Letters to the Editor

A Vision of Future Treatment in Chagas Heart Disease

We read the state-of-the-art paper by Nunes et al. (1), which presents the current knowledge on Chagas disease. For counteracting Chagas heart disease, the most life-threatening complication in chronic Chagas patients, the authors stated that "…management… followed… recommendations for… heart failure due to other conditions" (1), which includes the prevention of thromboembolism, arrhythmia, dysautonomia, and ventricular dysfunction.

As mentioned by the authors, there are agonistic autoantibodies against G-protein coupled receptors (GPCR-AABs), such as those against the muscarinergic-2 receptor (M2-AABs) and the beta1-adrenergic receptor (beta1-AABs), which are found in nearly all Chagas heart patients. M2-AABs are thought to contribute to patients' dysautonomia, whereas beta1-AABs are seen as drivers of cardiomyopathy. Consequently, to counteract the pathogenic potency of beta1-AABs, but presently only directed to beta1-AAB–positive patients with idiopathic dilated cardiomyopathy, new treatment strategies are under study that focus on beta1-AAB removal via an apheresis technique or drug treatment for in vivo beta1-AAB neutralization (2). However, both strategies could also be helpful for Chagas patients.

In beta1-AAB apheresis technology, aptamers, a new class of binders (in addition to peptides and proteins, the typical binders) and specifically, the recently identified beta1-AAB-binding aptamer, which was successfully tested in apheresis in animals (3), could be introduced. Due to the dual presence of beta1- and M2-AABs in Chagas heart patients, apheresis techniques that remove both GPCR-AABs in parallel, either by whole immunoglobulin G apheresis or using a column carrying our recently patented aptamer (4), which binds to the majority of cardiotropic GPCR-AABs, among which are M2- and beta1-AABs, should be optimal. However, the high costs and logistic problems of apheresis limit its application for the millions of Chagas heart patients. To overcome this, a treatment strategy using in vivo neutralization of GPCR-AABs would be, in view of costs and logistics, optimal. In view of "…excellent characteristics for systemic…administration application…" (5) of aptamers in general and combined with the evidenced neutralizing function of our GPCR-AAB-binding aptamer (4), we suggest that this molecule could be suitable for developing an innovative therapy for patients with Chagas heart disease.

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Reply

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We would like to thank Dr. Wallukat and colleagues for their letter regarding our review on Chagas heart disease (CHD) (1), which suggested the potential value of new treatment strategies that focus on removal or neutralization of beta1-autoantibodies (AABs). We agree that this is an appealing possibility, but we consider the role of beta1-AABs in the pathogenesis of Chagas cardiomyopathy (ChCM) to still be controversial. There are a number of studies showing a potential role of beta1-AABs in the genesis of major clinical manifestations of ChCM, such as ventricular dysfunction, ventricular arrhythmias, and conduction disturbances (reviewed in Medei et al. [2]), most of them in vitro or in experimental models. However, as observed for antimuscarinic AABs (3), some of the properties of beta1-AABs observed in vitro or in experimental models may not produce effects in clinical patients, due to the concomitant action of other factors. A major finding favoring a pathogenetic role of beta1-AABs in ChCM was published by Wallukat et al. (4), who showed a higher prevalence of chronotropically active beta1-AABs in CHD with cardiomyopathy than in those in the indeterminate form or with megacolon, as well as a higher activity of those AABs in ChCM patients.

However, much more data is necessary before a specific therapy aimed to neutralize or remove beta1-AABs in CHD could be used in clinical practice. Available clinical data does not show a dose-response effect (i.e., that patients with more severe ChCM have higher levels or activity of antiB1-AABs [4,5]). Longitudinal data that consistently shows that higher AAB activity may provoke or aggravate heart involvement in CHD would be desirable to further confirm the importance of the proposed mechanism. It is conceivable that the pathogenesis of ChCM is multifactorial, as discussed in our review (1). Finally, a formal proof-of-concept clinical trial is needed to determine if this novel approach is safe and effective in CHD. Because CHD is a neglected disease that kills thousands of persons each year, novel and innovative therapies should urgently be tested and are welcomed.

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Catheter Ablation to Treat Sustained Ventricular Tachycardia in Patients With Chagas Cardiomyopathy and Implantable Cardioverter-Defibrillator

We have read with great interest the recent paper by Nunes et al. (1). We congratulate the authors for this comprehensive review of Chagas cardiomyopathy, which is one of the most important cardiovascular problems in Latin America and also an emerging disease in nonendemic countries.

As the authors properly described, ventricular arrhythmias are very common in patients with Chagas heart disease, with prevalence and complexity related to the presence and extent of myocardial damage. Sustained rapid ventricular tachycardia (VT) is recognized as the most important cause of sudden cardiac death in Chagas disease. It has been identified in patients with a segmental disease, with or without important ventricular dysfunction, and the implantable cardioverter-defibrillator (ICD) has been recommended for those patients to prevent sudden cardiac death. However, some observations suggest that patients with Chagas disease receive more ICD shocks when compared with patients with other structural heart diseases (2,3). As previously shown (4), frequent ICD shocks are associated with higher mortality in patients with low ejection fraction of any etiology. So, it is not surprising that a similar observation applies to patients with Chagas VT and frequent ICD discharges that have shown a high total mortality rate when their defibrillators are conventionally programmed (5,6).

It is important to mention that catheter ablation is currently recommended to manage patients with incessant or recurrent VTs, mainly when receiving frequent ICD therapies (7). In treating hundreds of patients with these characteristics, we were able to define the substrate of most of these VTs: most re-entrant circuits in Chagas VTs originate in the inferior or lateral basal wall of the left ventricle. Moreover, after developing the technique of subxiphoid percutaneous access to the pericardial space in our laboratory, we were able to identify that subepicardial myocardial fibers were the cause for re-entrant circuits of sustained VT in many patients with Chagas disease (8,9). This finding has allowed us to successfully ablate VT for patients with prior endocardial ablation failures (10). These observations have been largely confirmed in the literature, and are currently recommended for managing specific patients with recurrent VTs, particularly those with Chagas VT and other nonischemic cardiomyopathies (11,12).

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