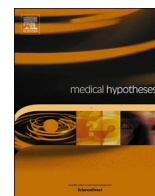




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COVID-19-related arrhythmias and the possible effects of ranolazine

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ABSTRACT

The COVID-19 pandemic has become a burden to the global healthcare community. Despite the severity of the complications associated with COVID-19, no antiviral agent is yet available for the treatment of this disease. Several studies have reported arrhythmias as one of the numerous manifestations associated with COVID-19 infection. Clinicians use different therapeutic agents in the management of COVID-19 patients with arrhythmias, apart from ranolazine; however, some of these drugs are administered with caution because of their significant side effects. In this study, we reviewed the potential antiarrhythmic effects of ranolazine in the management of cardiac arrhythmias associated with COVID-19. Ranolazine is a second-line drug approved for the treatment of chronic stable angina pectoris. Previous studies have shown that ranolazine produces its beneficial cardiac effects without any significant impact on the body's hemodynamics; hence, blood pressure is not altered. Due to its reduced side effects, ranolazine may be more effective than other drugs in producing the desired relief from COVID-19 related arrhythmias, since it produces its antiarrhythmic effect by modulating sodium, potassium and calcium channels, and suppressing cytokine expression.

Introduction

The coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [1] is currently the most pressing public health challenge. This virus has progressed to the level of a global pandemic, infecting more than 80 million people with over one million deaths worldwide as of early January 2021, as reported by the Johns Hopkins COVID-19 Resource Center [2]. SARS-CoV-2 has been linked with several pro-inflammatory mediators that may influence the pathophysiology of cardiac complications. Cardiac arrhythmia, cardiomyopathy and cardiac arrest have been reported as terminal events in patients with COVID-19 [3–5].

To date, no specific antiviral drug has been used for the treatment of COVID-19. However, infected patients are treated with a combination of anti-viral, anti-malarial drugs, corticosteroids and interferon (IFN) β , some of which have the ability to impair ventricular repolarization and increase the risk of malignant arrhythmias, through various mechanisms.

Ranolazine, a piperazine derivative approved for the treatment of chronic angina, is used off-label in the treatment of arrhythmia due its antiarrhythmic properties [6]. Ranolazine is available as an immediate-

release (IR) capsule or extended-release (ER) tablet designed to allow for twice-daily oral administration.

Hypothesis

Considering the promising role of ranolazine in the prevention and management of various arrhythmias, we hypothesized that the anti-anginal drug ranolazine, could be a potential therapeutic agent in the treatment of COVID-19-related cardiac arrhythmias through a variety of mechanisms including, modulating action potential duration (APD) [7] and diminishing pro-inflammatory mediators [8].

Arrhythmias and coronavirus

Arrhythmias are characterized by irregularities in the rate or rhythm of the heartbeat. A number of studies have shown that COVID-19 patients often present relatively high fast heart rates [9,10]. SARS-CoV-2 invades the host cells bound to angiotensin-converting enzyme 2 (ACE2), a membrane bound aminopeptidase which is expressed in different tissues [11–13]. It has been reported that spike (S) protein, a structural protein of the virus, binds strongly to ACE2 [14]; this strong

