ACEIs AND ARBs IN COVID-19: CONTINUE OR DISCONTINUE?

In the present issue of Mayo Clinic Proceedings, Sanchis-Gomar et al discuss the controversial topic regarding whether agents that interrupt the renin-angiotensin-aldosterone system (RAAS), such as angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs), exert exacerbatory or beneficial effects in patients with COVID-19. That such a controversy exists, at first glance, is surprising, as these agents are among the most effective and versatile medicines introduced in clinical practice in recent decades. These agents are of proven value in treating systemic hypertension and reducing its complications, in benefiting a range of cardiovascular diseases including heart failure, and in retarding the progression of diabetic nephropathy and other chronic nephropathies. Such concerns with ACEIs and ARBs have arisen because of clinical observations that patients hospitalized with COVID-19 are often on these medications at the time of admission to hospitals. Additionally, concerns also arose because of biologic observations demonstrating that SARS-CoV-2 gains entry into cells lining the respiratory tract through the ACE2 transmembrane protein that resides in these cells; and that ACEIs and ARBs, at least in some studies, may increase expression of ACE2, thereby possibly promoting the cellular entry of SARS-CoV-2. Sanchis-Gomar et al not only discuss the limitations of these clinical observations and the overinterpretation of the biologic ones, but also marshal evidence that ACEIs and ARBs, on the contrary, may be beneficial in COVID-19 through anti-inflammatory and other salutary effects. After entry into cells via the ACE2 membrane receptor, SARS-CoV-2 replicates intracellularly and damages and destroys cells, including alveolar cells with replicative capacity. This elicits intense immune and inflammatory responses, and it is inflammation as much as infection that damages target organs; in lungs, for example, the acute respiratory distress syndrome (ARDS) can ensue. Components of the RAAS, in particular, angiotensin II and aldosterone, are vasoconstrictive, proinflammatory, prooxidant, and profibrotic, actions that may contribute to the instigation of ARDS and its progression. ACEIs and ARBs may thus interrupt such RAAS-dependent pathways of ARDS, and indeed this has been observed in certain preclinical studies. ACE2, itself, may be tissue protective because of the following considerations. A homologue of ACE (the enzyme that converts angiotensin I to angiotensin II), ACE2 exerts a quite different enzyme activity from ACE: ACE2 degrades both angiotensin I and angiotensin II to products that are anti-inflammatory and cytoprotective. ACE2 thus replaces tissue-damaging components of the RAAS by ones that are potentially salutary; such actions of ACE2 may underlie the beneficial effects of ACE2 as observed in some preclinical models of lung injury. Moreover, this protective pathway of ACE2 may be lost in COVID-19 because when epithelial cells in the lungs are infected by SARS-CoV-2, the
cellular expression of ACE2 is attenuated. Sanchis-Gomar et al comprehensively summarize these and other lines of evidence to conclude that, on the balance, ACEIs and ARBs are protectants against, rather than participants in, organ injury that occurs in COVID-19. In view of these pathobiologic considerations and the clinical efficacy of ACEIs and ARBs in the assorted diseases for which they are prescribed, Sanchis-Gomar et al recommend that these agents be continued in patients with suspected or diagnosed COVID-19.

Sanchis-Gomar S, Lavie CJ, Perez-Quilis C, Henry BM, Lippi G. Angiotensin-converting enzyme 2 and antihypertensives (angiotensin receptor blockers and angiotensin-converting enzyme inhibitors) in coronavirus disease 2019. Mayo Clin Proc. 2020;95(6):1222-1230.

