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Arrhythmogenic Nitro-Oxidative Stress: A Working Hypothesis in Chagas' Heart Disease

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Abstract

We still need to learn a lot about the effects of redox therapy on complex ventricular arrhythmia in Chagas heart disease (ChHD), caused by the parasite *Trypanosoma cruzi*. The evidence has pointed toward oxidative stress and the consequent loss of modulation of redox signaling as an important pathogenic factor in ventricular arrhythmias in ChHD. The central purpose of this article will be to promote a better understanding of the arrhythmic influence of the loss of redox signaling-ROS and RNS modulation, focusing on the arrhythmogenic mechanisms of complex ventricular arrhythmias. Still, we will provide the reader a therapeutic rationality in relation to antioxidant and complex ventricular arrhythmias.

Keywords: Chagas heart disease; *Trypanosoma cruzi*; Oxidative stress; Ventricular arrhythmia; Arrhythmogenic mechanisms

Abbreviations: ChD: Chagas Disease; ChHD: Chagas heart disease; SCA: Sudden Cardiac Arrest; ICD: Implantable Cardioverter Defibrillator; ROS: Reactive Oxygen Species; GCS: Gamma-glutamylcysteine Synthetase; SOD2/ MnSOD: Superoxide dismutase – Mn; iNOS : NO synthase; TNF-α: Tumour Necrosis Factor-α; DADs: Delayed After Depolarization; QTc: corrected QT interval; NO: Nitric Oxide; VNS: Vagal Nervous System; OS: Oxidative Stress; nNOS/NOS1: Neuronal Nitric Oxide Synthase; RNS: Reactive Nitrogen Species; SIRT1: NAD-dependent deacetylase sirtuin-1; VCA: Ventricular Cardiac Arrhythmias; TBARS: Thiobarbituric Acid Reactive Substances

Introduction

Chagas' disease (ChD), also known as American trypanosomiasis, is a serious chronically debilitating and often fatal human endemic infectious-parasitic affection caused by *Trypanosoma cruzi*, transmitted through a hematophagous triatomine vector [1]. It is estimated that up to 5,800,000 people in Latin America endemic countries have chronic ChD causing around 12,500 deaths annually. Hundreds of thousands of infected people has migrated to non-endemic areas, mainly in many parts of Europe and North America, becoming an emerging disease and a worldwide problem [2].

Figure 1 show a diagram of the natural history of Chagas disease. There are 2 phases of the human disease: the acute, which begins about 1 week after the initial infection and is usually asymptomatic; and the chronic, which is subdivided into indeterminate and clinical (cardiac, digestive, or mixed) forms. The clinical presentation in cardiac form is usually mild (80-90%) with annual incidence relatively low (1.85%). The Figure 2 displays a proposed algorithm to guide diagnosis in patients with Chagas heart disease (ChHD).

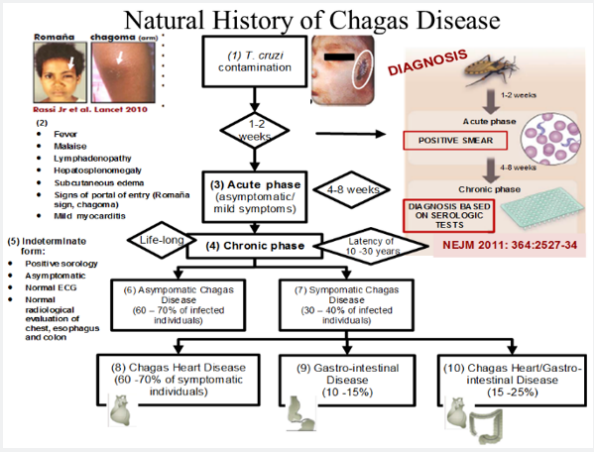

Figure 1: Diagram of the natural history of Chagas disease. There are 2 phases of the human disease: the acute, which begins about 1 week after the initial infection and is usually asymptomatic; and the chronic, which is subdivided into indeterminate and clinical (cardiac, digestive, or mixed) forms. The clinical presentation in cardiac form is usually mild (80-90%) with annual incidence relatively low (1.85%). Modificated from Rassi Jr A et al. [56] with permission.

