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COVID-19 Illness and Heart Failure

A Missing Link?

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In the throes of the COVID-19 crisis, a curious medical fact has emerged. The virus attacks universally and with high efficiency; however, its most menacing progression uniquely endangers the elderly, especially those with cardiovascular illness such as diabetes mellitus, hypertension, and coronary heart disease (1). In early reports investigating case fatality rates, elevated markers of cardiac injury such as troponin predict a more perilous course and appear later in the disease course, with some patients exhibiting extreme elevations in natriuretic peptides with the cause of death attributed to cardiac failure and arrest in up to 1 in 4 cases (1). In rare cases, a fulminant myocarditis-like presentation is observed, whereas in other post-mortem samples derived in the setting of death due to pulmonary complications and cardiac arrest, surprisingly few interstitial mononuclear inflammatory infiltrates are noted without substantial damage (2,3). As a result of these observations, a hypothesis is emerging positing the contribution of underlying structural cardiac disease and propensity for the emergence of a heart failure phenotype that ranges from a classic heart failure with preserved ejection fraction in the earlier stages of the illness in the context of pulmonary complications and, later, in the form of acute systolic heart failure as a response to the cytokine phase of COVID-19.

One of the most contested issues includes the use of drugs prescribed for comorbidities, such as hypertension and diabetes mellitus, in patients who go on to manifest the highest risk for complications with COVID-19. The question has, therefore, been raised on whether a blanket avoidance of some drugs, such as angiotensin-converting enzyme (ACE) inhibitor (ACEi) and angiotensin receptor blocker (ARB) drug therapy, should be advisable (4). This is based on the fact that the SARS-CoV-2 uses the ACE-2 receptor in the epithelial alveolar lining to establish infection, and there is ex vivo experimental data suggesting that drugs such as ACEi of ARBs may induce greater expression of ACE-2 in tissues other than the pulmonary vasculature (5). Others have begun to conjecture about the use of antidiabetic medications that are secretagogues, which may alter fluid homeostasis. Furthermore, perhaps more appropriately, some have advocated against the use of non-steroidal anti-inflammatory drugs (NSAIDs), which should only be used with caution or ideally, avoided (6). We believe that recommendations made universally may be risky if applied to those without the infection or in young patients who may be less likely to suffer advanced complications. In reality, interwoven segments of pathophysiological risk are complicit in determining the predilection for a more endangered infection in those with underlying cardiovascular disease and heart failure.

We have learned that during an influenza outbreak, elderly patients with cardiovascular illness have higher rates of acute coronary syndromes, cardiac arrhythmias, and heart failure–related events (7). The reasons underlying this may relate to increased

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TABLE 1 Clinical Cardiovascular Concerns in COVID-19 Illness

COVID-19 Infection	Concern	Interpretation
Asymptomatic or early mild disease with constitutional symptoms (fever, dry cough, diarrhea, and headache)	Should background cardiovascular medications be modified?	• There is no clear evidence that ACEi or ARBs should be discontinued • NSAIDs should be used with caution or, ideally, avoided
Moderate disease with pulmonary complications and shortness of breath (including hypoxia)	Is there a cardiovascular contribution to the lung complications?	• Check troponin (evidence of myocardial injury and prognosis) • Check natriuretic peptides • Consider cardiac echocardiography to evaluate for evidence of underlying structural heart disease, high filling pressures • Avoid overuse of intravenous fluids, which may worsen underlying pulmonary edema
Advanced-stage disease with hypoxia, vasoplegia, and shock	Is there evidence of cardiogenic contribution to shock, and what therapy may be potentially curative?	• Check for evidence of hyperinflammation or a cytokine release storm (elevated troponin, natriuretic peptides, CRP, and serum ferritin of >1,000 ng/ml (measure IL-6 levels if available) • If cardiac function is reduced (LVEF <0.50%), consider supportive care with inotropic therapy but move to consider anticytokine therapy with drugs such as tocilizumab and corticosteroids

Note that therapy in COVID-19 remains experimental.

ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; CRP = C-reactive protein; IL = interleukin; LVEF = left ventricular ejection fraction.

viscosity during febrile illnesses, heightened coagulation systems, proinflammatory effects, or endothelial cell dysfunction (7). Aging-related immunologic quiescence may also predispose to higher attack rates in the elderly. Thus, vulnerable populations are more prone to the early establishment of infection and its negative consequences. There is no reason to expect that this would be materially different in the case of COVID-19. What is somewhat unique in the observations with COVID-19 relates to the high frequency of pulmonary complications, noted as bilateral infiltrates on computerized scanning, with a high proportion of patients transitioning to hypoxic respiratory failure. This raises the issue of whether there is a cardiac contribution to these lung findings and whether raised filling pressures and a heart failure phenotype are also in play and are being ignored. Currently, no studies that examine hemodynamics in the setting of hypoxic failure in COVID-19 are available to answer this critical question.

Because respiratory disease is established in the setting of COVID-19, characteristically, acute respiratory distress syndrome is also accompanied by pulmonary edema, as noted in post-mortem studies (3). Elderly patients with cardiovascular disease and diabetes often have left ventricular hypertrophy, diastolic dysfunction, and even heart failure with preserved ejection fraction. Thus, if not attended to, these patients may be prone to higher pulmonary vascular pressures in the typical critical care scenario of fluid infusion to maintain blood pressure as well as administration of parenteral medications. Such individuals may also receive medications such as NSAIDs to abrogate constitutional disease symptoms such as fever and headache. They may also require insulin or secretagogues when diabetes mellitus is present, because blood sugars are often elevated in the stress of acute illness. These drugs notoriously alter salt and water handling and may worsen respiratory complications, including pulmonary edema and consequent hypoxia (8,9). If renal failure ensues, the ability to handle salt and water becomes even more precarious. Similarly, in situations of pulmonary disease, ACEi are associated with bronchial hyperreactivity and can induce a cough in selected patients, suggesting that their bradykinin upregulating effects may influence the respiratory system directly (10). Therefore, although there is little rationale to cease use of ACEi in the asymptomatic carrier state or very early COVID-19 illness without lung complications, it may be best to avoid the use of ACEi and even ARBs if COVID-19 results in pulmonary inflammation and acute respiratory distress syndrome, because it is likely that vasoplegia and renal dysfunction may be expected to ensue. Ideally, clinicians should exercise caution in the overuse of intravenous fluids in elderly patients presenting with COVID-19 illness.

In later stages of COVID-19 illness, a hyperinflammatory state is manifest that is akin to a cytokine release syndrome as described in response to cancer therapy as noted with immune checkpoint inhibition and T-cell–engaging therapies such as chimeric antigen receptor T cells (11). This multisystemic syndrome results in elevated cytokines and dysregulated T cells with lymphopenia (typically an

early finding), coupled with marked elevations in C-reactive protein, cytokines such as interleukin (IL) 2 and IL-6, elevated natriuretic peptides (suggesting cardiac inflammation or dysfunction), and high serum ferritin. Observations suggest a high frequency of cardiovascular events, with patients dying from cardiac arrhythmias and heart failure, once these biomarkers become established. Pathologically, such myocardial manifestations are akin to a stress cardiomyopathy or cytokine-related myocardial dysfunction, which occurs in the setting of progressive stages of COVID-19 illness and mimics the syndromes observed in secondary hemophagocytic lymphohistiocytosis syndrome or macrophage activation syndrome characterized by a fulminant and fatal cytokine release. In this phase, a terminal event could potentially be avoided by the targeted use of anticytokine measures such as the IL-6 blocker tocilizumab and by selected use of corticosteroids (12,13). Naturally, these concepts require validation in clinical trials.

We believe that until universal testing for COVID-19, clinical trials of antivirals, and a greater understanding of the late stages of disease become evident, heart failure specialists must develop a structured approach to the care of such patients and be included early in developing algorithms for care of these patients (**Table 1**). Destabilization of cardiometabolic regimens, including cessation of ACE inhibitors or ARBs in asymptomatic or early-phase situations, should be avoided, as has been stated by concerned societies (14). However, once a proinflammatory respiratory phase is established with evidence of inflammatory infiltrates and hypoxia, it may be prudent to avoid their use in that circumstance. In the elderly, care should be taken to avoid excessive fluid use and drugs that may alter salt and water balance, such as NSAIDs, are best avoided. Biomarkers should be used with distinct attention to the elderly at highest risk with underlying structural cardiac disease, and specialists should engage thoughtfully in defining and managing advanced heart failure during the hyperinflammation phase of this illness.

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