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Multi-organ damage by covid-19: congestive (cardio-pulmonary) heart failure, and blood-heart barrier leakage

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Abstract

Corona virus disease-19 (covid-19) is caused by a coronavirus that is also known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and is generally characterized by fever, respiratory inflammation, and multi-organ failure in susceptible hosts. One of the first things during inflammation is the response by acute phase proteins coupled with coagulation. The angiotensinogen (a substrate for hypertension) is one such acute phase protein and goes on to explain an association of covid-19 with that of angiotensin-converting enzyme-2 (ACE2, a metallopeptidase). Therefore, it is advisable to administer, and test the efficacy of specific blocker(s) of angiotensinogen such as siRNAs or antibodies to covid-19 subjects. Covid-19 activates neutrophils, macrophages, but decreases T-helper cells activity. The metalloproteinases promote the activation of these inflammatory immune cells, therefore; we surmise that doxycycline (a metalloproteinase inhibitor, and a safer antibiotic) would benefit the covid-19 subjects. Along these lines, an anti-acid has also been suggested for mitigation of the covid-19 complications. Interestingly, there are three primary vegetables (celery, carrot, and long-squash) which are alkaline in their pH-range as compared to many others. Hence, treatment with fresh juice (without any preservative) from these vegies or the antioxidants derived from purple carrot and cabbage together with appropriate anti-coagulants may also help prevent or lessen the detrimental effects of the covid-19 pathological outcomes. These suggested remedies might be included in the list of putative interventions that are currently being investigated towards mitigating the multi-organ damage by Covid-19 during the ongoing pandemic.

Keywords Connexin · Matrix metalloproteinases · Doxycycline · Endocardial endothelia · Fibrosis/remodeling

Introduction

Unfortunately, covid-19 related deaths in the Western hemisphere have already reached many thousands as compared to hundreds in the developing countries. This may, in part, be due to that hydroxychloroquine (HCQ) is being heavily prescribed to covid-19 patients as one of the treatments for covid-19 sickness. This review addresses that a low non-toxic dose of chloroquine (CQ) can benefit the patients against covid-19 (https://www.worldometers.info/coronaviruses/) [1, 2]. It is important to test the concept that complications by covid-19 or viral myocarditis such as congestive heart failure (CHF) can be mitigated by HCQ (a more potent derivative of CQ) (Fig. 1).

Several drugs have recently been either suggested or being clinically administered to relive the symptoms of covid-19. These include dapagliflozin (sodium glucose co-transporter 2; SGLT2 inhibitor; an antidiabetic), Lopinavir/Ritonavir, Darunavir/Umifenovir (anti-HIV), Remdesivir (anti-Ebola), Favipiravir, and Dipyridamole (anti-hypertensive) [2–13]. Also, an anti-acid (Famotidine) is also being promoted [14]. Drugs like Famotidine (tradename; Pepcid) are histamine receptor antagonists that are routinely used to treat, and prevent certain types ulcers, and to treat conditions that cause the stomach to produce too much acid, and also to treat gastroesophageal reflux disease condition. Clinical evidence of the role of histamine in heart has been well documented, and histamine receptor antagonist in hypertension are cardioprotective [15–17]. Interestingly, HCQ is unique in the sense that, at low doses, it mitigates or blunts both the virus's direct effects, as well as the immune reaction/response. It is, therefore; important to employ a low dose HCQ to mitigate CHF, and viral myocarditis-induced

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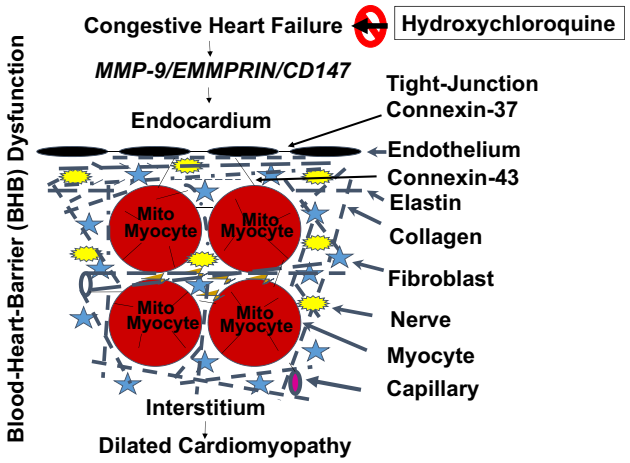

Fig. 1 HCQ, doxycycline, and the anti-acid mitigate CHF, and DCM, such as in aging, and viral myocarditis, caused by the chronic volume overload/preload. CHF instigates EE leakage and disrupts endothelial-endothelial, endothelial-myocyte, myocyte-myocyte and mitochondrial (Mito)-myocyte junctions. Activation of MMP-9 is the hallmark of CHF that disrupts connexin-37, and 43 leading to EE leakage, and DCM. HCQ, doxycycline, and anti-acid could help mitigate both CHF, and DCM. Abbreviations: HCQ; hydroxychloroquine, MMP-9; matrix metalloproteinase, EMMPRIN; extracellular matrix metalloproteinase inducer, CD-47; cluster of Differentiation 47

illness. In fact, a clinical study compared the suppressive effects of dipyridamole, and chloroquine on SARS-COV-2 replication, and suggested a similar titer at a concentration of just 100 nM [3]. All this may suggest that this lower dose may be more effective clinically.

