

A summary perspective on the clinical-functional significance of cardiac autonomic dysfunction in Chagas' disease

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This presentation summarizes some insights into the potential role of the cardiac autonomic dysfunction as a determining or conditioning condition of some functional disturbances and clinical manifestations and of unfavorable outcome in chronic Chagas' disease.

Diffuse damage almost always present in variable degree and extension of the autonomic nervous system is a striking pathological feature of the acute and all chronic forms of human Chagas' disease and the corresponding forms of experimental *Trypanosoma cruzi* infection in several animal models, early recognized following the description of the disease in the beginning of the past century. Different central and peripheral autonomic components, mainly related to the heart and digestive viscera, including neural structures at many levels, peripheral extrinsic and intrinsic ganglia, sympathetic and parasympathetic efferent neurons and the beta-adrenergic and muscarinic cholinergic neurotransmitter cellular receptors may be exclusively or combinately injured^{2 4 5 6 7 8 20 28 32 34 37 38 45 46 55}. Several studies have showed less conspicuous lesions of cardiac intrinsic autonomic innervation in the indeterminate form, which are usually represented by discrete to moderate focal or zonal neuroganglionitis. In the isolated or combined cardiac and digestive forms of disease the intrinsic innervation of heart is commonly more markedly damaged by inflammatory and degenerative alterations and decrease in the number of cardiac ganglion cells and neurons was undoubtedly showed^{2 6 8 20 28 32 37 38 46 55}.

Based on this pathological substrate, the consequent disturbance of cardiac parasympathetic and sympathetic control constitutes one outstanding functional aspect of Chagas' disease, which have been demonstrated to be present in variable intensity according to the form of the disease in almost every affected subject^{1 10 22 23 25 26 30 43 52}. Cardiac autonomic dysfunction is observed not only in chagasics with ostensive cardiopathy but also in those without overt manifestation of heart or digestive damage. Recently it was also demonstrated impaired cardiac parasympathetic modulation in hypertensive chagasic subjects, apparently in same degree that in chagasics without arterial hypertension⁴⁴. It seems that the intensity of the cardiac autonomic functional disturbance is strictly correlated with the clinical form of chagasic organic involvement. The less intense autonomic dysfunction occurs in the indeterminate form and in chagasics showing a borderline electrocardiogram, the more severe disturbance occurs in the cardiac-digestive and digestive forms, and moderate dysfunction in the exclusive cardiac form^{23 25 26 30}. On the other hand, elderly chagasics with the indeterminate form of the disease did not presented any alteration in cardiac autonomic function as compared with healthy elderly subjects⁵¹.

Besides the lesions at different levels in the autonomic nervous system, the cardiac autonomic dysfunction may also result of degenerative and inflammatory lesions in the

sinus node, since this structure is one of the effectors of the autonomic influence on the heart.

The diagram in Figure 1 shows proved and possible pathophysiological mechanisms of the cardiac autonomic dysfunction triggered by the *T. cruzi* infection, which may culminate in different clinical and functional manifestations.