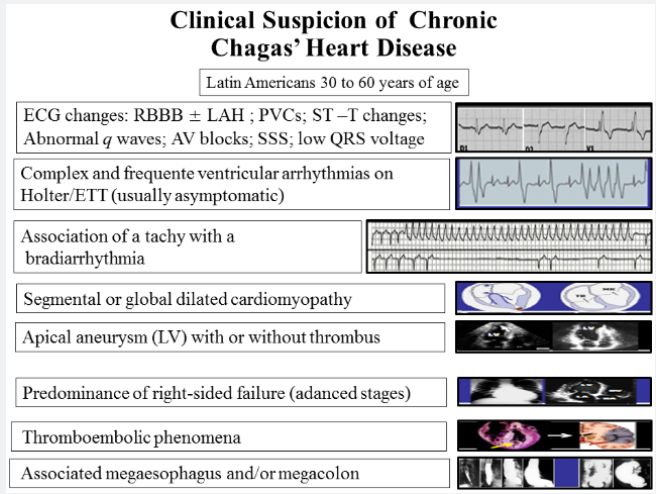

Figure 2: Proposed algorithm to guide diagnosis in patients with Chagas heart disease. People of risk to acquiring Chagas disease (people who lives in rural areas of South America, Central America and Mexico under poor housing conditions that contains infected bugs; who receives a blood transfusion or organ transplant from an infected donor; Children who are born from an infected mother) with ECG showing the 3 most typical alterations: right bundle branch block, left anterior hemiblock and ventricular extra systole. Two-dimensional echocardiogram showing left ventricular apical aneurysm with (arrow) and without thrombus. Modificated from Rassi Jr A et al. [56] with permission.

There is a consensus that for every chagasic patient with evidence of cardiac involvement we should consider the potential risk of death (annual mortality rate of 39/1000 patients) and of annual sudden cardiac arrest (SCA) rate of 24/1000 patients in the cardiac form of the disease) [3-5]. SCA is one of the main ways of death in ChHD and can occur at any stage of the disease [6]. The risk of SCA is related to the presence of ventricular arrhythmias, 10% are due to a first arrhythmic event in ChHD. At moment, in patients with ChHD, there is no data to support recommendations of implantable cardioverter defibrillator (ICD) for the primary prevention of sudden death and ICD are empirically and commonly used for secondary prevention with significant economic burden [5]. This is due to the fact that the mechanisms underlying these lethal arrhythmias are still poorly understood despite decades of research.

Typically, ChHD is characterized by a persistent chronic active myocarditis as resulted of an amplified immunoinflammatory response among other processes by generation of reactive oxygen species (ROS) in the presence of the parasite or its antigens [7-13]. It suggests that ChHD is, at least partially, a ROS-dependent pathology (Figure 3). In fact, in the last fifteen years, this concept of loss of redox signaling-ROS modulation has increased [14,15]. In addition, the incidence of ventricular arrhythmias, the leading cause of SCA, is associated with progression and extension of inflammatory processes, and, probably is especially related to re-entry pathways generated by resultant patchy fibrosis [2,6,12,13,16,17]. So, it is reasonable to speculate that loss of redox signaling-ROS modulation can be regarded as a potential driver of cardiac arrhythmia in ChHD.

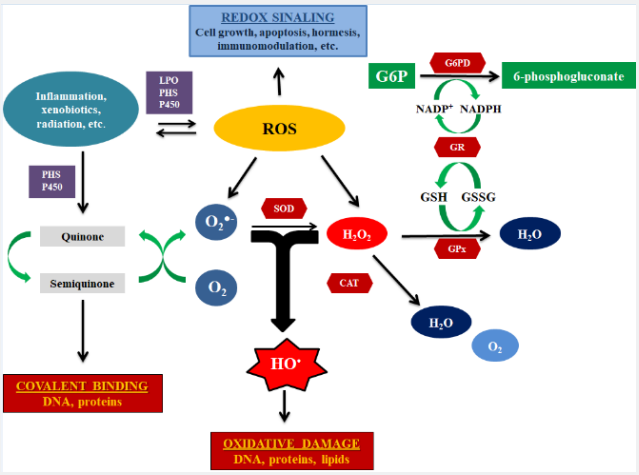

Figure 3: Schematic view of reactive oxygen species production. Diagram showing the inflammatory process leading to oxidative damage through the production of reactive oxygen species.