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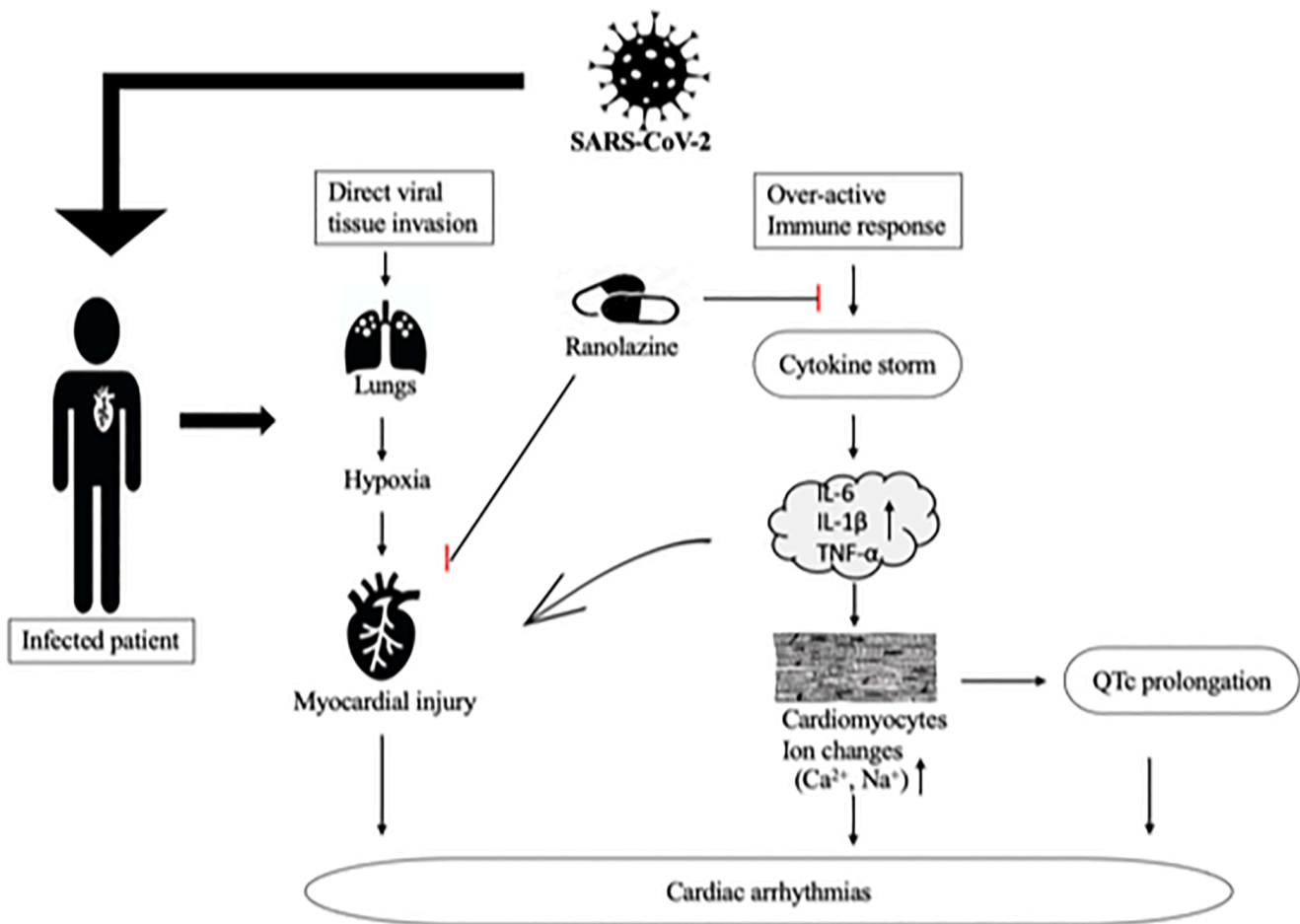


Fig. 1. SARS-CoV-2 triggers cardiac arrhythmias by disrupting the ion channels to cause increase in intracellular calcium and sodium levels via cytokine storm, and hypoxia-induced myocardial damage. Ranolazine shows its antiarrhythmic effect by blocking both hypoxia-induced increase in late sodium current (late I_{Na}) which prolongs action potential duration, and the cytokine storm; ultimately reducing damage to the cardiac tissues.

interaction between the S-protein and ACE2 may alter the electrolyte balance and induce cardiac injury which may precipitate arrhythmias. It has been reported that COVID-19 progresses through several stages in its disease course, starting from the actual viral infection to the direct viral cytotoxic effects, particularly in the respiratory tract, and finally, the hyperinflammatory response to the virus by the body systems including the cardiovascular system [15,16].

Patients with severe COVID-19 have high levels of circulating proinflammatory cytokines such as IL-6, IL-1 β , IL-2 and TNF- α [17–19]. A previous experimental study reported that there was a significant increase in intracellular calcium transients following acute exposure to IL-6 [20]. IL-1 β , through calmodulin-dependent protein kinase II (CaMKII) oxidation and phosphorylation, promotes arrhythmias by prolonging action potential duration (APD), reducing the transient outward potassium current and increasing calcium (Ca^{2+}) spark frequency in the cardiomyocytes [21]. It has also been reported that decreased rectifier potassium current (I_{Kr}), caused by TNF- α , prolonged the duration of action potential [22,23]. The respiratory distress and fever often associated with COVID-19 create an inconducive hypoxic environment for the myocardium which may lead to cell death. Hypoxemia [24], fever [25] and drugs like hydroxychloroquine [26], azithromycin [27] have all been reported to affect the cardiac electrophysiology. Colon et al. analyzed the 12-lead ECGs and telemetry of all patients admitted to a tertiary hospital and reported the presence of atrial tachyarrhythmia in 19 out of 69 COVID-19 patients after they were admitted to an intensive care unit [28]. Since atrial arrhythmias have been reported to be common among COVID-19 patients, particularly those admitted to the ICU,

proper management is required to prevent further complications that may worsen the conditions of infected patients.

