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Medical Hypotheses 144 (2020) 110177

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

COVID-19: Electrophysiological mechanisms underlying sudden cardiac death during exercise with facemasks

Sharen Lee[a], Guoliang Li[b], Tong Liu[c], Gary Tse[c,*]

[a] Laboratory of Cardiovascular Physiology, Li Ka Shing Institute of Health Sciences, Hong Kong, China
[b] Department of Cardiovascular Medicine, The First Affiliated Hospital of Xi'an Jiaotong University, 277 Yanta West Road, Xi'an 710061, China
[c] Tianjin Key Laboratory of Ionic-Molecular Function of Cardiovascular Disease, Department of Cardiology, Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University, Tianjin 300211, China

ABSTRACT

The mandatory use of facemasks is a public health measure implemented by various countries in response to the novel coronavirus disease 19 (COVID-19) pandemic. However, there have been case reports of sudden cardiac death (SCD) with the wearing of facemasks during exercise. In this paper, we hypothesize that exercise with facemasks may increase the risk of ventricular tachycardia/ventricular fibrillation (VT/VF) leading to SCD via the development of acute and/or intermittent hypoxia and hypercapnia. We discuss the potential underlying mechanisms including increases in adrenergic stimulation and oxidative stress leading to electrophysiological abnormalities that promote arrhythmias via non-reentrant and reentrant mechanisms. Given the interplay of multiple variables contributing to the increased arrhythmic risk, we advise avoidance of a facemask during high intensity exercise, or if wearing of a mask is mandatory, exercise intensity should remain low to avoid precipitation of lethal arrhythmias. However, we cannot exclude the possibility of an arrhythmic substrate even with low intensity exercise especially in those with established chronic cardiovascular disease in whom baseline electrophysiological abnormalities may be found.

Introduction

In response to the novel coronavirus disease 19 (COVID-19) pandemic, different countries have implemented public health measures, such as the mandatory use of facemasks. Recently, in this Journal, Chandrasekaran and Fernandes have provided an excellent account in which they discussed potential pathophysiological mechanisms that underlie dysfunction of different organs due to wearing of facemasks during exercise [1]. They discussed metabolic alterations, impairment in immune response, cardio-metabolic stress, abnormal renal function, and altered brain metabolism as well as mental health. Recently, there have been case reports of sudden cardiac death (SCD) occurring during exercise with facemasks. The aim of this article is to supplement their hypotheses in discussing potential physiological mechanisms of ventricular tachycardia/ventricular fibrillation (VT/VF) leading to SCD.

The hypothesis

In this paper, we hypothesize that exercise with facemasks may increase the risk of ventricular tachycardia/ventricular fibrillation (VT/VF) leading to SCD via the development of acute and/or intermittent hypoxia and hypercapnia.

Whilst the prolonged use of face mask may not lead to significant hypoxia and hypercapnia under normal use at rest, but can do so during stress [2] or exercise [3], and is associated with increased respiratory efforts, reduced work performance [4], adverse effects such as discomfort [5] and headaches [6], especially in individuals with increased basal metabolic demands such as pregnancy [7]. Such physiological changes can be observed with simple surgical masks [2] but is exacerbated with N95 [8] or full-face respirators [9]. Indeed, computational modelling studies report an increase in carbon dioxide level and a decrease in oxygen level with respiratory use due to rebreathed air [10]. Under such conditions, sympathetic stimulation and enhanced chemoreflex hypoxia can lead to tachycardia and hypertension, which can increase myocardial oxygen demand [11,12]. Whilst this may be tolerated in healthy individuals, where the flexible arteries are able to blunt the hypoxia-induced increased cardiac preload, arrhythmia may be aggravated in those with underlying pathology [13]. The mechanisms of arrhythmias can be divided into non-reentrant and reentrant activity [14]. This article discusses the electrophysiological abnormalities that can be induced by hypoxia and hypercapnia, with a summary provided in Fig. 1.

