

Chagas' Cardiomyopathy and Thrombosis: the Beginning and the End of a Dangerous Affair

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Almost a third of individuals with chronic infection by *Trypanosoma cruzi* develop, over the years, different typical cardiac disturbances that include conduction blocks, arrhythmias, ventricular dilation, ventricular aneurysms, and intracavity thrombi. In the final stages of Chagas' myocardiopathy cardiac thrombosis is a frequent phenomenon, found generally in the areas of dyskinesia of the cardiac cavities that are severely increased in size. In anatomopathological studies, for example, the presence of intracavity thrombi has been shown in 15% to 36% of patients who died due to sudden death syndrome or heart failure, respectively.¹ Although clinical studies are contradictory with respect to the frequency of the appearance of embolic phenomena in these patients,² some authors recommend the routine use of anticoagulants in the final stages of chronic Chagas' myocardiopathy. Nevertheless, thrombotic phenomena have not only been observed at the end of the natural course of the disease, but they are also intimately tied to the primary physiopathological mechanisms that lead to myocardiopathy. It is precisely the obscure physiopathology of this process that provokes the greatest controversy and debates among researchers studying the problem. Carlos Chagas, in his original description of the disease, observed that the parasitemias so frequently occurring in the acute stage practically disappear in the chronic stages, and that serious cardiac lesions occur in the apparent absence of the parasite. This observation triggered the search for alternative mechanisms of myocardial damage independent of the parasite, giving rise to different physiopathological theories, among them the

autoimmune, cardioneuropathy, and microvascular theses.³ In accordance with the latter theory, the existence of various structural and functional changes in the coronary microvasculature lead to ischemia and focal necrosis, which would then trigger the usual repair mechanisms with the consequent inflammation and fibrosis. The pathological changes found in the microvasculature of patients with chronic trypanosomiasis americana have been widely reviewed by other authors, and the evidence comes from experimental and clinical observation.⁴ In animal models, for example, the presence of endothelial edema, perivasculitis, microaneurysms, and platelet or fibrin thrombi in the vascular interior is a constant. In these models, distinct functional changes in the microvasculature have been observed, such as an increase in vascular tone and stimulation of platelet aggregation.⁵ It has also been shown that there is an increase in the generation of thromboxan A₂ and other inflammatory substances with prothrombotic properties such as IL-1 beta. In humans, the changes in microvasculature and endothelial dysfunction are evident in anatomopathological studies and their functional correlate is found in the disturbances in coronary vascular tone, the frequent change in myocardial perfusion,⁶ or the high plasma endothelin values found in patients with Chagas' myocardiopathy.⁷

In this issue of the REVISTA ESPAÑOLA DE CARDIOLOGÍA, Herrera et al⁸ present a patient cohort with chronic tripanosomiasis americana in which they measured the plasma activity of various markers for thrombosis and fibrinolysis. The authors found in the population with Chagas' disease significantly higher numbers of F1+2 and antithrombomodulin, which suggests intense activity in the formation of fibrin within the intravascular compartment as well as endothelial damage. In addition, they found high PDF and D-dimer values that reflect the presence of fibrin already formed with greater intensity in the study population. Of note, none of the patients included in the study had dilated myocardiopathy (class III); rather the great majority presented only with electrical con-

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duction disturbances or arrhythmias. In this population with incipient cardiac involvement, the authors showed the presence of biochemical markers that suggest an active thrombogenesis. This finding adds clinical information that enriches the microvascular theory of the genesis of chronic Chagas' myocardopathy.

As mentioned previously, the aggression of the vascular endothelium causes the appearance of vasospasm and coronary microvascular thrombosis, which causes myocardial damage. But, what factors are responsible for the permanent endothelial aggression present during the course of the disease? Although it has been postulated that immune activity could be responsible for this phenomenon, it is actually the parasite itself that is the protagonist of the physiopathological scene during the chronic stage of the disease. We now know that the parasite is present in all individuals with positive serology; it was simply that we were unable to detect it. Through modern parasitological techniques several authors have observed parasitemias in an increased percentage of individuals during the chronic stage of the disease⁹ and that their presence is associated without a doubt with the appearance of cardiac lesions.^{10,11} In addition to the vascular damage that it can produce via the immune system, *Trypanosoma cruzi* directly attacks the vascular endothelium, with the secretion of a neuraminidase that allows the removal of sialic acid from the endothelial cells it infects. It is precisely the periodic circulatory cycles of the parasite that may explain the phenomena of endothelial dysfunction, immune system activation, or, as Herrera et al observed, thrombosis.

Thrombosis, which is present both at the beginning and the end of Chagas' disease, has revived the interest of clinicians who treat patients with Chagas' myocardopathy. The information provided by Herrera et al moves the focus of attention to the initial stages of the disease and suggests the potential clinical benefit of the use of anticoagulants. Logically, controlled studies of therapeutic intervention and on a greater scale are necessary to provide the evidence necessary to justify

the indications for their use. While we are looking for the ideal antiparasitary to treat our patients with chronic *Trypanosoma cruzi* infection, it is possible that these therapeutic approaches may have a place in the natural history in the myocardopathy of Chagas' disease.

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