Pathogenesis of ChHD with special focus on Oxidative Stress

Mounting evidence have suggested that macrophages, neutrophils and natural killer cells control parasite replication in the early stages of human infection [18-21]. Experimental studies have indicated that Tc-derived molecules engage toll-like receptors to drive activation of macrophages and neutrophils that then produce oxidative burst [11,22]. Some studies have demonstrated that oxidative burst is due to mitochondrial oxidative dysfunction due to *T. cruzi*–induced intracellular Ca^{+2} flux, required for parasite invasion. The mitochondrial inefficiency in the setting of oxidative phosphorylation continues during the disease chronic phase [23,24] resulting in an inadequate coupling of the respiratory chain with oxidative phosphorylation and an excessive release of electrons to molecular oxygen, leading to an increased mitochondrial ROS production. The role played by ROS-producing macrophages at the chronic stage of infection has been little evaluated and it is still a matter of debate whether indeed oxidative environments provide ideal conditions (e.g., iron availability in macrophages) for *T. cruzi* growth and whether indeed redox signaling directly to stimulate growth. Garg et al considered the activation of SIRT1 a potential means to restore mitochondrial respiratory chain activity and oxidative phosphorylation capacity as well as to induce mitochondrial biogenesis, processes they found earlier to be impaired in the myocardium of chronically infected rodents [25]. The declines in left-ventricle function and in the expression of Nrf2, HO-1, and gamma-glutamylcysteine synthetase (GCS) were prevented in the hearts of Superoxide dismutase - SOD2 (MnSOD) super expressing transgenic mice [26]. Mice that are deficient for the IFN-y receptor and inducible •NO synthase (iNOS) showed an increased infection risk [27]. Experimental studies in animals infected with *Trypanosoma*

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cruzi are suggestive that drugs, which attenuate oxidative stress, prevent evolution of cardiac injury [28-30].

Studies in humans have provided indirect evidence for the oxidative function of activated macrophages and neutrophils [12,31-34]. It was recently demonstrated the interlinked effects of inflammatory responses, antioxidant status and oxidant levels in human ChHD [12,26,35]. These interlinked effects were thought to be related to heart function damaged. Thus, protection against ROS has the potential to decrease tissue damage in ChD [36-38]. Since then, several publications have followed this idea [36-40]. Our research group have shown that the progression of cardiac involvement in human ChD [7] might be mediated by ROS, and that the use of antioxidant vitamins E and C was effective in attenuating such oxidative insult in the different stages of cardiac involvement of the disease [7-10].

The central purpose of this manuscript will be to promote a better understanding of the arrhythmic influence of the loss of redox signaling-ROS modulation, focusing on the arrhythmogenic mechanisms of complex ventricular arrhythmia. Still, we will provide the reader a therapeutic rationality in relation to antioxidant and complex ventricular arrhythmias

Oxidative stress and ventricular arrhythmias in ChHD

Studies relating ventricular arrhythmias and ROS in ChHD are scarce, and the current load of knowledge relies largely on studies transposed from other cardiomyopathies.

Information on how alterations of ROS may alter ventricular arrhythmia susceptibility are still to be fully understood. Many of the experimental observations agree with the more limited number of human studies. Mice engineered to over-express tumour necrosis factor-α(TNF-α) have been commonly used as a model of congestive HF, exhibiting many ion channel conductance abnormalities and increased susceptibility to induced arrhythmias compared to wild-type controls [41]. These are associated with change in the electrical restitution property of the heart and dysregulated intracellular calcium homoeostasis [42]. Accumulation of ROS resultant from loss of modulation of redox signaling very possibly by over boarding inflammation may lead to cardiac Ca^{++} overload, and then induce delayed after depolarization (DADs), which is likely to initiate triggered activity and ventricular arrhythmias. It was reported that complex ventricular arrhythmias may be derived from calcium wave [43] and caused by diastolic calcium leakage [44]. When the calcium wave reaches threshold potential, DADs are induced, leading to ventricular arrhythmia or even SCA. These abnormal findings were corroborated in an experimental mouse model of *T. cruzi* infection that showed shortens corrected QT interval (QTc) after the intervention of the antioxidant resveratrol [36]. These effects of ROS leading to cardiac Ca++ overload in animal's studies have been consistent in the related literature and point to as the mechanism underlying in the ventricular arrhythmogenesis. Although the full mechanism of action remains to be elucidated, several research groups have explored the possibility that nitric oxide (•NO) is involved in both central and peripheral aspects of vagal control in terms cardiac arrhythmogenesis [45]. In the last years, studies have shown that stimulation of the vagal nervous system (VNS) makes induction of VF more difficult underscoring that VNS has a direct and prominent electrophysiological effect on the ventricular myocardium. It was also showed that this anti-fibrillatory effect is associated with a change in the electrical restitution property of the heart [45], which is considered a key mechanistic factor in the initiation of ventricular fibrillation [46]. These effects are blocked during nitric oxide synthase (NOS) inhibition, providing indirect evidence that •NO is involved [47]. A further study showed direct evidence that VNS lead to the release of •NO in the ventricle via neuronal nitric oxide synthase (nNOS/NOS1) activation [48]. This effect was showed in other related studies [49,50]. At the same time, it is known that nNOS is present in many parasympathetic neurones innervating the heart [51] and there is also evidence of a subpopulation of intracardiac nerve fibres that contain solely •NO coursing towards the ventricle in humans [52]. It has been postulated to cause electrical restitution property disturbances and to ultimately leading to the development of complex ventricular arrhythmias [53,54]. These results indicate a physiological role of these intermediaries in loss of modulation of redox signaling with important impact on ventricular arrhythmogenesis.

