MAYO CLINIC

Sex-Biased Vulnerability of the Heart to COVID-19

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Coronavirus disease 2019 (COVID-19) is a quickly evolving public health emergency. Currently, actual death rates associated with COVID-19 cannot be calculated with accuracy. Among other things, this is due to availability of testing modalities and selection procedures for testing, as well as asymptomatic disease, all leading to undetected cases, thereby impacting the estimation of death rates. Nevertheless, on the basis of data released from several countries and a recent study using a multinational COVID-19 registry,[1] despite similar infection rates or even in some cases more female than male infections, men appear to be disproportionately affected by COVID-19 and at higher risk of mortality than women.

A significant proportion of COVID-19 patients have underlying cardiovascular disease (CVD). Importantly, it appears that elderly individuals with coronary heart disease or hypertension are more likely to be infected and to develop more severe symptoms. Consequently, CVD and hypertension are generally associated with increased crude fatality rates. Although sex-disaggregated data are currently scarce, it is not unreasonable to expect that the proportion of COVID-19 patients with CVD would be predominantly male.[2] This could be an explanation for the increased mortality observed in male COVID-19 patients and is a hypothesis that can be tested as data become available.

However, independent of pre-existing cardiovascular conditions, increasing evidence supports a link between COVID-19 and increased morbidity and mortality from cardiovascular complications. Generally, respiratory infections are associated with a short-term increase in cardiovascular risk and the emerging data show that COVID-19 patients have acute coronary events. Myocardial injury was demonstrated by elevated cardiac biomarkers, that is, high sensitivity troponin I, indicating myocardial ischemia or non-ischemic myocardial events, including myocarditis. This is not surprising, given the severe respiratory infection and hypoxia due to COVID-19. Cardiac arrhythmias have also been reported in COVID-19 patients. Furthermore, among patients who died, substantial cardiac damage was observed. All these findings have been discussed in detail.[3] We put forward that male COVID-19 patients have an elevated risk of cardiovascular complications, thereby contributing to increased mortality.

POTENTIAL MECHANISMS OF SEX-SPECIFIC CARDIOVASCULAR RISK

In light of this hypothesis, we propose here potential mechanisms implicated in COVID-19 pathogenesis that may provoke cardiovascular injury and dysfunction in a sex-biased manner, contributing to a greater risk in male patients (Figure). These may include pathways that regulate immune responses associated with elevated risk of incident CVD. Local and systemic inflammation may lead to plaque instability and rupture. Patients with COVID-19 have elevated inflammatory markers and neutrophilia. Furthermore, inflammatory mononuclear infiltrate in myocardial tissue of patients with COVID-19 indicates myocardial inflammation. Dysregulation of cellular pathways associated with circulating leukocytes and imbalanced responses of T helper cells are indicative of cytokine storm, which may result in cardiomyocyte injury with loss of membrane integrity. A hyper-inflammatory state further sustained by aberrant cytokine release may promote hypercoagulability