STEMI AND ACUTE MYOCARDIAL INJURY IN SUSPECTED OR CONFIRMED COVID-19 PATIENTS

The relationship between cardiovascular disease and COVID-19 is at least three-fold. First, both diseases share many of the same risk factors including age, systemic hypertension, diabetes, obesity, chronic obstructive pulmonary disease, and chronic kidney disease. Second, the presence of cardiovascular disease is a predisposing factor for COVID-19. And, third, the development of COVID-19 can incite the occurrence of acute myocardial injury. Based on these considerations, the risk of a potentially life-threatening manifestation of cardiovascular disease, specifically, acute myocardial infarction (AMI), would seem to be increased in patients with COVID-19. Indeed, recent observations clearly document the occurrence of AMI in these patients, but the true incidence of AMI in COVID-19 remains unknown. COVID-19, as it progresses, promotes a proinflammatory, prothrombotic, and hypoxic milieu. Such an inimical milieu can exert a disruptive effect on cardiovascular homeostasis in any one or combination of the following ways: 1) the destabilization of pre-existing atherosclerotic plaques in the coronary arteries, thereby causing plaque rupture, thrombosis, and occlusion of coronary arteries; 2) the disturbance of vasodilator/vasoconstrictor balance in favor of vasoconstriction, with attendant coronary artery vasospasm; 3) the perturbation of myocardial metabolism, thereby giving rise to a supply-demand mismatch; and 4) the development of acute myopericarditis which can mimic AMI. COVID-19 may thus predispose to either type 1 or type 2 myocardial infarction, either of which may present with ST elevation, elevated troponin biomarkers, or both. The management of subtypes of STEMI may be markedly different as AMIs caused by occlusive coronary artery lesions are conventionally diagnosed and managed by coronary angiography and percutaneous intervention (PCI), whereas others may be medically managed. PCI, as for any invasive procedure, imposes risks to the patient, and PCI necessitates the activation and use of the cardiac catheterization laboratory (CCL). For patients with suspected or confirmed COVID-19, the CCL-based management pathway incurs the risk of exposure to personnel to a highly infectious, potentially fatal disease. Additionally, depending upon the severity of COVID-19, respiratory failure and the need for intubation may develop in COVID-19 patients in the course of the CCL-based management pathway; respiratory failure signifies deterioration in the clinical status of the patient, and its management imposes added risks of exposure of personnel in the CCL to the virus. In the present issue of Mayo Clinic Proceedings, Bennett et al discuss such diagnostic and management challenges and competing risks in suspected or confirmed COVID-19 patients with ST elevation. Other germane considerations covered by Bennett et al include caveats regarding the significance of increased levels of high sensitivity troponin in this setting and the need for evidence for myocardial ischemia in the diagnosis of AMI; the role for adjunct cardiac imaging; how resources and expertise that are center-dependent may modify pathways of care; and, as important, ethical considerations. Bennett et al distill their discussion into the timely provision of a helpful algorithm that outlines three management pathways based on the level of clinical suspicion for acute coronary artery occlusion. Finally, the broad and
salient issues discussed by Bennett et al may be generally relevant to decision-making processes for potentially life-saving procedures for suspected or confirmed COVID-19 patients acutely in need of such interventions.

Bennett CE, Anavekar NS, Gulati R, et al. ST-segment elevation, myocardial injury, and suspected or confirmed COVID-19 patients: diagnostic and treatment uncertainties. Mayo Clin Proc. 2020;95(6):1107-1111.

CLINICAL CLUES IN DIAGNOSING COVID-19 AND THE DANGER OF FALSE-NEGATIVE TESTS

A now well appreciated triad of symptoms used to suspect COVID-19 consists of fever, cough, and dyspnea. However, each one of these symptoms may reflect myriad causes and the combination of all three, while limiting the range of possibilities, is hardly diagnostic. In the current issue of Mayo Clinic Proceedings, Cohen et al discuss important diagnostic clues for the presence of COVID-19 based on their experience in a large urban ambulatory clinic specifically established to care for patients with COVID-19. Their emphasis on the patient’s history, clinical symptoms, and physical exam arose because of three salient considerations. First, while having access to reverse transcription-polymerase chain reaction (RT-PCR) testing, such testing required at least 4 days before results would be available. Second, no readily available laboratory tests proved diagnostically helpful. Third, prior reports regarding early symptoms in COVID-19 were largely derived from specialized settings such as fever clinics or hospitalized patients; such observations may not readily reflect the warning symptoms of COVID-19 in patients seen in an ambulatory clinic in the community. Cohen et al discuss the differentiating features of other causes of upper and lower respiratory tract infections, influenza, community acquired pneumonias, and gastroenteritides. These authors emphasize the tempo, severity, relative temporal appearance, and resolution or lack thereof of each component of this triad of fever, cough, and dyspnea; they also underscore other accompanying symptoms and features including oxygen desaturation with minimal exertion, anosmia, and gastrointestinal symptomatology. What is clear from the discerning, careful, and timely observations of Cohen et al (based on more than 1000 patients) is that, even for a relatively newly recognized disease as COVID-19, the history and physical examination (H & P) is the cornerstone in medical practice, as has long been established but so often either forgotten or dismissed. The H & P clearly needs to be corroborated by diagnostic testing, but in addition to the delay in obtaining such results are the lack of sensitivity and attendant false-negative findings with currently available RT-PCR diagnostic tests. In this issue of Mayo Clinic Proceedings, West et al discuss the peril posed by such false-negative results in COVID-19 testing and how individuals with false-negative results may either promote the continued dissemination of the disease or drive a recrudescence after the disease has plateaued and begun its descent. Based on reasonable assumptions regarding infectivity in a given population, West et al estimate that, even for an RT-PCR test with a 90% sensitivity, an alarming number of individuals with false-negative results exist in that population. These authors delineate strategies that may lessen the danger posed by false-negative results, including approaches to be considered in individuals and settings with an increased risk for COVID-19, the urgent need for tests with greater sensitivity, and, not the least of all, the stringent attentiveness to and compliance with infection control measures.

Cohen PA, Hall L, John JN, Rapoport AB. The early natural history of SARS-CoV-2 infection: clinical observations from an urban, ambulatory COVID-19 clinic. Mayo Clin Proc. 2020;95(6):1124-1126.

West CP, Montori VM, Sampathkumar P. COVID-19 testing: the threat of false-negative results. Mayo Clin Proc. 2020;95(6):1127-1129.

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