom 60% had myocardial inflammation based largely on interpretation of findings from cardiac magnetic resonance (CMR) imaging. This was supported by detectable high-sensitivity troponin T (hsTnT) in 71% of the patients. More recently, Rajpal et al[2] reported an uncontrolled study of 26 SARS-CoV-2–positive athletes at The Ohio State University, where 12/26 (46%) demonstrated late gadolinium enhancement and 4/26 (15%) had both abnormal T2 values and late gadolinium enhancement by CMR.

Despite being potentially useful studies to begin the conversation on long-term outcomes, we have concerns that these initial datasets investigating the long-term effects of SARS-CoV-2 are overly alarming and not generalizable. The finding that 60% of patients have myocardial inflammation is >10 times higher than the summation of current autopsy data, in which only 6 cases of myocarditis were noted from 165 individuals across 12 studies. Another concern was the high rate of detectable troponin values in the adult but not the athlete population. However, the extent of mild hsTnT elevation in that COVID-19 population was expected and not dissimilar from the matched population (54% versus 71%).

Both studies reported significant CMR abnormalities. These discrepancies may be attributable to an overinterpretation of the CMR, in which elevated native myocardial T1 and T2 values and delayed enhancement are purported to reflect inflammation from myocarditis. These values are affected by numerous physiologic and technical variables, and values outside established normal ranges are not specific to an underlying pathology of myocarditis.[3]

In the first article, the cutoff for the upper limit of normal T2 values (37.4 ms) is lower than is frequently cited, and there is significant overlap of the range of

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reported T1 and T2 values in risk factor matched controls and COVID-19 home recovery and hospitalized groups. It is not clear whether the findings are related to myocarditis instead of cardiovascular risk factors themselves. In the second article, 4 of 26 patients had late gadolinium enhancement, which is similar to other highly trained athlete populations in larger studies.[4] The mean T2 value of positive cases was 59±3 ms, which is marginally above the threshold of 58.8 ms in the MyoRacer trial, a threshold shown to have a specificity of 68%.

It is also unclear how these elevated values or imaging findings compare with populations recovering from other viral infections or acute illnesses because troponin measurements and CMR examinations are not routinely obtained in these settings. In light of this, it would be prudent to exercise caution in interpretation of CMR findings indicating myocarditis in the absence of baseline pre–COVID-19 infection values, serial follow-up, and robust pathologic correlation.

It is worth considering SARS-CoV-2 in the context of other coronaviruses. Historically, coronaviruses have not been commonly associated with myocardial damage. Severe acute respiratory syndrome coronavirus (SARS-CoV) infected >8000 individuals with no reports of myocarditis. In the 1 notable autopsy series, SARS-CoV was polymerase chain reaction amplifiable in 7 of 20 (35%) hearts.[5] This finding was associated only with an increase in macrophages, not an increase in lymphocytes, the hallmark of classic viral myocarditis. Middle East respiratory syndrome coronavirus (MERS-CoV) infected >2000 individuals, with only a single case report of CMR-diagnosed MERS-CoV myocarditis. Only reports of reduced long-term pulmonary function, not reduced cardiovascular function, exist from the SARS-CoV and MERS-CoV epidemics. Thus, unless SARS-CoV-2 is functionally different from previous coronaviruses, long-term cardiac inflammation should be less than feared. Anecdotally of note, cardiologists at our institutions are not being inundated with post–COVID-19 patients.

There are little additional data on which to gauge the long-term cardiovascular health risks of SARS-CoV-2. It is clear that a multidisciplinary approach is needed. The infographic in the (Figure) lists important questions and the studies needed to address them. It will be critical to undertake such investigations in diversely representative populations, including adolescents, both sexes, and a range of ethnicities, from which we can develop risk assessment strategies. Projects such as PHOSP-COVID (Posthospitalisation COVID-19 Study), designed to address long-term COVID-19 complications, should specifically address the cardiovascular system.

Adolescents and young adults (especially athletes) are a special group with which to be concerned. It is clear that overall mortality is extremely low in individuals <30 years of age. As a result, that population has become emboldened to assume more risk than older and less healthy populations. However, children and young adults would have the most lifetime risk should chronic long-term effects of COVID-19 appear. The absence of a control group makes it difficult to draw definitive conclusions from the Rajpal et al[2] study.