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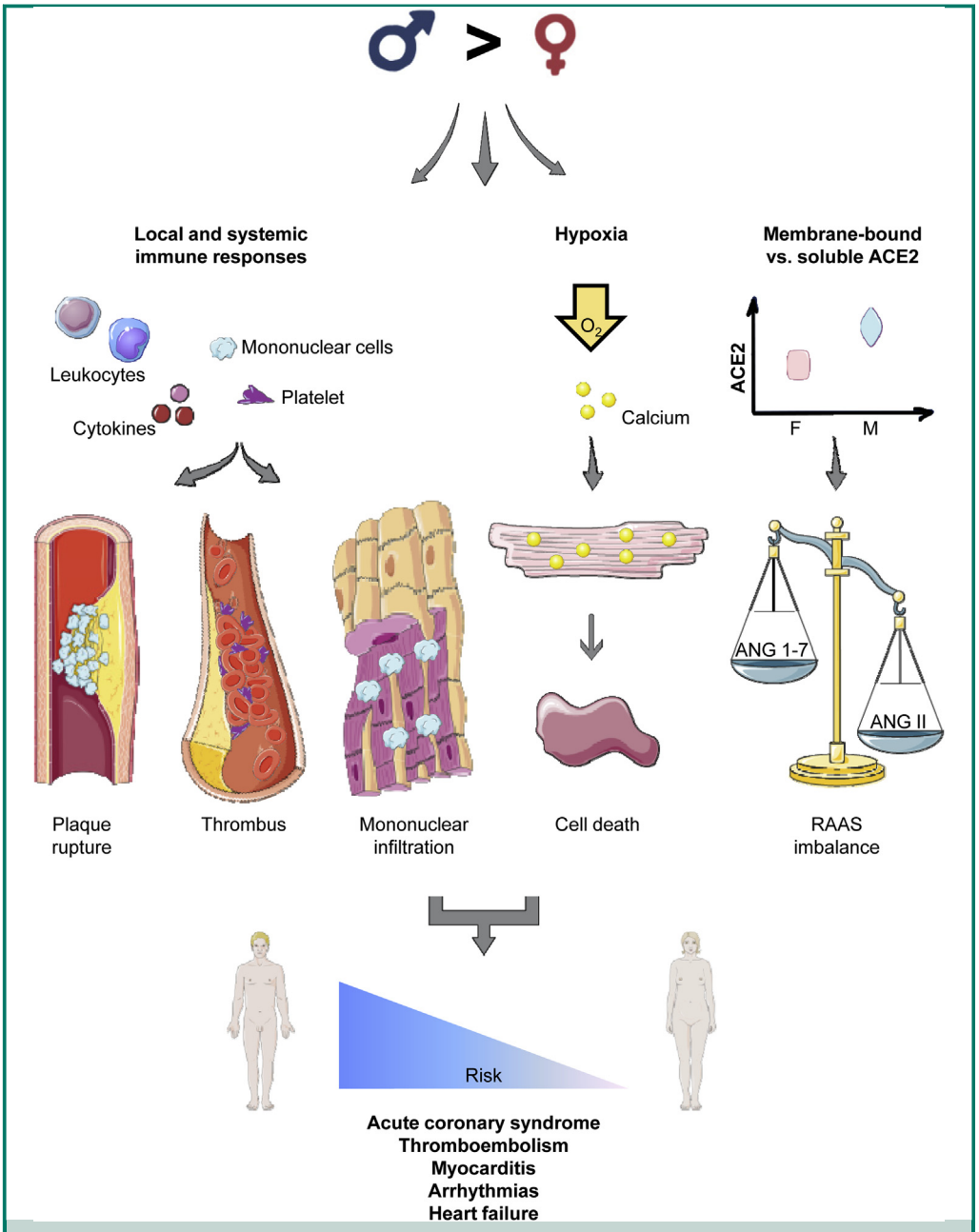

FIGURE. Potential mechanisms of sex-biased cardiovascular risk in coronavirus disease 2019 (COVID-19) patients. Biological sex leads to male-biased regulation of several pathomechanisms that may contribute to increased cardiovascular vulnerability of male patients to COVID-19, thereby leading to worse outcomes. ACE = angiotensin-converting enzyme; ANG = angiotensin; F = female; M = male; RAAS = renin-angiotensin-aldosterone system.

and thrombotic microangiopathy, ultimately leading to myocardial infarction. Therefore, increases in inflammatory factors and cell infiltration may contribute to greater vulnerability to cardiac dysfunction and worse prognosis in male COVID-19 patients. In this context, male-biased cardiac inflammatory responses are negatively related to

cardiac function.[4,5] In contrast, the female sex is associated with finely tuned physiological inflammatory responses linked to improved functional recovery.[6] Hypoxia-dependent excessive intracellular calcium may lead to cardiomyocyte death. Patients with COVID-19 present with increased lactate dehydrogenase levels. Notably, the degree of cardiac cell death is more pronounced in males than females under various conditions.[7]

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) uses angiotensin-converting enzyme 2 (ACE2) as a host cell entry receptor.[8] *ACE2* is an X-linked gene with male-biased expression in several tissues, including the heart.[9] However, it is currently unclear how circulating and tissue concentrations of ACE2 could influence SARS-CoV-2 susceptibility and disease virulence in the heart. In patients with heart failure, plasma concentrations of ACE2 were found to be higher in men than in women, with the investigators suggesting that this might explain the higher incidence and fatality rate of COVID-19 in men.[10] However, soluble ACE2 converts angiotensin II, a potent vasoconstrictor also involved in cell proliferation, hypertrophy, generation of oxidative radicals, and inflammation, into angiotensin 1-7, an angiotensin with antioxidant and anti-inflammatory effects, which further decreases angiotensin II levels. As a functional receptor on the cell surface also for SARS-CoV, ACE2 is downregulated via endocytosis upon viral entry into cells.[8,11] As a result, there is decreased availability of ACE2 for shedding, thereby affecting soluble ACE2 levels and angiotensin II production, ultimately promoting further pro-inflammatory effects, oxidative stress and vasoconstriction.[11] In this context, there appears to be an important distinction in the potential regulatory role between the membrane-bound and soluble forms of ACE2, with the latter conferring protection. Consequently, lower soluble ACE2 levels may be a contributing factor to increased vulnerability of male patients to COVID-19, accounting for imbalance of the renin-angiotensin-aldosterone system. Assessment of soluble and membrane-bound ACE2 levels in the presence of SARS-CoV-2 and the interplay with biological sex would contribute to clarifying this seemingly conflicting situation indicating the complexity of the renin-angiotensin-aldosterone system.

