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OBSERVATIONAL STUDY

Respiratory modulation of cardiac vagal tone in Lyme disease

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Abstract

AIM: To conduct the first systematic test of the hypothesis that modulation of cardiac vagal tone is impaired in Lyme disease.

METHODS: The response of cardiac vagal tone to respiratory modulation was measured in 18 serologically positive Lyme disease patients and in 18 controls.

RESULTS: The two groups were matched in respect of age, sex, body mass, mean arterial blood pressure, mean resting heart rate and mean resting cardiac vagal tone. The mean maximum cardiac vagal tone during deep breathing in the Lyme disease patients [11.2 (standard error 1.3)] was lower than in the matched controls [16.5 (standard error 1.7); $P = 0.02$].

CONCLUSION: Respiratory modulation of cardiac vagal tone is impaired in Lyme disease, which suggests that Lyme disease may directly affect the vagus nerve or the brainstem.

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Key words: Cardiac vagal tone; Lyme disease

Core tip: Given that immune dysfunction, postural orthostatic tachycardia syndrome, fatigue, cognitive dysfunction, orthostatic palpitations, syncope, and stress, which may occur in Lyme disease, are associated with parasympathetic activity and reduced modulation of cardiac vagal tone, we hypothesized that modulation of cardiac vagal tone is impaired in this disease. This was confirmed in our study of 18 patients and 18 matched controls. Cardiac vagal tone is reflexly generated through arterial baroreceptor stimulation, by the afferents of the latter facilitating cardiac vagal motoneuron discharge relaying through interneurons in the nucleus tractus solitarius, implying that Lyme disease may directly affect the vagus or brainstem.

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INTRODUCTION

Lyme disease or Lyme borreliosis is an arthropod-borne zoonosis caused by *Borrelia* spirochetes, the incidence of which has recently been increasing with the geographical spread of infected ticks and which was previously identified clinically in Europe as Garin-Bujadoux-Bannwarth syndrome and in the United States as Lyme arthritis[1-3]. There is growing evidence for the role of the autonomic

nervous system in a wide range of diseases[4] and autonomic instability has been reported in Lyme disease[5] but has not, thus far, been systematically studied in this illness. It has recently been reported that a series of five female Lyme disease patients developed postural orthostatic tachycardia syndrome; they suffered from symptoms of fatigue, cognitive dysfunction, orthostatic palpitations and either near syncope or frank syncope[6]. Again, a case report has been published of a 16-year-old female patient with clinical, radiological and scintigraphic features consistent with reflex sympathetic dystrophy associated with Lyme disease[7].

Given that immune dysfunction, postural orthostatic tachycardia syndrome, fatigue, cognitive dysfunction, orthostatic palpitations, syncope, and stress, which may occur in Lyme disease[6-11], are associated with parasympathetic activity and reduced modulation of cardiac vagal tone (or the related measure of heart rate variability)[4,12-14], we hypothesized that modulation of cardiac vagal tone might be impaired in this illness. The aim of our study was to test this hypothesis by comparing the response of cardiac vagal tone to respiratory modulation in a sample of Lyme disease patients and matched controls. To the best of our knowledge, this was the first such study.

MATERIALS AND METHODS

The arterial blood pressure, resting cardiac rate, resting cardiac vagal tone, and the cardiac vagal tone following deep breathing were measured in 18 serologically positive Lyme disease patients who were undergoing routine clinical investigation, and in 18 normal controls; all subjects were asked to refrain from any caffeine-containing beverages from midnight before testing. For inclusion in this study, the Lyme disease patients, who were selected from outpatient attendees, were required to be IgM positive for Lyme disease and to be aged 18 years or over. The control subjects were identified as subjects who were not suffering from any autonomic nervous system dysfunction (dysautonomia) or from any condition that might directly or indirectly affect the autonomic nervous system, and were recruited from hospital staff, and from friends and family of staff members. The exclusion criteria for the normal controls included: under 18 years of age; subjects with dysautonomia; taking medications that affect the autonomic nervous system, such as stimulants, tricyclic antidepressants, anti-histaminergic medication, calcium-channel blockers, beta-adrenoceptor blocking drugs, beta agonists, monoamine oxidase inhibitors, levodopa, anti-psychotic drugs, clonidine and vasopressin; medical problems that affect the autonomic nervous system, such as neurodegenerative disorders, peripheral neuropathies, diabetes, connective tissue disease and infectious diseases. The clinical stage and presentation of the patients were early, presumed localized and without cardiac involvement (that is, without clinical evidence of Lyme carditis). As there has been no previous work in this area, it was not possible to calculate the value of beta, and therefore calculate the statistical power, for this study. Written informed consent was obtained and a local research ethics committee approved the study. The study was carried out in accordance with the Declaration of Helsinki.

Resting cardiac rate and cardiac vagal tone were measured in real time using the NeuroScope Model 300BA (Brainstem Autonomic Function Monitor) (Medifit Instruments Ltd, London, United Kingdom) as described by Little *et al*[15] and during a 10-s cycle of deep breathing as described by Julu *et al*[16]. In particular, the non-invasive cardiac vagal tone was measured on a continuous, beat-to-beat basis and was defined as pulse-synchronized phase shifts in consecutive cardiac cycles; it is essentially a form of pulse interval variability which is quantified continuously from the electrocardiogram. The index of cardiac vagal tone was measured and quantified in arbitrary units of a linear vagal scale; the minimum value of this scale is zero, which corresponds to full atropinisation of human subjects.

Arterial blood pressure was measured using the Ohmeda 2300 Finapres (Ohmeda, Engleswood, CO, United States).