Arrhythmia initiation

Arrhythmia initiation requires premature ventricular beats, which can be generated by enhanced automaticity, parasystole, triggered activity (early afterdepolarizations (EADs) and delayed

* Corresponding author.
E-mail address: gary.tse@doctors.org.uk (G. Tse).

https://doi.org/10.1016/j.mehy.2020.110177
Received 3 August 2020; Accepted 9 August 2020
Available online 11 August 2020
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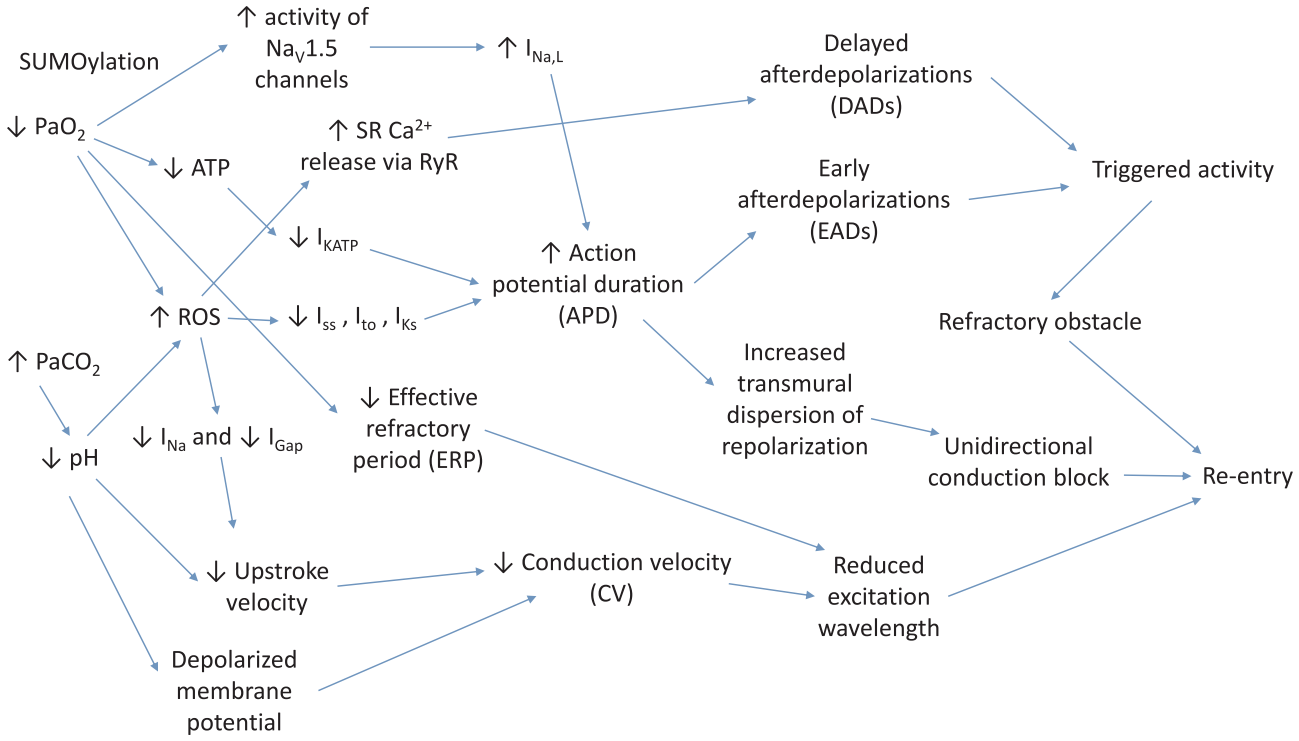

Fig. 1. Electrophysiological mechanisms underlying ventricular arrhythmogenesis during exercise with facemasks.

afterdepolarizations (DADs)) or reentry. Some of these mechanisms may play a role in the initiation of arrhythmia during hypoxia. Firstly, during hypoxia-induced adrenergic stimulation, increased phosphorylation of L-type calcium channel increases Ca^{2+} influx into cardiac myocytes during the plateau phase of the cardiac action potential, leading to prolonged action potential duration (APD), induction of EADs and triggered activity [15]. Secondly, there is accumulation of cyclic AMP during ischaemia [16], which can generate DADs [17]. Indeed, studies on isolated canine ventricular tissues reported oscillatory afterpotentials which initiated extrasystoles during the reperfusion phase of ischemia–reperfusion injury [18]. Hypoxia alone is also sufficient to generate ectopic foci through micro-reentry in a human ventricular model, suggesting that hypoxic episodes can led to lethal ventricular tachyarrhythmia in those with underlying myocardial fibrosis [19].

