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Review article

The complex crosstalk between inflammatory cytokines and ventricular arrhythmias

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ABSTRACT

The network of cytokines consists one of the most extensively studied signaling systems of human body. Cytokines appear to modulate pathogenesis and progress of many different diseases in the human body, particularly in regards to cardiovascular system. However, their effects on the electrical system of the heart has been neglected. Over the past decade, attemps to understand this relationship led to the uncovering of the direct and indirect effects of cytokines on action potential propagation and cell depolarization. This relationship has been depicted in clinical practice as serum levels of cytokines are increasingly associated with prevalence of ventricular arrhythmias either isolated or secondary to either a heart condition or a systemic auto-immune disease. Thus, they present an appealing potential as a biomarker for prediction of arrhythmia generation, as well as the ourtcome of electrophysiological interventions.

1. Introduction

Ventricular arrhythmias, mainly represented by ventricular tachycardia (VT) and ventricular fibrillation (VF) are serious adverse events occurring in the setting of ischemic heart disease (IHD), chronic heart failure (CHF) and other conditions involving the heart muscle, which can lead to sudden cardiac death (SCD) and portend an unfavorable prognosis in these patients. Ischemic heart disease is responsible for approximately 65 percent of SCD cases, while the rest 35% and 5% is linked to structural heart disease (hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy (ARVC), valvular heart disease, myocarditis) and pro-arrhythmic diseases (long QT, short QT, Brugada and pre-excitation syndromes) respectively[1]. In children and young adult population, epidemiology is different with IHD accounting for 24 percent of SCD, inherited cardiomyopthies for 16 percent while the majority of cases remains unexplained. The percentage of unexplained cases is becoming more and more limited thanks to the use genetic testing [2].

Inflammation plays significant role in the pathogenesis of heart disease. Particularly, certain pro-inflammatory cytokines such as tumor necrosis factor- alpha (TNF-a), interleukin 1 (IL-1) and interleukin 6 (IL-6) are involved in the progression of CHF [3] and are linked to increased IHD [4] risk. In the case of CHF, expression of these cytokines by stressed myocytes leads to the recruitment of fibroblasts and macrophages thus creating the inflammatory environment of chronic remodeling and fibrosis of the myocardium [5]. These changes lead to susceptibility of ventricular tissue to arrhythmia as a consequence of the deterioration of systolic function and ventricular hypertrophy and dilation. The abolishment of the effect of TNF-a on the failing heart can have direct effects on its function as represented by a decrease of N-terminal pro-brain natriuretic peptide (NT pro-BNP) levels, thus improving myocardial burden [6]. Concerning IHD, the role of inflammation in the formation and stability of atherosclerotic plaque is now well established. In the presence of CD4 lymphocytes, TNF-a promotes oxidized Low Density Lipoprotein uptake by macrophages and facilitates leukocyte migration through vascular cell adhesion molecule 1 expression [7] increasing this way oxidative stress in the plaque [8]. IL-1 and IL-6 also act as chemotactic mediators, with IL-1 levels indicating the presence of unstable atheromatous disease [9]. After an acute coronary syndrome, repair of damaged tissue is also mediated by the expression of IL-1, IL-6 and TNFa, which is followed by collagen formation, myofibroblast proliferation and angiogenesis on the site of infarct [10]. As a consequence, inflammation is involved in the cumulative process of atherosclerosis, the generation of acute ischemic

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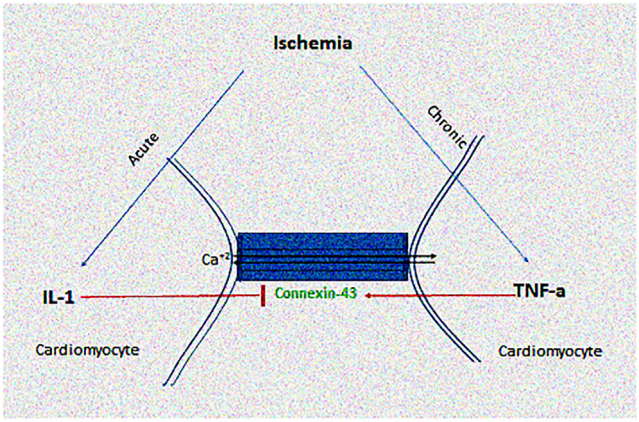

Fig. 1. The differential effects of ischemia related inflammation in arrhythmia generation. Chronic ischemia leads to a TNF-dependent induction of connexin-43 while IL-1 in the settings of acute ischemia suppresses it. Reduction of connexin-43 ion channels leads to cell uncoupling and increased potential for arrhythmias.