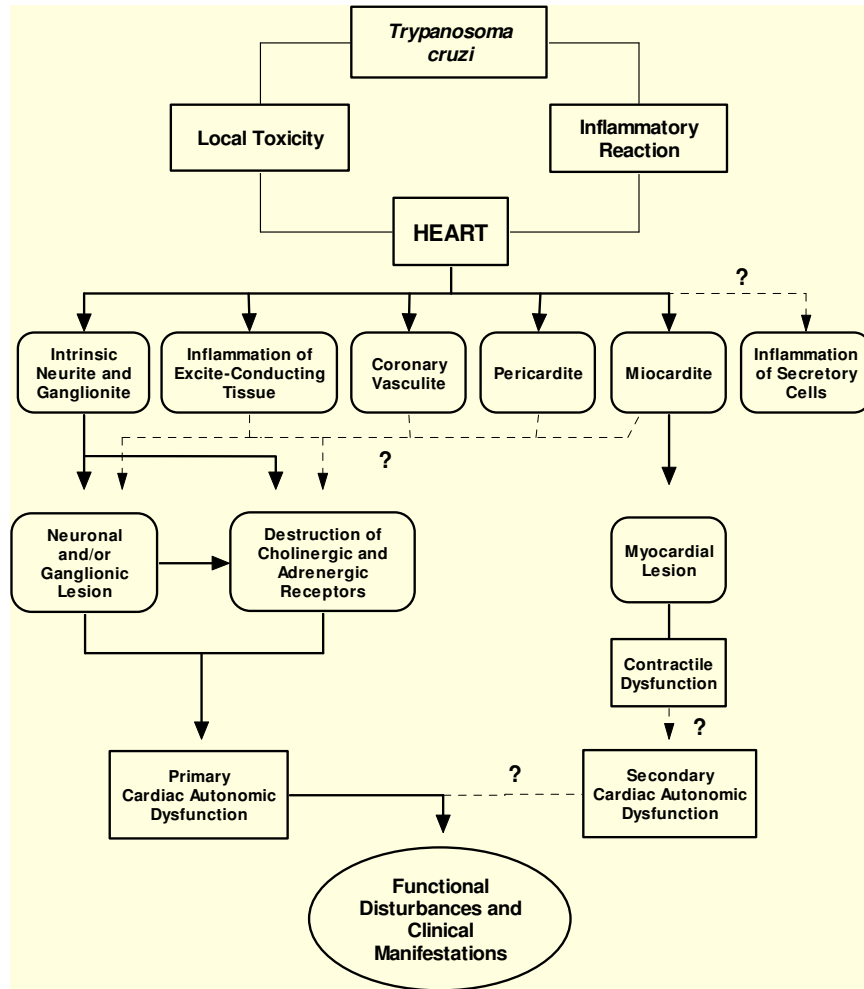


Figure 1. The *Trypanosoma cruzi* may affect, combinately or exclusively, all the structures of the heart, by means toxic or inflammatory effects, resulting in lesions that include the intrinsic autonomic innervation and the contractile myocardial fibers. One of the important consequences is the cardiac autonomic dysfunction, repeatedly demonstrated to be a primary disturbance independent of the contractile dysfunction. The impaired autonomic function may be the substrate for different secondary functional and clinical manifestations.

Although the significant accumulated knowledge, the pathophysiological and clinical significance of the cardiac autonomic dysfunction remains one of the major challenges to be overcome almost one century after the discovery of Chagas' disease.

Is the cardiac autonomic dysfunction in Chagas' disease simple epiphenomenon without any functional, clinical or prognostic significance? Does it constitute a key physiopathogenetic link or triggering factor for the development of secondary disturbances or manifestations, such as different arrhythmias, sudden death, and progressive contractile deterioration? Could it represent yet a risk factor for cardiovascular or overall morbidity

and mortality? Alternatively, is it an underlying mechanism for altered homeostasis imposing inappropriate short- and long-term cardiovascular adaptation to multiple internal or external stressful stimuli?

Initially, it was supposed that the cardiac intrinsic autonomic denervation would be the direct and primary responsible for the cardiac enlargement as well as by the progression of the Chagas' cardiopathy to the phase of congestive heart failure^{31 32}. However, a great number of subsequent studies of pathological, functional and clinical nature firmed consensually a widely accepted physiopathogenetic concept according to which the cardiac autonomic denervation and the consequent functional disturbance is not the determining mechanism of the progressive cardiomegaly neither of the ensuing heart failure. The progressive contractile dysfunction of heart critically depends on the underlying evolutive fibrosing chronic inflammation of myocardium³⁸. That is to say, the autonomic denervation and the consequent neural control disturbance of heart do not seem to be directly related with the contractile dysfunction as a causal determining factor. Several evidences also demonstrate that the progressive contractile mechanical disturbance did not result in secondary autonomic dysfunction^{25 26 43 47 52}, although an alternative hypothesis considers that cardiac autonomic dysfunction is consequence of contractile ventricular dysfunction and others primary pathophysiological mechanisms¹².

