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Review article

Metabolic stress, reactive oxygen species, and arrhythmia

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ABSTRACT

Cardiac arrhythmias can cause sudden cardiac death (SCD) and add to the current heart failure (HF) health crisis. Nevertheless, the pathological processes underlying arrhythmias are unclear. Arrhythmic conditions are associated with systemic and cardiac oxidative stress caused by reactive oxygen species (ROS). In excitable cardiac cells, ROS regulate both cellular metabolism and ion homeostasis. Increasing evidence suggests that elevated cellular ROS can cause alterations of the cardiac sodium channel ($Na_v1.5$), abnormal Ca^{2+} handling, changes of mitochondrial function, and gap junction remodeling, leading to arrhythmogenesis. This review summarizes our knowledge of the mechanisms by which ROS may cause arrhythmias and discusses potential therapeutic strategies to prevent arrhythmias by targeting ROS and its consequences. This article is part of a Special Issue entitled "Local Signaling in Myocytes".

Contents

Abbreviations: $\Delta\Psi_m$, mitochondrial membrane potential; ACE, angiotensin converting enzyme; ADP, adenosine diphosphate; AF, atrial fibrillation; AngII, angiotensin II; AP, action potential; ATP, adenosine-5′-triphosphate; $[Ca^{2+}]_i$, intracellular Ca^{2+} concentration; CICR, Ca^{2+}-induced Ca^{2+} release CICR; Cx, connexins; DTT, dithiothreitol; E-C coupling, excitation–contraction coupling; ETC, electron transport chain; GSH, glutathione; GPD1-L, glycerol-3-phosphate dehydrogenase 1-like protein; hERG, human *ether-a-go-go*-related gene; HF, heart failure; HIFα, Hypoxia inducing factor-1α; IMAC, inner membrane anion channel; I_{Na}, sodium current; I_{Kr}, delayed rapid rectifier K^+ current; I_{Ks}, delayed slow rectifier K^+ current; MAP, monophasic action potential; mitoK$_{ATP}$, mitochondrial ATP-sensitive potassium channel; NAD, nicotinamide adenine dinucleotide; $Na_v1.5$, cardiac sodium channel; NCX, Na^+–Ca^{2+} exchanger; NO, nitric oxide; NOS, nitric oxide synthase; PES, programmed electrical stimulation; PK, protein kinase; RAS, renin-angiotensin system; ROS, reactive oxygen species; RyR, ryanodine receptor; sarcK$_{ATP}$, sarcolemmal ATP-sensitive potassium channel; SCD, sudden cardiac death; SCN5A, cardiac sodium channel gene; SERCA, sarcoplasmic reticulum Ca^{2+}-ATPase; SR, sarcoplasmic reticulum; TCA, tricarboxylic acid; TdP, torsades de pointes; VT, ventricular tachycardia.

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1. Introduction

The majority of sudden cardiac death (SCD) results from the occurrence of potentially lethal ventricular tachycardia (VT) or ventricular fibrillation (VF), only two of many types of arrhythmia. Arrhythmia is an irregular heart rhythm and is classified by rate as either tachycardia or bradycardia (resting heart rate >100 beats/min or <60 beats/min, respectively). Arrhythmias are also mechanistically classified as automatic, reentrant, and triggered. Reentry is favored by slow, inhomogeneous conduction. Types of arrhythmia include (1) premature beats; (2) supraventricular arrhythmias (e.g., atrial fibrillation (AF), atrial flutter, and paroxysmal supraventricular tachycardia); (3) ventricular arrhythmias (e.g., VT and VF); and (4) bradyarrhythmias.

SCD occurs in approximately 180,000–250,000 cases annually in the United States, and an estimated 4–5 million cases worldwide [1]. SCD occurs in hypertrophic cardiomyopathy, dilated cardiomyopathies, arrhythmogenic right ventricular dysplasia, myocardial infiltrative diseases, and other related disease states [2]. The prevalence of cardiovascular diseases potentially associated with lethal ventricular arrhythmia is estimated at approximately 13 million US individuals, which is about 5% of the middle-aged population [3].

Paroxysmal or persistent AF afflicts approximately 2.2 million Americans in addition to 4.5 million people in the European Union. AF is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with consequential deterioration of atrial mechanical function. It is the most common arrhythmia clinically encountered, accounting for over 30% of hospital admissions for cardiac rhythm disturbances [4] and is associated with increased risks for stroke, heart failure (HF), and death [5,6]. The incidence of AF noticeably increases over the age of 60, afflicts 3–5% of the population 65 to 75 years old and occurs in up to 8% of those older than 80 years [7–9]. The prevalence of this arrhythmia has significantly increased recently, and the number of Americans with AF is expected to surpass 5 million by 2050 [10].

Despite the high prevalence and significance of arrhythmias, the mechanisms of arrhythmogenesis are not fully understood. Some molecular mechanisms known to contribute to arrhythmias include genetic alterations of ion channels leading to electrophysiological dysregulations and structural remodeling of the left ventricle (LV) in hypertrophy and HF [11–14]. Increasing evidence suggests that altered cardiac ion homeostasis and structural remodeling are highly associated with elevated reactive oxygen species (ROS) and metabolic stress [15,16]. In this review, we summarize possible mechanisms whereby the imbalanced cellular redox state may cause arrhythmogenesis by ROS-induced alterations of ion homeostasis and ion channel behavior.