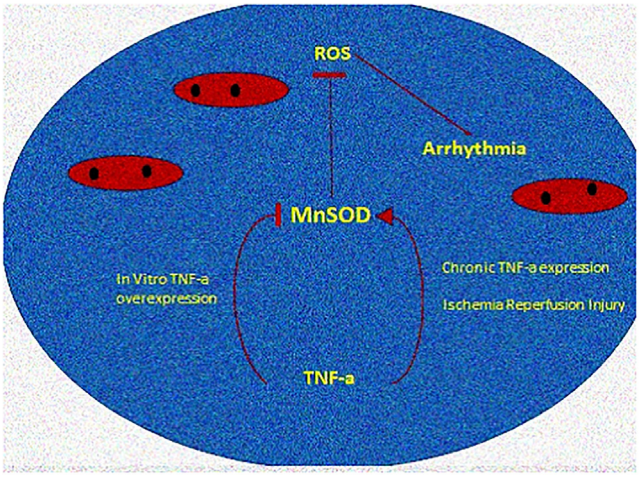

Fig. 2. TNF-a upregulation has a non-linear relationship with ROS levels. Experimental in vitro as well as in vivo TNF-a overexpression resulted in increased ROS production through downregulation of MnSOD. In the case of ischemia reperfusion injury as well as when expressed chronically TNF-a extinguishes intracellular ROS through triggering of MnSOD production.

events and the post-ischemic tissue changes, such as collagen scar formation. Since all of these stages of IHD can be complicated by the generation of ventricular arrhythmias, the inflammatory profiles of such patients before, shortly after or long after the acute ischemic event, are linked to the risk of arrhythmia occurrence (see Figs. 1 and 2).

In addition, the serum profiles of such mediators have been found to convey information about the prognosis of CHF patients [11] and the outcome of acute ischemic events [12]. Given that the risk of ventricular arrhythmia is an important contributing factor in the outcome of such patients, it is logical to hypothesize that inflammatory mediators are directly associated with the generation of such arrhythmias.

1.1. Pathophysiology

Cytokines interact with the conduction system of the heart across multiple layers, as described in detail later in the text. On cellular level, inflammatory mediators determine the rate of both production and neutralization of Reactive Oxygen Species (ROS) which in turn affect action potential propagation. ROS can alter ion channel synthesis in cardiomyocytes and therefore affect directly the electrical properties of the heart. On tissue level, cytokines have a significant interplay with autonomic nervous system, especially regarding innervation of myocardium. These changes may trigger or prevent ventricular arrhythmias through modification of myocyte electrophysiology, action potential and corrected QT (QTc) duration. Prolongation of QTc in the setting of systemic inflammation is a recently described entity [13] which seems to influence the prognosis of many chronic inflammatory diseases. It involves the action of certain cytokines as remote mediators on the heart muscle.

1.1.1. Reactive oxygen species

The electrical effects of cytokines through changes in ROS levels have been mostly studied in the settings of ischemia preconditioning, a process which prepares the myocardium before ischemia and limits myocardial damage and arrhythmia. Modulation of the antioxidant mechanisms of the myocyte by cytokines seems to play an important role. More specifically, cytokines affect the production as well as neutralization of ROS. ROS, apart from their pivotal role in the pathogenesis of many other heart conditions, alter directly the electrophysiologic properties of myocardium through changes on sodium and potassium currents, intracellular calcium handling and connexin 43 (Cx43) expression [14].

1.1.1.1. Ischemic reperfusion injury and TNF-a. Table 1 demonstrates the effects of cytokines in ROS generated myocardial injury. TNF-a modulates ROS production in a varying and condition-dependent manner. TNF-a overexpression has been demonstrated to induce ROS generation in both ventricular rat myocytes [15] and transgenic mice through downregulation of Mn-dependent superoxide dismutase (MnSOD). On the other hand, when induced by exercise, it exerts a protective effect against ischemia–reperfusion injury (IRI) on the rat heart, through MnSOD upregulation, which was abolished by administration of TNF-a-neutralizing antibodies [16]. This protective effect was also observed in vitro, on isolated rat hearts exposed to low

Table 1
A summary of cytokine effects on ROS induced heart dysrhythmias.

Study	Cytokine	Experimental model	Mechanism	Effect on ischemia-reperfusion injury
Yamashita et al. [16]	TNF-a; IL-1b	Rat Heart	MnSOD upregulation	Protective (after exercise)
Suematsu et al. [15]	TNF-α	rat myocytes, transgenic mice	MnSOD downregulation- ROS production	contributing
Lecour et al. [17]	TNF-α	rat heart	catalase upregulation	protective (after normobaric hypoxia)
Alanova et al. [18]	TNF-α	Rat	TNF-α receptor type 2	protective
Nogae et al. [19]	IL-1	rat, rat heart	MnSOD upregulation	protective
Repine et al. [20]	IL-1alpha	rat heart	G6PD upregulation	protective
Maulik et al. [21]	IL-1alpha	Rat	G6PD, Zn/Cu-dependent SOD, catalase, glutathione peroxidase upregulation	protective

Abbreviations: ROS; reactive oxygen species, TNF-a; Tumor Necrosis Factor alpha, IL; interleukin, G6PD; glucose 6 phosphate dehydrogenase, SOD; superoxide dismutase