Ranolazine effect on cardiac arrhythmias

Infections usually trigger an immune response and as such, the first line of defense to any invading microbe is usually fast and well organized. Cytokines play vital roles in viral infections [17] and any imbalance in cytokine production following over-activation of immune system can lead to local or systemic pathology, as seen in COVID-19 patients [18]. Elevated expressions of these proinflammatory cytokines disrupt the intracellular sodium (Na^+) and calcium (Ca^{2+}) concentrations through several mechanisms, which may lead to electrical instability in the myocardial cells (see Fig. 1). Recent studies have shown that ranolazine increases anti-inflammatory $PPAR-\gamma$ expressions and suppresses the expression of pro-inflammatory cytokines such as TNF- α and IL-1 β , which are capable of releasing glutamate from astrocytes via a Ca^{2+} -dependent mechanism to increase excitation in the neurons [8]. By activating $PPAR-\gamma$, ranolazine suppresses $NF-\kappa B$ signaling, asymmetric dimethylarginine (ADMA) and C-reactive protein plasma levels and promotes endothelial release of vasodilators in ischemic conditions [8,29].

An increase in late sodium current (late I_{Na}) can be arrhythmogenic, and ranolazine, an inhibitor of late sodium current, blocks this arrhythmogenic effect in the heart muscle when the late I_{Na} is inhibited. The inhibitory effect of ranolazine on late I_{Na} reduces the intracellular sodium concentration and subsequent calcium overload, thus reducing

tension in the myocardial wall and other factors that may trigger arrhythmias [30,31] (see Fig. 1). It has been shown that at a slow pace, ranolazine shortens the duration of action potential (APD) in pathological atrial myocytes; however, this effect is dependent on repolarization time and cell type [32,33,34].

Ranolazine has also been reported to affect the transmembrane atrial and ventricular action potential [35]. The effects of ranolazine on atrial fibrillation have been investigated in both experimental and clinical studies and in all, ranolazine significantly reduced atrial fibrillation duration and frequency. Murdock et al. retrospectively reviewed the charts of 25 patients who had received oral ranolazine shortly after they failed to respond to electrical cardioversion. The authors reported that due to ranolazine's effect on preventing early relapse to atrial fibrillation, sinus rhythm was successfully restored in 19 of 25 electrical cardioversion-resistant patients and no adverse effects were noted [36]. In another case report of a 72-year-old patient with left ventricular hypertrophy, the authors reported that there was a significant decrease in ventricular ectopy within two hours of the initial dose of ranolazine [37]. Ranolazine has also been shown to have complementary effects with drugs like dronedarone [38] and amiodarone [39] in reducing the risk of atrial fibrillation.

In a multicenter case series, Yeung et al. systematically evaluated the effects of ranolazine on symptomatic ventricular arrhythmias and reported that in 6 patients treated for symptomatic premature ventricular complexes (PVCs), there was a 60% decrease in PVC burden, and sustained ventricular arrhythmias were eliminated in 2 patients with incessant ventricular tachycardia [40]. This finding suggests that the electrophysiological actions of ranolazine in the ventricles are linked to its inhibitory effect on the late I_{Na} . In the MERLIN-TIMI 36 clinical trial involving 6560 hospitalized patients with non-ST segment elevation acute coronary syndrome (NSTEMI-ACS), it was reported that ranolazine significantly reduced the incidence of ventricular arrhythmias, supra-ventricular arrhythmias and new-onset atrial fibrillation during the first week of treatment [41].

The inhibitory effect of ranolazine on rectifier potassium current (I_{Kr}) prolongs QTc interval; however, this action is rapid and brief with no proarrhythmic effect at low doses [42]. Ranolazine is a substrate for P-glycoprotein and is primarily metabolized by cytochrome P450, particularly CYP3A4 and CYP2D6 [43]; hence, ranolazine is contraindicated in patients with congenital or acquired QT syndrome, and in patients taking medications such as quinidine or hydroxychloroquine, with a QT prolonging effect.

Conclusion

Arrhythmias are one of the extrapulmonary manifestations of COVID-19, which may complicate the conditions of patients with COVID-19 infection. Ranolazine, an FDA approved second-line anti-anginal agent, mainly produces its effects by inhibiting the late inward sodium current (I_{Na}) and suppressing pro-inflammatory cytokines expression. Even with its brief QTc prolongation effect and fewer side effects compared with other approved antiarrhythmic agents, ranolazine may be more effective in the clinical management of COVID-19-related cardiac arrhythmias. In light of this review, we recommend that quality randomized controlled clinical studies be conducted in order to further ascertain the anti-arrhythmic effect of ranolazine in the treatment of COVID-19-related arrhythmias.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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