Title
SARS-CoV-2 infection and cardiac arrhythmias

Journal
Nature Cardiovascular Research, 1(12)

ISSN
2731-0590

Authors
Dewland, Thomas A
Marcus, Gregory M

Publication Date
2022

DOI
10.1038/s44161-022-00166-x

Peer reviewed

COVID-19 and arrhythmia

https://doi.org/10.1038/s44161-022-00166-x

SARS-CoV-2 infection and cardiac arrhythmias

Thomas A. Dewland & Gregory M. Marcus

Although cardiac arrhythmias have been observed and described during and after SARS-CoV-2 infection, rigorous studies designed to untangle the complex relationship between this proinflammatory illness and arrhythmogenesis are limited. Despite a pervasive opinion to the contrary, there is presently no definitive data to establish a causal, viral-specific association between COVID-19 and incident arrhythmia.

Early in the COVID-19 pandemic, case series describing clinical outcomes among hospitalized and critically ill infected patients attracted widespread attention and concern[1]. In the absence of evidence-based therapies and vaccination, mortality was devastatingly high. These initial series also suggested SARS-CoV-2 infection could result in substantial cardiac complications, including an apparent high risk of atrial and ventricular arrhythmias during acute illness. Recognition that the virus enters cells via the angiotensin-converting enzyme-2 receptor, which is present on cardiomyocytes, further raised concerns about a potential viral tropism for cardiac tissue that could result in direct injury and arrhythmogenesis.

Estimates of cardiac arrhythmia frequency during inpatient COVID-19 hospitalization have varied widely: an initial report described a 17% incidence of atrial fibrillation[2], whereas only 4.8% of individuals randomized to the control arm in the RECOVERY trial (dexamethasone versus usual care) showed atrial fibrillation or flutter[3]. Direct comparisons between studies or with historical cohorts has been impaired by imprecise definitions of arrhythmia (including the frequent combination of atrial and ventricular arrhythmias into a single endpoint), lack of systematic enrollment of all infected inpatients, temporal changes in COVID-19 prevention and treatment patterns, ascertainment bias related to heart rhythm monitoring intensity, and mediators such as underlying patient susceptibility to arrhythmia and infection severity. Lack of a reasonable control group has substantially limited causal inference in most investigations.

Notably, it is well established that any critical illness imparts an increased risk of cardiac arrhythmias. A variety of factors, including fever, autonomic aberration, hypoxia, systemic inflammation, myocardial ischemia, mechanical ventilation strategies, electrolyte abnormalities and medication effects, may account for this widely observed and well-characterized association. As many of these pro-arrhythmic mechanisms not specific to COVID-19 are frequently present among inpatients, establishing a causal relationship between COVID-19 and cardiac arrhythmias has proved difficult. Importantly, a study conducted within a single hospital system (potentially reducing ascertainment and measurement bias) found a very similar incidence of atrial fibrillation among individuals hospitalized with COVID-19 and a near-contemporary historical control group of individuals hospitalized for influenza[4]. These findings strongly suggest that arrhythmias in these populations are not virus specific.

Enrollment of less severely symptomatic patients with COVID-19 has the potential to minimize the pro-arrhythmic confounders frequently encountered in a hospital setting and may be more relevant to the general population. We recently utilized 14-day ambulatory monitoring in a cohort of 52 outpatients with documented SARS-CoV-2 infection to better understand ambient arrhythmia burden and to determine whether palpitation symptoms correlated with significant rhythm abnormalities[5]. In this prospective study, we did not observe any sustained arrhythmias, and nearly all (96%) of participants had an atrial and ventricular ectopic burden within the normal range (<1%). Furthermore, although most participants triggered the monitor for palpitations, nearly 80% of these patient-triggered events were for sinus rhythm or sinus tachycardia. These findings, although derived from only a moderately sized cohort, provide reasonable reassurance that COVID-19 does not result in a pervasive or substantially elevated risk of serious arrhythmia.

Broader examination of outpatients with ambulatory rhythm monitoring has thus far been limited, in part due to logistical complexity and cost. Some of these obstacles can be overcome with an ecological study design. We found that higher regional COVID-19 incidence rates were associated with an increased risk of emergency medical services (EMS) activation for cardiac arrest due to ventricular arrhythmias[6]. Similarly higher rates of out-of-hospital cardiac arrests have been observed in European countries during the COVID-19 pandemic[7]. This interesting association between COVID-19 and cardiac arrest is complicated, however, by the simultaneous recognition that higher COVID-19 rates predict a significant decrease in EMS calls for chest pain and non-ST elevation myocardial infarction[6]. Although it remains possible that COVID-19 truly increases the risk of malignant ventricular arrhythmias, it is also plausible that individuals suffering a myocardial infarction were less likely to seek emergency care and, as a result, experienced higher rates of post-infarction arrhythmias[6].