Proteinase and covid-19

An association of covid-19, and angiotensin-converting enzyme-2; ACE2 (a metallo-endopeptidase) has been put forward. Hence, covid-19 effects can possibly be mitigated by an inhibitor of metallo-enzymes. Because cardiac matrix is highly unique, and in that very context a cardio-specific matrix metalloproteinase (MMP) inhibitor may well suitably mitigate the blood-heart-barrier (BHB) leakage, and the subsequent dilated cardiomyopathy (DCM) phenotypes. We along this very line propose a cardiac-specific MMP inhibitor regulator (i.e. tissue inhibitor of metalloproteinase;TIMP) to reduce the chances of mortality that is related to covid-19 (Fig. 1).

HCQ intervention will be like the treatment with doxycycline; a suggested MMP inhibitor as reported in the prestigious journal; Nature Reviews for the purpose of tissue remodeling that reverses the endocardial endothelial (EE) dysfunction. Previously, we also demonstrated that an antibiotic mitigated matrix metalloproteinases (MMPs) activation during heart failure [18, 19]. However, it is worth mentioning here that other common antibiotics such as azithromycin, clarithromycin, and erythromycin belonging to the 'macrolide' class have been shown to increase the risk of cardiac arrhythmias or even cardiac death [20]. Although, the use of broad-spectrum antibiotics as an antimicrobial therapy is a lifesaving strategy for patients in the intensive care but antibiotics also dramatically increase the risk for nosocomial infections, for example, the hospital-acquired pneumonia [21]. In a different context, it is unclear whether a salubrious effect arising from the use of a probiotic could also mitigate the MMPs' activation by covid-19. We showed by a 2-D zymography (that is MMPs' function and the proteome), the constitutive expression of MMP-2 in the control autopsy human heart sample; however, in the end-stage of the heart failure, the MMP-2, as well as, MMP-9 activities were found to be robust [22, 23]. More recently, we went on to provide an evidence that a long-term probiotic treatment could help decrease the MMPs' activities [24] (Fig. 1). Further, nicotinamide, and mitochondria via SIRT mechanism regulate bioenergetics as demonstrated by us way back in 2002, showing that nicotinamide did alleviate chronic heart failure syndrome [25]. A little later in 2004, our laboratory revealed that doxycycline could mitigate the deleterious implications between the endothelial- myocyte interaction(s) during the heart failure condition [19].

By now we are aware that the thromboembolic complications are responsible for morbidity and mortality among the susceptible covid-19 patients; however, the data also suggest a possible multifactorial basis of these complications. While every effort is being made by the medical experts to treat patients by taking suitable preventive measures employing anticoagulation therapeutics to deal with the coagulation issues. Despite superb benefits with the use of systemic anticoagulation therapies, the data seem to be retrospective in nature thus raising some questions on the possible interplay of other confounders, as well as, long-term benefits and safety of the systemic anticoagulation approach [26–34].

Blood-heart-barrier (BHB) leakage

The endothelium, whether it is in the endocardium or in coronary or capillaries, is the primary barrier against BHB dysfunction. The tight-junction proteins, viz., connexin-37 between endothelium and endothelium, connexin-43 between endothelium and myocyte, myocyte and myocyte, and mitochondria (mito) and myocyte are the primary connexins; however, it is important to determine the details of the events and mechanism(s) of BHB leakage during covid-19 infection, though. The juxtacrine endothelial-myocyte (E-M), myocyte-myocyte (M-M), and mitochondria (mito)-myocyte uncoupling(s) [23, 35–40] are the hallmarks of cardiac failure (Fig. 1). The role

of connexin-43 which connects myocyte-myocyte, and mitochondria (mito)-myocyte should also be studied in the productive covid-19 infection scenario [41–43]. It is already known that the connexin-37 connects the endothelial and myocyte (E-M). In E-M, M-M, and mito-myocyte uncoupling(s), the role of MMP in degrading the connexins that are responsible for causing BHB dysfunction is unclear, as of today. Basement membrane between the endothelium, and muscle contains an extracellular matrix (ECM), latent MMPs/TIMPs/nitric oxide; NO (the ternary complex) (Fig. 1). However, oxidative stress during CHF activates MMPs, and inactivates the TIMPs via the peroxinitrite, and tyrosine/arginine nitosylation process [22].

The usage of antioxidants has been widely mentioned in the literature for their beneficial effects in chronic conditions because anthocyanins, phenolic acids, and carotenoids are the predominant phytochemicals that are present in purple carrots, and cabbage. Accordingly, they have been promoted in treatment of the metabolic syndromes because anthocyanins improve dyslipidemia, glucose tolerance, hypertension, and insulin resistance. Moreover, these phenolic acids may also protect against the cardiovascular diseases and, in fact. the β-carotene was shown to protect against the oxidative processes, as well [44, 45].

Conclusion and perspective

The role of HCQ in cardiac, and skeletal muscle remodeling is novel. The mitigation of systemic remodeling during CHF by HCQ is an innovative approach. The cardiac-specific MMP-9 can be inhibited by HCQ, and going by the foregoing discussion, it is therapeutically novel, including its potential clinical applications in the covid-19 patients (Fig. 1).

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Author contributions MS and SCT conceived, wrote, edited, and finalized the manuscript while. The lab members helped in providing reagents, and the necessary feedback in moving forward this project. Authors approved the final version of the manuscript before its submission.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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