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Editorial

Role of Autoimmunity in Heart Disease: Is Chagas Heart Disease the Definitive Proof?

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See article by Vicco et al., pages 332-337 of this issue.

Chagas disease is caused by an infection of the parasite *Trypanosoma cruzi*. It is endemic to Latin America, where it affects about 8 million individuals. However, Chagas disease has been increasingly detected in other countries in the Americas, as well as the western Pacific region and Europe, because of population migration, leading to a worldwide prevalence of chronic infection by *T. cruzi* of 10 million individuals.[1] About 30%-40% of these persons will have chronic Chagas heart disease (CCHD).[2,3] The infection is characterized by an initial acute phase, with high parasite loads in the first few months of infection, and a chronic phase, in which parasite levels are reduced but a complex array of parasite/host interactions can cause numerous adverse effects on the heart. Clinical manifestations of CCHD are heterogeneous but commonly include impaired autonomic cardiac regulation, conduction abnormalities, chamber dilatation and dysfunction, ventricular aneurysm, and a high risk for thrombosis and sudden cardiac death.[4,5]

A central factor in this parasite/host relationship is based on homologous overlap between the parasitic antigens and the host proteins, resulting in host antibody production and autoimmunity. Several of these autoantibodies may have important roles in the pathogenesis of CCHD, including antibodies that recognize host neuronal cells and may contribute to the depopulation of cardiac parasympathetic innervation,[6] which is common in advanced CCHD. Other autoantibodies associated with CCHD target cardiac myosin heavy chain, with possible adverse effects in the heart. A preclinical model showed that autoimmunity against the heart-specific α-myosin heavy chain, when combined with adjuvant stimulation of the immune response through Toll-like receptors, resulted in dilated cardiomyopathy.[7] Also, in a preclinical model of CCHD, mice infected with *T. cruzi* developed myocardial inflammation and fibrosis, but this was resolved by a previous immunologic tolerization to a myosin-rich extract.[8]

Patients with Chagas disease are also positive for anti-p2β antibodies that bind and stimulate both β1-adrenergic receptors (β1ARs) and M2 cholinergic receptors,[9] which are involved in cyclic adenosine monophosphate–dependent homeostatic regulation of heart function. Chronic stimulation of β1ARs is a well characterized and common contributing factor to the pathogenesis of heart disease, promoting myocyte cell death, cardiac hypertrophy, and reduced function (Fig. 1).[10] *T. cruzi* may have originally adapted the use of muscarinic cholinergic and β-adrenergic receptors to facilitate both invasion of host myocyte cells and immune suppression through signalling to lymphocytes during the acute phase of infection.[11,12] The production of host autoantibodies that cause chronic activation of β1ARs is a further complication of this manipulation of host signalling pathways by the invading parasite. Anti–β1-adrenergic receptor antibodies (anti-β1AR) have been implicated in the pathogenesis of dilated cardiomyopathy, whereby these autoantibodies bind to and constitutively stimulate the β1AR to promote pathologic cardiac remodelling and β1AR desensitization and downregulation. The prevalence of anti-β1AR antibodies in patients with dilated cardiomyopathy ranges from 26%-60%, and the presence of these autoantibodies correlate with a poor prognosis.[10,13,14]

In this issue of the *Canadian Journal of Cardiology*, Vicco et al. show that blocking β1ARs, as is common in standard care for heart disease,[15] is correlated with a significant increase in plasma levels of anti-p2β antibodies. Their proposed mechanism is that by blocking ß1ARs, β-adrenoceptor blockers displace anti-p2ß antibodies from the receptors, thereby inhibiting chronic ß1AR activation by anti-p2ß antibodies but also causing increased plasma levels of anti-p2ß antibodies (Fig. 1). Not surprisingly, patients with advanced CCHD (stage III) who received β1AR blockers, angiotensin-converting enzyme inhibitors, and statins had a lower risk of mortality than did those who were not treated. Their finding that anti-p2β antibodies were increased in patients undergoing β1AR inhibitor therapy suggests that a direct mechanism for the beneficial effects of β1AR inhibition in these patients may be through displacement of anti-p2β antibodies