In fact, in a correlative functional study in chagasic subjects with different clinical forms of disease we observed that contractile, electrical and autonomic disturbances detected by means of echocardiography, conventional electrocardiogram and Valsalva manoeuvre, respectively, occurred isolately or in combination in any of the clinical forms. Otherwise, some chagasics did not presented evidence of any of these disturbances²⁴. These findings suggest that the functional disturbances of heart are not necessarily related one another on the basis of a causal relationship. This suggestion is reinforced by the demonstration that contractile alteration of the right ventricle is independent of the autonomic dysfunction⁴³, the parasympathetic impairment precedes the left ventricular systolic dysfunction⁵² and that chronotropic incompetence in response to exercise testing is an early sign of cardiac autonomic disturbance independently of ventricular function⁵⁴.

Therefore, the dominant evidence pointed out for the fact that cardiac autonomic impairment neither is cause nor consequence of the progressive chronic contractile dysfunction of Chagas' heart disease. Despite of this, however, it is possible that both autonomic and contractile dysfunctions may mutually influence or aggravate one another.

An attractive hypothesized alternative implication of cardiac autonomic dysfunction, perhaps that of higher relevance and clinical consequence, is concerned to the participation of these alterations as determining or predisposing factors in the physiopathogenesis of some arrhythmias and sudden cardiac death²⁷, so common in the chagasic involvement of heart^{27 49 50}. The autonomic nervous system exerts important modulation on all the electrophysiological properties of heart - automatism, conductivity and excitability, whose alterations are the underlying causes of arrhythmogenesis. The parasympathetic limb exerts depressor or stabilizing electrophysiological, anti-arrhythmogenic effect, while the sympathetic limb a pro-arrhythmogenic stimulating effect on the different properties, and an adequate balance between these influences on the heart is critical for maintaining the electrical stability of the myocardium and excite-conducting system. Consequently, absolute or relative modifications in variable degree of the sympathetic-parasympathetic balance, triggered or exacerbated by different intrinsic or extrinsic factors, may result in electrophysiological instability and induce arrhythmias of distinct types and broad spectrum of severity, which are able of provoke up till the sudden death in the dependence of the degree and velocity of installing of such alterations and of

the pathological and functional substrate of myocardium and excite-conducting tissue. It is possible that even physiological changes of cardiac autonomic influences actuating on an injured substrate are able to induce arrhythmias.

In Chagas' disease, the isolated or combined lesions of variable intensity and extension of the atrial and ventricular myocardium, excite-conducting specialized system and intrinsic autonomic innervation of heart peculiarly propitiate the development of arrhythmias of different types, severity and duration, of which may ensue life-threatening events resulting in unexpected or expected sudden death. Distinctive patterns of autonomic disturbances, associated or not to the myocardial and specialized tissue lesions, are critically important considering its potentiality to induce or aggravate modifications in all the electrophysiological properties of heart, eventually triggering some type of arrhythmia. Hypothetically, as more discrete the autonomic dysfunction with subtle sympathetic-parasympathetic imbalance resulting of focal or zonal intrinsic neuroganglionic lesions, the higher is the vulnerability for arrhythmogenesis and the potential for unexpected sudden death, as occur in chagasic subjects with less serious cardiac form and possibly in those with indeterminate form or borderline electrocardiogram^{27 36 49 50}. On the other hand, how much pronounced the autonomic impairment consequent of marked and extensive lesions at different levels of the intrinsic nervous system, possibly lesser is the chance of arrhythmogenesis and sudden death. Therefore, chagasics with relatively severe cardiac intrinsic autonomic denervation may be protected against the phenomenon of arrhythmogenesis, considering that in such case the heart is practically disconnected of the central nervous system and free of neural influences onto its electrophysiological properties resulting of internal or external stimuli²⁷. Studies from hearts with myocardial infarction has raised the possibility that heterogeneous sympathetic nerves axonal regeneration and proliferation following any type of injury may induce electrical instability with consequent arrhythmias, as result of regional hyperinnervation or nerve sprouting^{9 58}. In this context, it is plausible suppose that in Chagas' disease the same pathophysiological mechanisms may trigger arrhythmogenesis, considering the distinctive regional lesions in the intrinsic innervation of the chagasic heart.