This pandemic has shown the importance of the postmortem examination. High-quality hospital autopsies allow us to calibrate the clinical, radiologic, and laboratory test findings to what is occurring in the body. They have already demonstrated that the high frequency of aberrant cardiovascular findings in patients with

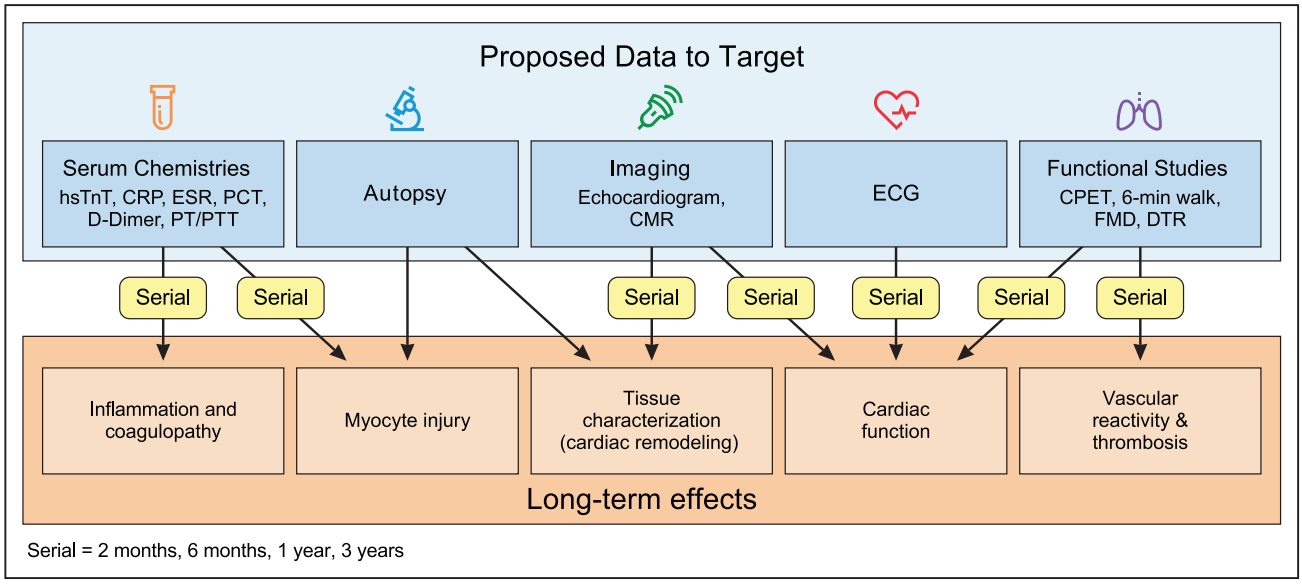

Figure. Studies needed to understand the long-term cardiovascular effects of COVID-19.
A multidisciplinary approach is needed to gauge the frequency and severity of cardiovascular complications. CMR indicates cardiac magnetic resonance imaging; COVID-19, coronavirus disease 2019; CPET, cardiopulmonary exercise test; CRP, C-reactive protein; DTR, digital thermal reactivity studies; ESR, erythrocyte sedimentation rate; FMD, flow-mediated dilation; hsTnT, high-sensitivity troponin T; PCT, procalcitonin; and PT/PTT, prothrombin/partial thromboplastin time.

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COVID-19 are not associated with true myocarditis in most cases and suggest a more frequent secondary and perhaps transient heart involvement. More autopsy studies, both acute and delayed relative to infection, will contextualize our understanding of the pathobiology of SARS-CoV-2.

A diverse set of cardiovascular effects of COVID-19 will likely be seen, and it is essential to calculate each population's risk and understand their time courses. It would be unwise to have the tail wag the dog on policy decisions or predictions of long-term needs of the health care system where extremely rare outcomes guide the overall approach to the disease. We must properly gauge the frequency of late cardiovascular events from much larger and robust data sources. Ultimately, there is a need to balance the long-term societal COVID-19 health risks with other considerations of individual physical, mental, and emotional health.

ARTICLE INFORMATION

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Disclosures

None.

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