2. Cardiac conditions associated with metabolic stress, ROS, and arrhythmias

Cardiac metabolism is reflected by adenosine-5′-triphosphate (ATP), which is the source of energy for maintenance of ion homeostasis as well as repetitive mechanical contraction and relaxation. Approximately 60–70% of ATP is used for cardiac muscle contraction, and the remaining 30–40% is used for Ca^{2+} uptake into the sarcoplasmic reticulum (SR) to initiate diastolic relaxation and to sustain ion current homeostasis including the maintenance of Na^+ and K^+ gradients across the plasma membrane [17,18].

Mitochondria occupy approximately 30% of the volume of ventricular cardiomyocytes and form a network around the myofilaments resulting in the location of ATP production sites being adjacent to ATP consumption sites [19]. Although there are several sources of ROS in cardiac muscle including NADPH oxidase, xanthine oxidase, and uncoupled NOS, mitochondria are the major ROS source. Electron leakage from complex I and III is associated with the generation of ROS in the failing heart [20], ischemia/reperfusion [21] and arrhythmia [16]. Complex I (i.e. NADH and ubiquinone oxidoreductase) produces superoxide ($O_2^{\bullet -}$) in the mitochondrial matrix whereas complex III (i.e. Q-cycle, cytochrome bc1 complex and coenzyme Q) produces superoxide in the matrix and intermembrane space [22]. Oxidative phosphorylation is tightly linked to mitochondrial regulation so that the cellular ATP content remains constant even with large increases in cardiac ATP consumption [23]. The electron transport chain (ETC) of the mitochondria matrix transfers electrons from carbon substrates (e.g., fatty acids and pyruvate) to nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$) in order to synthesize ATP. During the occurrence of abnormal pathophysiological conditions that cause arrhythmia (when the balances of blood flow, oxygen delivery, mitochondrial metabolism, NADH formation, and ATP synthesis are disrupted), NADH, protons, and lactate accumulate, potentially contribute to arrhythmic risk. Moreover, when disrupted, mitochondria produce ROS via electrons leaking from the ETC that react with molecular oxygen to form superoxide. The accumulation of ROS in the mitochondria can lead to oscillations in the mitochondrial membrane potential ($\Delta\Psi_m$) and changes in matrix concentrations of Ca^{2+}, NADH, ADP, and tricarboxylic acid (TCA) cycle intermediates [24]. Hypoxia also decreases the rate of metabolism, resulting in the decrease of intracellular NADH/NAD^+ ratio and an increase in ROS production [25–27]. Accumulating ROS further increases the rate of ROS production, a phenomenon known as ROS induced ROS release [28].

ROS, also called reactive oxygen intermediates, are comprised of superoxide, hydrogen peroxide (H_2O_2), hydroxyl radicals (•OH) and peroxynitrite ($ONOO^-$) [29]. ROS are highly reactive and unstable molecules leading to irreversible, deleterious reactions with lipids and proteins. Cardiac conditions such as hypertension [30], diabetes mellitus [31], coronary artery disease [32,33], cardiomyopathies, and HF [34,35] are associated with altered metabolism and arrhythmias. In diabetes mellitus, arrhythmias and oxidative stress are well correlated [31]. In ischemia/reperfusion injury, the mitochondrial ETC serves as the major source of ROS [21]. In chronic HF, ROS levels increase [20,36] and myocardial anti-oxidant reserve decreases [37,38].

Trace amounts of ROS serve as signaling molecules in physiological conditions, but the excessive production of ROS elicits pathologic cellular processes [39]. To protect cellular functions from ROS, cells have two defense mechanisms, enzymatic and nonenzymatic pathways. The enzymatic pathway includes three superoxide dismutases, catalase, and glutathione peroxidase [40]. The dismutation of superoxide by superoxide dismutase results in the generation of H_2O_2, which catalase further metabolizes to water and oxygen. In the nonenzymatic pathways, there are a variety of redox-defense system including anti-oxidant scavengers, such as vitamins E and C [41], the ratio of reduced glutathione (GSH) to oxidized glutathione disulfide (GSSH), the ratio of oxidized and reduced forms nicotinamide adenine dinucleotide, NADH/NAD^+, and the thioredoxin [14,42].

One of the main consequences of oxidative stress is the depletion of key intracellular anti-oxidants such as glutathione (GSH), the largest anti-oxidant pool in the heart [43]. In ischemia [44–46], HF [47], and type 2 diabetes [48], conditions associated with arrhythmia, the oxidized GSH ratio (GSH/GSSH) of ~200–300 to 1 is decreased by 50–70%. During AF, there is biochemical evidence of oxidation by peroxynitrite and hydroxyl radicals [49]. Systemically, serum oxidative markers are elevated in individuals with AF [50]. Other oxidative serum markers including malondialdehyde and nitrotyrosine are also increased in arrhythmias [20,51].

Another important cellular redox defense system is a cytosolic NADH/NAD^+ level [43]. HF is associated with reduced NAD^+ and increased NADH [52–54]. The balance of oxidized and reduced NAD forms varies some between species and tissues. In the monkey, the estimated ratio between free NADH to NAD^+ in the cytoplasm is ~0.002. In rodents and swine, the ratio of total NADH/NAD^+ ranges from 0.05