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Enhanced parasympathetic activity in Chagas disease still stands in need of proof

Antonio Luiz P. Ribeiro^{a,*}, Antonio Carlos Campos de Carvalho^b, Federico Lombardi^c, Mauro Martins Teixeira^d, and Manoel Otávio Costa Rocha^a

^aHospital das Clínicas and Post-Graduation in Tropical Medicine, School of Medicine, Federal University of Minas Gerais, Av. Alfredo Balena, 190-Campus Saúde, 30130-100, Belo Horizonte, Brazil

^bLaboratório de Cardiologia Celular e Molecular, Instituto de Biofísica Carlos Chagas Filho CCS, Federal University of Rio de Janeiro, Bloco G, Sala G2-045. Cidade Universitaria - Ilha do Fundão Rio de Janeiro, RJ, 21949-900, Brazil

^cCardiologia, Ospedale San Paolo, Dipartimento di Medicina, Chirurgia e Odontoiatria, Università di Milano, Via A. De Rudini, 8, 20142, Milano, Italy

^dDepartment of Biochemistry and Immunology, Institute of Biological Sciences, Federal University of Minas Gerais, Av. Antônio Carlos, 6627 - Pampulha, 31270-910. Belo Horizonte, Brazil

Abstract

Cardiac vagal modulation impairment is a typical feature of Chagas disease (ChD) and is correlated to antagonistic anti-M2 autoantibodies activity. In this letter, we analyze the hypothesis that, in ChD, anti-muscarinic antibody activity could simultaneously increase parasympathetic tonus (decreasing heart rate) and decrease vagal modulation over cardiac sinus node (reducing heart rate variability — HRV). Although attractive, this hypothesis is not supported by empirical data, since reduction of vagal-specific HRV indexes has been demonstrated in the absence of bradycardia. Moreover, anti-muscarinic antibody levels correlate with HRV indexes, but not with heart rate. In the absence of reduced heart rate and, consequently, of tonic vagal enhancement, it is impossible to explain the reduction of vagal-mediated HRV by continuous and strong muscarinic activity of autoantibodies in ChD.

Keywords

Chagas disease; Heart rate variability; Autonomic nervous system

Dear Sir,

We read with great interest the text of Benchimol-Barbosa [1] about our letter, [2] in which we stated that although cardiac vagal impairment has been repeatedly demonstrated in Chagas disease (ChD), *in vivo* detection of vagal enhancement was still lacking. Benchimol-Barbosa elegantly hypothesized that a continuous effect of anti-muscarinic antibody acting on sinus node M2 receptors would both steadily hold heart rate at a lower level and limit acute heart rate variations secondary to oscillation in spontaneous neural parasympathetic efferent. In other words, that continuous and strong muscarinic activity of autoantibodies in

Chagas disease could simultaneously increase parasympathetic tonus (decreasing heart rate) and decrease vagal modulation over cardiac sinus node, reducing parasympathetic-mediated heart rate variability indexes.

There are few empiric data to support the Benchimol-Barbosa hypothesis, such as the study of Goin et al., [3] in which a group of ChD patients with bradycardia and abnormal autonomic tests had a higher frequency of antimuscarinic autoantibodies than those without these abnormalities, and the control group. Another recently released study [4] showed interdependence (using the log linear model) between sinus node dysfunction and the muscarinic antibodies in Chagas disease. Although this association is in accordance with a positive agonistic action of the antibodies *in vivo*, the transversal nature of this study, the absence of autonomic function tests and the well-known existence of anatomical lesions in the sinus node of Chagas disease patients [5] preclude further definite conclusions about their findings.

Nonetheless, the Benchimol-Barbosa hypothesis cannot explain most of the available clinical studies of autonomic function in Chagas disease, in which blunted vagal modulation is not accompanied by rest sinus bradycardia [6–14]. Unlike other diseases, such as diabetes and chronic renal disease, in which autonomic dysfunction is intense and may cause symptoms and alter prognosis, cardiac vagal dysfunction in Chagas disease is usually subtle, asymptomatic and with uncertain clinical and prognostic meaning [15]. It can occur early in the evolution of the disease, in patients with the indeterminate form or without cardiopathy, in whom no evidence of strong agonistic muscarinic activity could be demonstrated, since mean heart rate and AV conduction are not different from normal subjects [6,9,11,13,14]. Indeed, we have found in previous studies that several vagal indexes are reduced in a sample of Chagas disease patients without cardiopathy when compared to healthy controls, although mean, maximal and minimal 24 h heart rates during 24 h Holter monitoring are almost identical between groups (see Table 1). In the absence of reduced heart rate and, consequently, of tonic vagal enhancement, it seems impossible to explain the reduced vagal-mediated heart rate oscillation to several different stimuli by a strong agonistic effect of antimuscarinic autoantibodies.

