Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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EDITORIAL COMMENT

Atrial Arrhythmias and the Pandemic*

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The novel coronavirus disease-2019 (COVID-19) was designated a pandemic by the World Health Organization on March 11, 2020. Exactly 1 year later, after more than 2.6 million deaths worldwide, we examine what we have learned and reassess the effect of the pandemic on our practice of medicine. The rapid, ubiquitous spread of this pathogen will probably be the greatest threat that societies will face in the 21st century, wreaking enormous turmoil on every aspect of our lives. Health care providers have been on the frontlines of the COVID-19 pandemic, often redeployed out of our comfort zones and asked to care for extraordinarily sick patients and illnesses remote from our primary area of expertise. As we witnessed the surging mortality, the harnessing of the clinical and basic research community to work together and identify best practices has been extraordinary and clearly made a profound impact on survival. We have had to adapt personally and professionally, and at present, even though the circumstances appear to be improving, it still feels that returning to our previous lives may never be possible. This may be particularly true for the practice of medicine, which will need to incorporate COVID-19, mutations, vaccinations, and personal protective equipment into daily planning. What may be most important for the electrophysiology community is recognizing the consequences of widespread community infections on typically noninfectious clinical scenarios such as atrial fibrillation (AF).

Physicians treating patients with arrhythmias participated in this pandemic both clinically and academically, manifest by the many publications addressing ventricular arrhythmias, QT intervals, AF, and cardiac arrest. Atrial fibrillation is the most common arrhythmia confronted by cardiologists, and this remains true for patients with COVID-19 infections. In studies published from China, Europe, and the United States, AF was seen in 15% to 20% of all hospitalized patients and in 35% to 40% of patients with underlying cardiovascular disease and intensive care unit admission (1,2). Consistently, the presence of AF was associated with a significantly higher mortality confirming that the interaction between AF and COVID-19 merits particular attention for scientists and practitioners. In fact, the evolution of our understanding of AF, progressing from complete chaos to progressive organization and intervention, is remarkably similar to the events over the past year. Beginning in March 2020, we watched and corralled what we could (hydroxychloroquine) until we confronted the chaotic and devastating impacts of the novel coronavirus on our immune system and used all the resources available to us to create organization and now meaningful intervention.

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In this issue of *JACC: Clinical Electrophysiology,* Musikantow et al. (3) present a comprehensive retrospective analysis of the incidence, predictors, and outcomes of AF or atrial flutter (AFL) in patients hospitalized with COVID-19. The importance and conclusions of the study are greatly enhanced by the analysis of almost 4,000 very acute patients (28% mortality) and a direct comparison of the patients hospitalized with COVID-19 to a cohort of patients hospitalized with the influenza virus. The latter proved essential in discerning the direct effects of

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COVID-19 as opposed to a nonspecific response to an acute respiratory virus. In this study, the incidence of atrial arrhythmias in the influenza cohort was not significantly different than that of patients hospitalized with COVID-19 (10% to 13%), suggesting that AF may not be a unique attribute of severe acute respiratory syndrome coronavirus 2. The presented data suggest that arrhythmias and cardiac arrest are likely the consequence of systemic illness and not a, direct effect of COVID-19. In addition, the principal automated electronic record abstraction cohort of patients with COVID-19 were compared to a manually adjudicated patient cohort drawn from the same population of patients. This is essential in validating the automatic record abstraction technique frequently used in COVID-19 reporting, and it identified significant differences in the frequency of AF/AFL.

The mortality and disease severity associated with COVID-19 appears to be strongly related to an inflammatory immune response triggered by the virus. This has been correlated with elevated markers of inflammation such as C-reactive protein and cytokine interleukin 6 (4). Prior investigation has shown that AF is linked to many conditions characterized by elevated inflammatory markers, further highlighting the important association between COVID-19 and atrial arrhythmias (5). The present study revealed that in the group of patients with a prior history of AF/AFL, 71% manifested AF/AFL during the hospitalization. The possible pathological and immunological mechanism behind the development of AF in patients with COVID-19 remains unclear. The ability of severe acute respiratory syndrome coronavirus to interact with cardiac cells expressing the angiotensin-converting enzyme-2 receptor can result in direct damage to the microvascular circulation and cause inflammation, cardiac fibrosis, and thrombosis. This may perturb atrial cellular electrophysiology and contribute to the development or persistence of AF and stroke (6). The present study clearly demonstrates that patients with higher levels of peak inflammatory markers or markers of disease severity were more likely to develop AF (C-reactive protein, interleukin-6, troponin, D-dimer, and B-type natriuretic peptide) and the presence of AF/AFL was associated with worse outcomes including rates of intubation and ischemic stroke as well as mortality.