A recent finding of myocardial lesions similar to those induced by catecholaminogenic cardiotoxicity, which can represent substrate for induction of arrhythmias, observed in chagasic subjects without clinical manifestations who died suddenly and unexpectedly³, reinforces the hypothesis of dysautonomic arrhythmogenesis raised for explain the Chagas' sudden death²⁷. In addition, some other observations of impaired cardiac autonomic function detected by conventional or nonlinear heart rate variability analysis in subjects with Chagas' heart disease have also stressed the possibility of link autonomic dysfunction and arrhythmias^{14 53}. Moreover, numerous studies based on the heart rate variability analysis in patients usually with coronary disease have evidenced that altered autonomic influence on the heart has an important role in the genesis and maintenance of life-threatening arrhythmias, which can result in sudden death. Shift of sympatho-vagal balance toward a sympathetic predominance has been demonstrated before the onset of arrhythmic events such as ventricular tachycardia or fibrillation^{35 58}. Reduced complexity of heart rate variability assessed by nonlinear dynamic analysis was also noted before the initiation of ventricular tachyarrhythmias in patients with Chagas' heart disease, suggesting impaired cardiac autonomic regulation as the underlying mechanism¹⁴.

Figure 2 depicts possible clinical and functional disturbances that may be determined or influenced by impaired autonomic influence on the different structures and functional properties of heart.

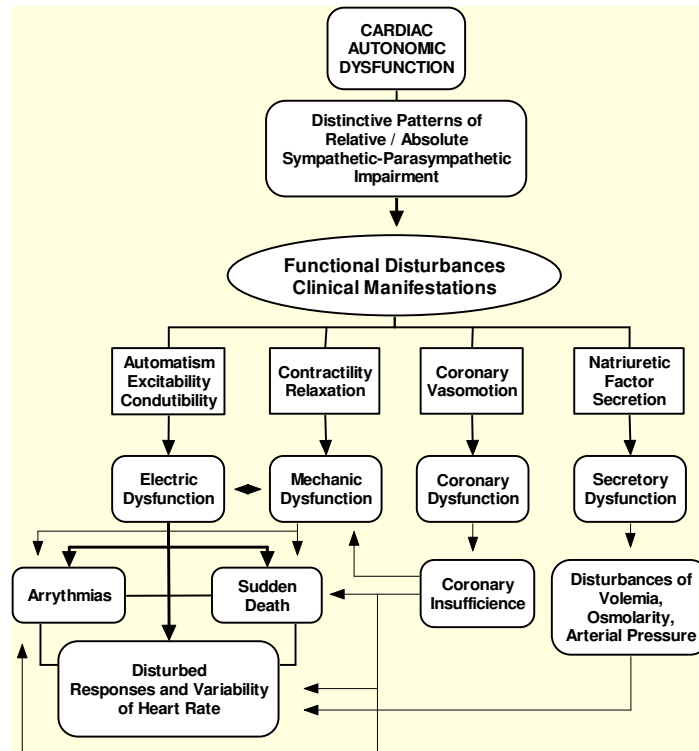


Figure 2. Sympathetic and parasympathetic impairments of variable degree may affect all the functions of the heart, by alterations of their electrical and mechanical properties, the coronary circulation and possibly the secretion of atrial natriuretic factor. In consequence, different functional and clinical disturbances may result conferring to the autonomic impairment a possible important pathophysiological and prognostic significance in Chagas' disease.