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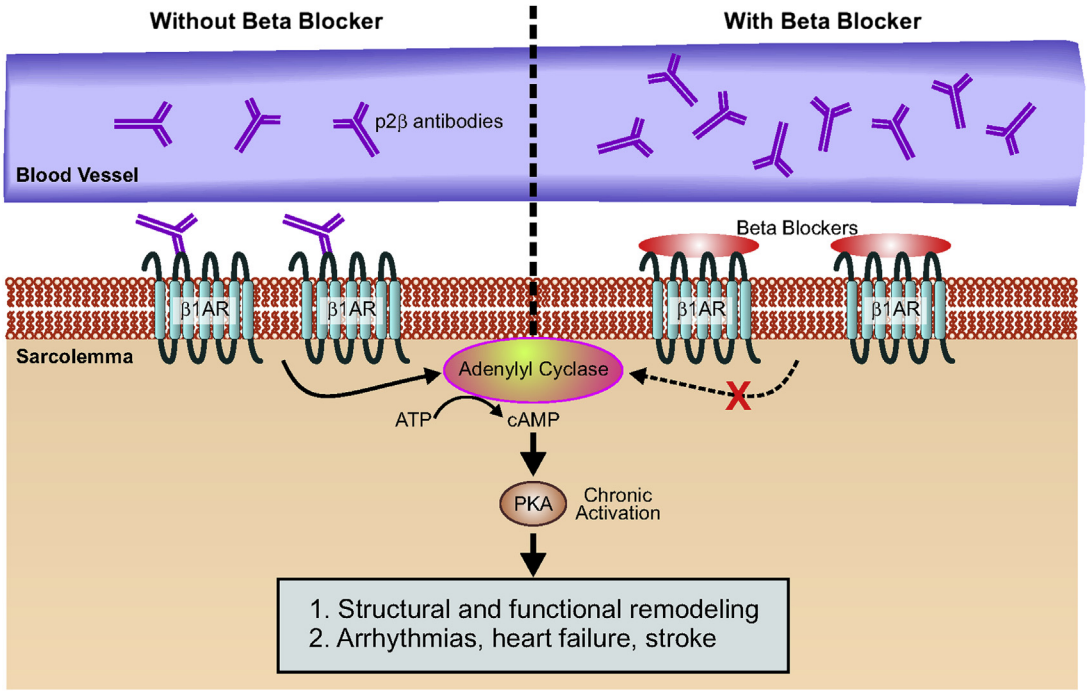

Figure 1. Proposed role of anti-p27 antibodies and interaction with the β-adrenergic receptors in a cardiomyocyte, leading to chronic elevation of cyclic adenosine monophosphate (cAMP) and activation of protein kinase A (PKA) and its downstream pathologic effects. A β-blocker, by functioning as a competitive antagonist of β-adrenergic receptors, results in elevation of plasma anti-p27 antibodies and relief of the chronic maladaptive effects of β-adrenergic receptor activation. ATP, adenosine triphosphate; β1AR, β1-adrenergic receptor.

from cardiac β1ARs, leading to elevated circulating anti-p2β antibody levels. The enzyme-linked immunosorbent assay used to measure plasma anti-p27 antibodies had excellent performance characteristics, with a sensitivity and specificity of 99% and interassay and intra-assay variability of 1.7% and 1.2%, respectively. However, the β1AR is widely expressed, and the reciprocal relationship between plasma anti-p2β antibody levels and the occupancy of myocardial β1ARs is correlative at best.

The study by Vicco et al. raises a number of follow-up questions that should be investigated in both preclinical and clinical models.[15] For example, the use of plasma anti-p2ß antibodies as a biomarker is complicated by the observation that higher plasma levels indicate more of these autoantibodies (and a worse prognosis), whereas β-blocker administration would also elevate plasma anti-p2ß levels, but this change would be indicative of an improved prognosis. As such, the association between β1AR inhibition and plasma levels of anti-p2β antibodies would be strengthened by a prospective study. For example, patients not currently receiving β1AR blockers, assuming no contraindications, could begin receiving β1AR blockers and then undergo assessment for changes in plasma p2β antibody levels. Preclinical models for *T. cruzi* infection could also be used to more fully assess the variation in activation of β1AR signalling and inflammatory cell infiltration in the myocardium with and without β1AR blockade. It would also be interesting to see if M2 cholinergic receptor activation is altered after β1AR inhibition. We would hypothesize that the increased plasma anti-p2β antibody levels may result in enhanced M2 cholinergic receptor activation, with possible effects on sinus (and heart rate) and atrioventricular node conduction. Stimulation of the M2 cholinergic receptors may contribute to the development of chronotropic incompetence characterized by bradycardia or atrioventricular block, or both, thereby also limiting the use of β-blockers in these patients. Conversely, atropine may cause a further increase in plasma levels of p2β antibodies through displacement from M2 cholinergic receptors. Vicco et al. also included a variable phenotype in patients with CCHD stage III and included patients with heart failure with reduced ejection fraction and heart failure with preserved ejection. This is a striking demonstration of the variable phenotypic changes seen in patients with CCHD,[4,5,16] and autoimmunity is likely to play a larger pathogenic role in patients with heart failure with reduced ejection fraction, which is typically characterized by dilated cardiomyopathy.

Treatment strategies for chronic *T. cruzi* infection must not only consider how to clear the remaining parasites but also how to reduce or ameliorate adverse effects of the autoimmune response. β-Blockers are a standard pillar of modern therapy for heart failure,[3] reducing the incidence of adverse electrophysiologic and functional remodelling caused by chronic sympathetic activation in the failing heart. In CCHD, inhibition of β1ARs may be especially critical for displacing p2β autoantibodies, thereby curtailing the chronic maladaptive activation of β1ARs.

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