Arrhythmia persistence

Following initiation, the trigger must persist or mechanisms such as reentry are needed to sustain the arrhythmia. Reentry may occur in the presence of an obstacle around which an action potential can circulate, or without such obstacles. The commonest form of reentry requires an obstacle. The obstacle in reentry may be an anatomical abnormality, such as an area of fibrosis, or can be generated functionally such as an area of refractoriness. Mines proposed three criteria for this type of reentry [20]: (a) an area of unidirectional block must be present; (b) the excitation wave propagates along a distinct pathway, returns to its point of origin, and starts again; and (c) interruption of the circuit at any point would terminate this circus movement. In this circus-type reentry, the conduction velocity (CV) of the cardiac action potential must be reduced or the effective refractory period (ERP) must be reduced, such that the activation wavefront can activate the tissue ahead of it. This can be summarized in excitation wavelength (λ) given by CV × ERP.

The roles of increased oxidative stress

During acute hypoxia, action potential duration is shortened, which is expected to be associated with a reduction in the ventricular ERP with more rapid recovery of the membrane potential to baseline [21]. If hypoxia becomes more sustained or intermittent, results in the uncoupling of endothelial nitic oxide synthase, thereby increasing the production of reactive oxygen species (ROS). The resulting increase in oxidative stress was found to be associated with the initiation and perpetuation of ventricular arrhythmias [22,23], which can be explained by abnormalities in the activity or expression of cardiac ion channels [24]. These in turn lead to alterations in CV, APD or ERP, which serve as the substrate for arrhythmogenesis. CV is determined by sodium channel activation and gap junction conduction. Action potential duration (APD) is determined by a balance of inward and outward currents, and ERP is determined by a combination of membrane potential recovery and sodium channel reactivation.

Hypoxia leads to reduced function of the voltage-gated sodium channel $Na_v1.5$, leading to smaller I_{Na}, or to altered function of gap junctions that mediate electrical coupling between adjacent cardiomyocytes [25]. Moreover, acidosis from hypercapnia can lead to both persistent membrane depolarization and reduced phase 0 slope of the cardiac action potential [26]. Together, these abnormalities can lead to reduced CV and smaller λ, and/or increased heterogeneity in conduction. Moreover, hypoxia can increase the late component of I_{Na} through SUMOlysation [27], leading to prolonged APDs that can predispose to reentry.

The uptake and release of calcium ions are also interfered by increased oxidative stress [28]. Reduction of oxidation-sensitive cysteine residues in sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA), responsible for releasing intracytoplasmic Ca^{2+} back to the sarcoplasmic reticulum, results in cytosolic Ca^{2+} accumulation and calcium-mediated arrhythmias [29,30]. Furthermore, increased cytosolic Ca^{2+} level promotes Na^+-Ca^{2+} exchanger (NCX) activity, which can generate late EADs [31,32]. Increased oxidative stress also acts on the activity of NCX directly through the activation of TRP channels and epigenetic alterations [33,34].

Acute hypoxia can also induce prolonged APDs by reducing outward K^+ currents. The activity of hERG1 potassium channels, which contributes to the outward K^+ currents and underlies the long QT syndrome when mutated, was found to be significantly inhibited during mild oxidative stress [35], as is the transient outward potassium current [36]. The high sensitivity and complex interplay of different ion channels under increased oxidative stress explains the electrocardiographic QT_c and T_{peak}-T_{end} interval prolongation under intermittent hypoxia, reflecting prolonged repolarization and increased dispersion of repolarization, leading to increased reentry risk [37–40].

Conclusion

In conclusion, exercise with facemasks may increase the risk of SCD via the development of acute and/or intermittent hypoxia and hypercapnia. The hypothesized mechanisms include increased adrenergic stimulation, increased oxidative stress leading to electrophysiological abnormalities that promote arrhythmias via non-reentrant and reentrant mechanisms. Given the interplay of multiple variables contributing to the increased arrhythmic risk, we advise avoidance of a facemask during high intensity exercise, or if wearing of a mask is mandatory, exercise intensity should remain low to avoid precipitation of lethal arrhythmias. However, we cannot exclude the possibility of an arrhythmic substrate even with low intensity exercise especially in those with established chronic cardiovascular disease in whom baseline electrophysiological abnormalities may be found [41,42].

Funding

None.

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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