Several of the proposed mechanisms have been implicated in sex-biased regulation of cardiovascular (patho)physiology[7] and could be relevant to sex-dependent cardiovascular morbidity and mortality in COVID-19 patients, ultimately leading to male-biased susceptibility and severity. Certainly, this is an area for future investigation.

THERAPEUTIC OPPORTUNITIES

Although strategies such as social distancing to slow the transmission of the virus are important, hospitals must be prepared to care for cardiovascular complications in COVID-19 patients. This is particularly important given that several therapeutic agents evaluated for the treatment of COVID-19 have not been shown to be efficacious. In light of the present theory, there must be extra consideration of sex-specific aspects in the management of these patients. Subsequently, treatment strategies for cardiovascular complications arising from COVID-19 are necessary, which, however, include the sex-biased epidemiologic observations made so far. Along this line, overall immunomodulation may be among the therapeutic options for targeting pathways discussed here. In particular, anti-inflammatory drugs/immunosuppressive agents, cytokine inhibitors, monoclonal antibodies, including anti—interleukin-1 and anti—interleukin-6, could protect against cardiac injury particularly in male patients. A glucocorticoid and interferon-backbone combination regimen could also confer cardiovascular benefit. Complement inhibitors, anticoagulants, antiplatelets, and fibrinolytics may also be important components of a combination therapy in COVID-19 patients protecting against cardiovascular complications. Furthermore, considering

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the potentially sex-biased imbalance of the renin-angiotensin-aldosterone system, soluble human recombinant ACE2 would be expected to be beneficial. Several trials are underway. However, there is a lack of sex-specific analysis in the emerging concepts and in the development of treatment strategies. Nevertheless, the interaction of biological sex with potential pharmacologic agents under investigation and clinical testing should not be neglected.[12]

CONCLUSION

Early identification of risk factors for morbidity and mortality is necessary during a pandemic, and overwhelmed health care systems need to facilitate appropriate care and prompt access to treatment strategies for those at highest risk. Cardiovascular comorbidities and complications are common in patients with COVID-19. Male patients appear to be at higher risk of mortality and we have highlighted potential mechanisms that may provoke cardiovascular injury and dysfunction in a sex-dependent manner. However, it is currently unclear if biological sex imposes an independent risk or there is an effect of other (pre-existing) factors (eg., smoking and limited intensive care support). We call upon public health agencies and health care systems to report and release sex-disaggregated data to facilitate further analyses.

Abbreviations and Acronyms: **ACE2** = angiotensin-converting enzyme 2; **COVID-19** = coronavirus disease 2019; **CVD** = cardiovascular disease

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REFERENCES

1. Alkhouli M, Nanjundappa A, Annie F, Bates MC, Bhatt DL. Sex differences in COVID-19 case fatality rate: insights from a multinational registry. *Mayo Clinic Proc*. 2020;95(8):1613-1620.
2. Inciardi RM, Adamo M, Lupi L, et al. Characteristics and outcomes of patients hospitalized for COVID-19 and cardiac disease in Northern Italy. *Eur Heart J*. 2020;41(19):1821-1829.
3. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential effects of coronaviruses on the cardiovascular system: a review. *JAMA Cardiol*. 2020;5(7):831-840.
4. Gaignebet L, Kandula MM, Lehmann D, Knosalla C, Kreil DP, Kararigas G. Sex-specific human cardiomyocyte gene regulation in left ventricular pressure overload. *Mayo Clin Proc*. 2020;95(4):688-697.
5. Kararigas G, Dworatzek E, Petrov G, et al. Sex-dependent regulation of fibrosis and inflammation in human left ventricular remodelling under pressure overload. *Eur J Heart Fail*. 2014;16(11):1160-1167.
6. Pullen AB, Kain V, Serhan CN, Halade GV. Molecular and cellular differences in cardiac repair of male and female mice. *J Am Heart Assoc*. 2020;9(8):e015672.
7. Regitz-Zagrosek V, Kararigas G. Mechanistic pathways of sex differences in cardiovascular disease. *Physiol Rev*. 2017;97(1):1-37.
8. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*. 2020;181(2):271-280.e8.
9. Tukiainen T, Villani AC, Yen A, et al. Landscape of X chromosome inactivation across human tissues. *Nature*. 2017;550(7675):244-248.
10. Sama IE, Ravera A, Santema BT, et al. Circulating plasma concentrations of angiotensin-converting enzyme 2 in men and women with heart failure and effects of renin-angiotensin-aldosterone inhibitors. *Eur Heart J*. 2020;41(19):1810-1817.
11. Kuba K, Imai Y, Rao S, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med*. 2005;11(8):875-879.
12. Gaignebet L, Kararigas G. En route to precision medicine through the integration of biological sex into pharmacogenomics. *Clin Sci (Lond)*. 2017;131(4):329-342.