Systemic autonomic lesions may also influence metabolic and endocrine mechanisms and different homeostatic controls, and cardiac autonomic dysfunction is hypothesized to be correlated with metabolic, hormonal and functional renal disturbances, considering the intricate relationship between different organic systems and processes. Indeed, cardiac autonomic dysfunction has been observed in the same chagasic subjects with indeterminate or cardiac forms of disease or in experimentally *T. cruzi*-infected animals, simultaneously with alteration in the osmoregulation dependent on antidiuretic hormone response⁵⁷, in hydroelectrolytic balance⁵⁶ and tolerance to glucose¹⁸.

Another possible pathophysiological role of the chagasic autonomic dysfunction, irrespective of the organ involved, is concerned to induction of immunomodulated disturbances and alterations of immunological mechanisms participating in the defense against the parasite responsible for the disease, considering recent evidences showing that the autonomic nervous system importantly modulates process implicated in the cellular and humoral immunity as a consequence of the intimate anatomical and functional relationship between this system and the immunological one¹⁵. It can be raised the possibility that the autonomic dysfunction associated to chagasic infection could be an influencing or

determinant factor for immunological alterations that would contribute to develop and maintain the Chagas' chronic infection.

Deficiencies in short- and long-term autonomic adjustments of heart rate in response to different functional demands or to stressful physiological or psychological stimuli might also affect the efficiency and precision of the moment-to-moment cardiovascular adaptation^{11 17 26 29 30 41 42 54}. The background of this adaptive inability is the relative or absolute impairment in sympathetic and parasympathetic cardiac modulation, which reflect poor homeostasis and vulnerability to functional disturbances and deleterious effects of some stimuli. In consequence, the individuals affected by the Chagas' disease may be incapacitated for adequately perform their physical and physiological activities or may show subtle or ostensive manifestations traducing deficient cardiovascular health, or still present the substrate for progressive development of cardiovascular disturbances. In fact, several observations suggest that alterations of regulatory physiologic processes or influences responsible for cardiovascular adaptation dynamics may be a mechanism for the development of functional derangements and disease states^{19 33 48}.

Finally, a supposition may be additionally done on the basis of recent findings for coronary disease, diabetes mellitus, heart failure and non-coronary sudden death, correlating reduction in heart rate responses and spontaneous variability, as expression of disturbed autonomic modulation, with poor prognosis, increased morbidity and mortality and higher risk for arrhythmogenesis and sudden death and others functional disturbances and clinical manifestations. Higher the depression of heart rate responses or variability worse the outcome^{11 13 16 21 35 39 40}. That is, the loss of homeostatic adaptive capacity dependent on changes of heart rate consequent to permanent impairment of cardiac autonomic modulation capacity in Chagas' disease may contribute for its progression and elevation of cardiovascular and overall mortality and morbidity of subjects affected.

Concluding, the pathophysiological and clinical implications or significance of the cardiac autonomic impairment in Chagas' disease, however, is incompletely understood and can only be conjectured, in spite of the significant advances achieved in almost one century of research since the discovery of the disease. There are no sufficient and convincing direct pathological, physiopathological, clinical and epidemiological evidences linking variable degrees of cardiac autonomic dysfunction with any other disturbance and clinical manifestations of Chagas' disease, notwithstanding the probability of such relationship. However, several indirect evidences points for a very probable important role of the cardiac autonomic dysfunction as a primary cause favoring the development of different cardiovascular functional disturbances and the emergence of some clinical consequences, and influencing the cardiovascular outcome. Transitory arrhythmic events or sustained arrhythmias, sudden cardiac death, adverse overall and cardiovascular prognosis, incapacity of the cardiovascular system adequately to adapt moment-to-moment by means of heart rate variability to meet functional demands or to respond to all sort of internal or external stimuli, are among the probable effects that the ostensive or subtle cardiac autonomic dysfunction might variably to provoke in subjects affected by the Chagas' disease. Impairment of autonomic modulation of the heart in Chagas' disease might not be a mere epiphenomenon without significance, and is intuitive accept that it might be an important primary predisposing or triggering factor or marker for different secondary functional disturbances and clinical manifestations.

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