In fact, our recently published data about the effect of muscarinic autoantibodies in Chagas disease [16] confirm that reduced vagal modulation of heart rate is not accompanied by tonic vagal enhancement: in this distinct study sample, mean 5-minute R–R interval registered during the period in which spectral analysis was performed was not different among control and Chagas disease groups, indicating the absence of tonic vagal stimulation. However, both Chagas disease groups displayed reduced frequency-domain heart rate variability indexes, an established marker of reduced cardiac vagal modulation. Moreover, anti-muscarinic antibodies optical density values were significantly correlated with HF power values and LF/HF ratio, but not with mean 5-minute heart period ($r=0.112$, $p=0.38$, data not shown in the cited paper), strongly suggesting that muscarinic autoantibodies alter vagal modulation (HRV indexes) but not vagal tonus (heart period, that corresponds to heart rate).

At this point, it is clear that Benchimol-Barbosa's attractive hypothesis could not explain all aspects of Chagas vagal dysautonomia, confirming how intriguing and complex is the physiopathology of this pleomorphic and potentially lethal illness [15,17]. Other mechanisms, such as neuronal degeneration and cholinergic terminal nerve destruction, mediated by inflammatory and/or immune processes, [18,19] may play a significant pathogenic role in Chagas disease dysautonomia. Indeed, in laboratory experiments on rats, a close relationship was observed between the presence of inflammatory and degenerative lesions of the intrinsic cardiac innervation and impaired efferent parasympathetic activity, expressed by reduced barore-flex bradycardia [20]. It is probable that more than one

mechanism may act in the genesis of vagal dysfunction in Chagas disease, since the coexistence and interaction of different pathological processes and clinical manifestations is more the rule than the exception in this multifaceted disease [21]. Detectable vagal enhancement, however, has been until now much more a theoretical hypothesis than a clinical phenomenon and still has to be demonstrated. Neuronal lesions and antagonistic anti-M2 autoantibodies activity are the most plausible causes of vagal impairment, an early and specific process in Chagas disease.

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Table 1

24-hour mean, maximal and minimum heart rate and adjusted indices of vagal heart control obtained by short tests and 24-h heart rate variability analysis in controls and Chagas disease patients with normal left ventricular systolic function.

Index	Control (n=38)	Chagas disease (n=61)	<i>p</i>
Mean 24 h heart rate (bpm)	73 (10)	72 (8)	0.51
Maximum 24 h heart rate (bpm)	139 (20)	138 (21)	0.83
Minimum 24 h heart rate (bpm)	49 (8)	48 (8)	0.60
Respiratory E:I ratio	1.38 (0.02)	1.25 (0.02)	0.0000
Valsalva ratio	2.01 (0.41)	1.81 (0.41)	0.0174
Orthostatic R–R max:min ratio*	1.52 (1.44–1.74)	1.43 (1.33–1.51)	0.0000
RMSSD (ms)*	23 (18–27)	17 (13–23)	0.0045
P3	118 (5)	100 (4)	0.0065

Respiratory E:I ratio [6, 9] and Orthostatic R–R max:min ratio [6] were measured in 38 controls and 61 patients; Valsalva ratio in 37 controls and 59 patients; [11] 24-hour heart rates in 35 controls and 54 patients (data not previously shown) and indexes of heart rate variability were measured in 31 controls and 42 patients. [9] Values were adjusted for significant covariates (such as age and mean 24-h cardiac interval of normal sinus beats) and expressed by mean $\pm$ SD when appropriate, except *, expressed by medians (interquartile range). HR = heart rate, bpm = beats per minute, RMSSD = square root of the mean of the sum of the squares of differences between adjacent R–R intervals in 24 h Holter monitoring, P3 = vagal index derived from a 3-dimensional return map of 24 h R–R interval series. Data in bold signifies $P < 0.0001$.