In many aspects the ChHD follows a pattern like that described in experimental models of Oxidative stress (OS), via overgeneration of ROS and RNS disturbances in the ventricle. The mechanistic studies identifying i) the mediators produced by cardiomyocytes in response to *Trypanosoma cruzi* infection, that may trigger the migration of leukocytes and other cells to the heart; ii) the signaling mechanisms regulated by the inflammatory cytokines (e.g. TNF-α and IL-1) that may evoke cell survival/cell growth or cell death responses in chagasic myocardium; and iii) the destructive effects of "oxidative burst" of activated inflammatory cells in ChHD, are discussed elsewhere [35]. Nevertheless, highly complex interactions are far from being completely clarified, mainly regarding the basic mechanisms, thereby creating difficulties in understanding the extensive cardiac damage in chronic chagasic patients. With the increased demonstration of overgeneration of ROS and RNS disturbances in ChHD, the hypothesis that ROS may contribute, at least in part, to ventricular arrhythmogenesis in ChHD has gained plausibility [35,47,48].

Recently, in a study reported by our group, we speculate a possible beneficial effect of the antioxidant supplementation limiting the arrhythmic consequences of chronic inflammatory response, which is so common in ChHD. We showed that the etiological treatment with benznidazole followed by supplementation with the antioxidant vitamins E and C decreased episodes of complex ventricular arrhythmias in patients with severe ChHD [55] as showed in Figure 4. Therefore, the antioxidant

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supplementation was above all be capable of restoring the balance of redox signaling [56].

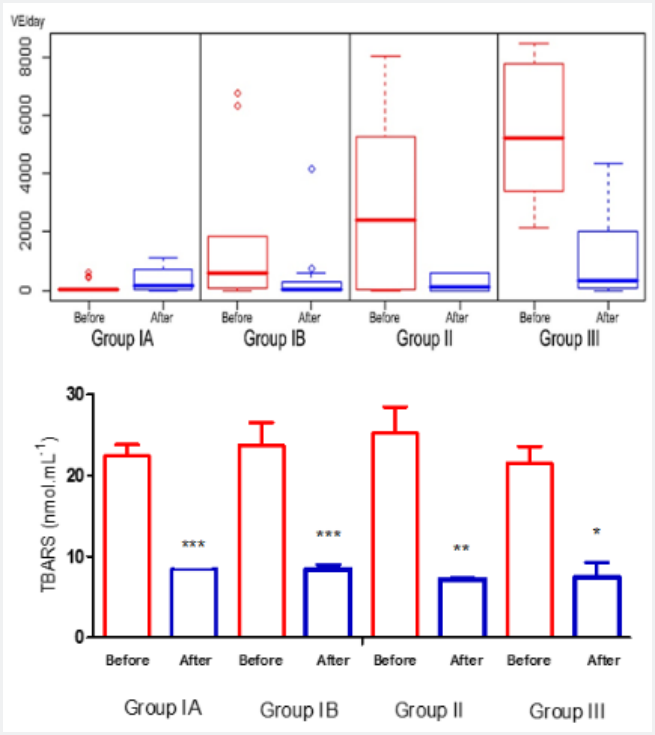

Figure 4: Impact therapeutic of antioxidant in the prevalence of ventricular cardiac arrhythmias (VCA) in patients with chronic Chagas heart disease. Patients with chronic Chagas heart disease in different degrees of cardiac involvement have a significant prevalence of VCA, and these are attenuated by antioxidant therapy, particularly in patients with advanced degree of cardiac involvement. The reduction of VCA is accompanied by decrease of serum marker of oxidative stress (Thiobarbituric Acid Reactive Substances-TBARS) in all patients in different groups.

Conclusion

A relevant and often ignored facet of chronic ChD is the presence, in all chagasic patients in the cardiac form, of ROS and the consequent loss of modulation of redox signaling. It is reasonable to speculate that ROS can be regarded as a potential driver of cardiac arrhythmia in ChHD. Consequently, to counteract the arrhythmogenic potency of ROS and RNS, strategies that focus on restoration of the balance of redox signaling could be helpful for chagasic patients with complex ventricular arrhythmias, who are refractory to conventional treatments. Not treating a patient with ChHD and complex ventricular arrhythmia is an active and more difficult decision to make than to proceed with the doubt. Nevertheless, a formal proof-of-concept clinical trial is needed to determine if this novel approach is safe and effective in ChHD. Because ChD is a neglected disease that kills thousands of persons each year, novel and innovative therapies should urgently be tested.

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