Certain individuals with COVID-19 will manifest systolic dysfunction, troponin elevation or other concerning findings that raise suspicion for viral myocarditis, especially when encountered in the context of a newly diagnosed arrhythmia. Select studies using cardiac magnetic resonance imaging have reported frequent abnormalities indicative of active myocardial inflammation or fibrosis after infection[8,9]. The etiology and clinical significance of these findings, however, have been debated. Rigorous criteria typically used to confirm a myocarditis diagnosis, including histological and viral genome analysis of myocardial tissue, are seldom applied owing to clinical circumstance; it therefore remains unclear whether COVID-19 results in viral myocarditis more often than other viral infections. From a broader perspective, there is no epidemiological evidence to support the frequent development of ventricular (or atrial) arrhythmias as a consequence of these observed abnormalities, regardless of whether their ultimate etiology is a COVID-19-mediated myocarditis.

Although a direct, causal pathway between COVID-19 and cardiac arrhythmias remains unsubstantiated, it is readily apparent that patients commonly report palpitations after recovery from acute illness[10]. This frequent complaint has further fueled concern among patients and clinicians regarding pro-arrhythmic effects of the virus. Importantly, as mentioned above, these symptoms have been frequently associated with sinus tachycardia. In addition, many of these individuals have been found to meet diagnostic criteria for postural orthostatic tachycardia syndrome or orthostatic intolerance, suggesting that the virus can cause or unmask autonomic dysfunction[11]. Abnormalities of the autonomic nervous system have also been reported after other viral illnesses, and the underlying mechanism remains unknown. These potential etiologies are important to consider when evaluating a patient with palpitations after COVID-19, especially as ambulatory monitoring may not demonstrate an apparent rhythm abnormality during patient-triggered events.

Individuals with a pre-existing arrhythmia disorder (particularly atrial fibrillation) may experience a worsening of arrhythmia frequency or symptoms following SARS-CoV-2 infection. Although there is little data to quantify the regularity of this phenomenon, we have anecdotally noted this to be common in our clinical practices. As previously discussed, it is not clear whether this process is specifically due to SARS-CoV-2 infection or is instead a broader manifestation of the systemic inflammatory response generated by viral illness. Similarly, we have also noted a tendency to associate palpitation symptoms and documented arrhythmias with COVID-19 vaccination. The mechanism of the commonly used mRNA COVID-19 vaccines, in contrast to other vaccines that use an attenuated virus, indicates that these findings are an inflammatory-related phenomenon; further discussion regarding potential mechanisms is beyond the scope of this commentary.

Although both incident and recurrent arrhythmias are commonly seen during COVID-19 infection and recovery, these can be readily explained by generalized inflammation and other pro-arrhythmic factors that accompany systemic illness. Our knowledge regarding the cardiovascular effects of COVID-19 infection, including intermediate and long-term outcomes, is clearly incomplete. Furthermore, it remains possible that certain patients with specific risk factors may be uniquely prone to developing arrhythmias during or after SARS-CoV-2 infection. However, we do not believe that the current literature substantiates a widespread, clinically significant and virus-specific causal association between SARS-CoV-2 infection and arrhythmogenesis. Substantial uncertainty remains and justifies the inclusion of arrhythmias among the most rigorously obtained outcomes of COVID-19-related investigations, including assessments of preventive measures and randomized trials of various potential therapeutics.

Thomas A. Dewland & Gregory M. Marcus
Electrophysiology Section, Division of Cardiology, Department of Medicine, University of California, San Francisco, USA.
e-mail: greg.marcus@ucsf.edu

Published online: 23 November 2022

References

1. Wang, D. et al. *JAMA* **323**, 1061–1069 (2020).
2. Colon, C. M. et al. *JACC Clin. Electrophysiol.* **6**, 1189–1190 (2020).
3. RECOVERY Collaborative Group. *N. Engl. J. Med.* **384**, 693–704 (2021).
4. Musikantow, D. R. et al. *JACC Clin. Electrophysiol.* **7**, 1120–1130 (2021).
5. Dewland, T. A. et al. *Open Heart* **9**, e001758 (2022).
6. Aung, S. et al. *Sci. Rep.* **11**, 23959 (2021).
7. Baldi, E. et al. *N. Engl. J. Med.* **383**, 496–498 (2020).
8. Puntmann, V. O. et al. *JAMA Cardiol.* **5**, 1265–1273 (2020).
9. Puntmann, V. O. et al. *Nat. Med.* **28**, 2117–2123 (2022).
10. Carvalho-Schneider, C. et al. *Clin. Microbiol. Infect.* **27**, 258–263 (2020).
11. Jamal, S. M. et al. *J. Am. Coll. Cardiol.* **79**, 2325–2330 (2022).

Competing interests

The authors declare no competing interests.