The association of AF/AFL with mortality was similar in both influenza and COVID-19. The study's conclusions strongly suggest a mechanistic link involving inflammation, atrial arrhythmias, and mortality in patients with COVID-19 or influenza. Not surprisingly, despite more frequent comorbidities, the influenza cohort had a substantially lower incidence of in-hospital mortality, but the association of atrial arrhythmias with mortality was similar in both patients with influenza and those with COVID-19.

Whereas most of the patients with AF during hospitalization had a prior history of atrial arrhythmias, only 4% to 6.6% of the study population with no prior history of AF/AFL developed an atrial arrhythmia during hospitalization. Despite this, inflammatory markers still predicted who would be at greater risk of developing new onset AF, irrespective of baseline comorbidities. This group also had a higher incidence of myocardial injury (troponin I) and likely had more severe disease based on steroid requirements and the use of mechanical ventilation. The surprisingly low percentage of patients with observed atrial arrhythmias without a previous diagnosis suggests that the specific COVID-19 viral infection arrhythmia risk is not of a magnitude that results in many first-time presentations but may identify patients with more extensive virally mediated systemic illness or cardiac injury.

In the urgency to publish information related to COVID-19, many studies have used "big data," automated abstraction techniques to obtain information from electronic medical records (7). Traditional analytics tools are not adapted to process such large amounts of unstructured data to pursue outcomes research. New tools that combine machine learning models for data analysis are being developed and will certainly be helpful (8). At present, these automated techniques need to be validated by a manual process and Musikantow et al. (3) should be commended for their meticulous efforts. In fact, the manual review identified a greater incidence of AF in patients with COVID-19 as well as a greater percentage of patients demonstrating new onset of atrial arrhythmias. Overall, the presence of atrial arrhythmias was associated with doubling of the mortality risk of hospitalized patients with COVID-19.

There are many publications analyzing the prothrombotic state that appears to be present in patients with COVID-19 (9). Hospitalized patients with COVID-19 have been observed to have a 16% incidence of any thrombotic event, of which 1.6% presented with an ischemic stroke. D-dimer level at presentation was independently associated with thrombotic events consistent with an early coagulopathy (10). Initial anticoagulant treatment with low molecular weight heparin has been shown to reduce mortality by 48% at 7 days and 37% at 28 days (10). Given the established association of increased risk of

thromboembolism with AF, an increase in ischemic stroke in patients with AF and COVID-19 may have been expected. In fact, only a modest 1% absolute increase in risk was observed. The extraordinary collaboration of clinical research organizations that together described the prothrombotic state associated with COVID-19 and established protocols for anticoagulation likely mitigated the frequency with which thromboembolic complications of COVID-19 occurred. In the present study, 76% of patients were receiving therapeutic anticoagulation. These collaborations remain critical even today in defining best practices such as pharmacotherapy, intubation protocols, cardiopulmonary support, and vaccine development.

Studies such as the one by Musikantow et al (3) empower us with information to care for patients with greater skill and efficacy. There are currently several studies that describe changes in electrophysiology practice that will likely persist after the pandemic subsides (11). These include same-day discharge in patients undergoing catheter ablation, telemedicine, and remote monitoring. Physicians have developed an acute awareness of the potential drug interactions that may occur in severely ill patients when combining emergent COVID-19 therapies with anticoagulants, antiarrhythmics, and steroids. Many have focused on the QT interval and identifying patients who may be at higher risk of developing life-threatening ventricular arrhythmias. This awareness and the unprecedented alliance within the medical community has undoubtedly lowered mortality and given us "breathing room" while we await the widespread distribution of vaccines and herd immunity.

The exceptionally high mortality in patients with COVID-19 with AF/AFL (46%) should alert providers to disease severity and the need for aggressive treatment addressing inflammation and thromboembolic risk. The effect of a rhythm control strategy on morbidity or mortality will require further investigation. Until recently, many noncritical medical appointments in hospitals have been postponed and practitioners have been asked to see only patients with the utmost needs. The collateral health care effects of a worldwide lockdown are just beginning to be understood and with the insights learned during the peak of the pandemic, the next stage of our recovery from this nightmare will become increasingly clear.

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