Continuous variables for which data did not differ significantly from normality and for which the two groups did not have significantly different variances were compared between the Lyme disease and control groups using independent samples *t*-tests (equal variances), while the discrete nominal variable (sex) was compared between groups using Fisher's exact probability test. The software package IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp, Armonk, NY, United States) was used for the statistical analyses.

RESULTS

The main findings are shown in Table 1. The two groups were matched in respect of age, sex, body mass, mean arterial blood pressure, mean resting heart rate, and mean resting cardiac vagal tone.

Details of the heart rate for each of the 18 patients before, during, and following the deep breathing procedure are provided in Table 2.

Corresponding details of the heart rate for each of the 18 control subjects before, during, and following the deep breathing are provided in Table 3.

The mean (± standard error) maximum cardiac vagal tone during deep breathing in the Lyme disease patients (11.2 ± 1.3) was significantly lower than that in the matched controls (16.5 ± 1.7; $P = 0.02$); these data are illustrated in Figure 1.

DISCUSSION

This study has demonstrated impairment of respiratory modulation of cardiac vagal tone in Lyme disease. This is an original finding which has not previously been described.

At the outset, it should be noted that our results demonstrate impaired respiratory modulation of cardiac vagal tone in Lyme disease; this is not the same as show-

Table 1 Main findings

	Lyme disease patients $n = 18$ mean (standard error)	Controls $n = 18$ mean (standard error)	*P*-value
Age, yr	35.6 (3.7)	44.7 (3.9)	0.10
Sex	7 males, 11 females	7 males, 11 females	1.00
Body mass	25.0 (1.2) kg	24.6 (0.80) kg	0.44
Arterial blood pressure	74.1 (3.9) mmHg	66.9 (4.4) mmHg	0.23
Resting cardiac rate	72.0 (3.1) min^{-1}	63.7 (4.5) min^{-1}	0.14
Resting cardiac vagal tone	4.7 (0.8)	5.7 (1.1)	0.46
Maximum cardiac vagal tone during deep breathing	11.2 (1.3)	16.5 (1.7)	0.02

Table 2 Heart rate data for the patients

Patient number	Heart rate at 20 beats before the deep breathing procedure	Heart rate 20 beats before the end of the deep breathing procedure	Heart rate two minutes after the deep breathing procedure
1	71.8	80.5	76.0
2	90.8	90.7	83.1
3	89.8	120.7	83.5
4	68.0	73.6	66.0
5	70.3	86.4	66.3
6	90.5	83.6	90.6
7	69.0	68.6	70.2
8	64.4	65.5	61.7
9	141.8	125.9	137.8
10	69.5	76.1	70.3
11	71.9	71.6	74.5
12	69.4	71.6	71.4
13	74.6	78.1	79.7
14	68.4	69.9	66.7
15	68.7	77.2	68.3
16	62.0	72.9	65.3
17	69.2	72.1	67.5
18	63.0	69.1	68.3

Table 3 Heart rate data for the controls

Patient number	Heart rate at 20 beats before the deep breathing procedure	Heart rate 20 beats before the end of the deep breathing procedure	Heart rate two minutes after the deep breathing procedure
1	86.8	88.7	90.9
2	52.8	70.2	52.0
3	67.0	74.9	69.5
4	73.7	83.7	75.8
5	62.9	63.9	54.3
6	65.0	73.4	61.8
7	65.2	69.2	65.6
8	73.8	78.0	76.0
9	64.5	70.6	53.8
10	66.6	66.7	64.2
11	63.4	72.6	66.7
12	62.9	69.8	63.1
13	75.4	73.5	79.0
14	78.8	81.8	72.1
15	70.6	81.2	66.4
16	76.0	70.9	74.9
17	88.0	92.3	81.8
18	75.9	74.8	68.3

ing changed cardiac vagal tone *per se*. Indeed, the resting cardiac vagal tone in the Lyme disease patients was found not to differ significantly from that in the matched control group. Therefore, in attempting to provide an explanation for our results, it will not suffice simply to look for causes of altered (*e.g.*, reduced) cardiac vagal tone in the patient group.

The cause of the observed abnormalities might be vagal nerve changes resulting from Lyme disease. It is also worth bearing in mind that, since cardiac vagal tone is reflexly generated through arterial baroreceptor stimulation, by the afferents of the latter facilitating cardiac va-

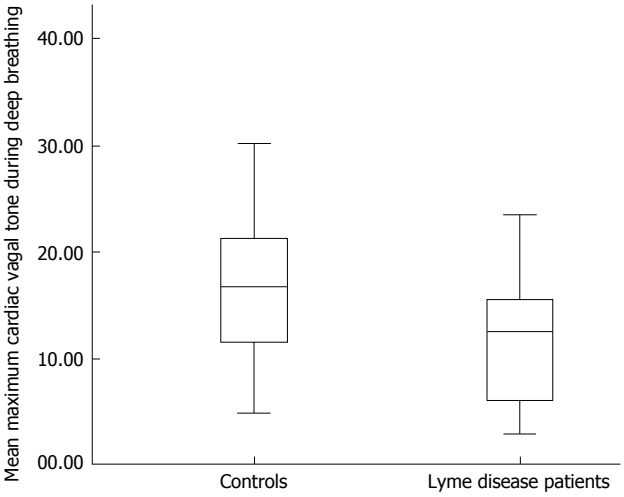

Figure 1 Boxplot of mean maximum cardiac vagal tone during deep breathing for the two groups.

gal motoneuron discharge relaying through interneurons in the nucleus tractus solitarius[15,17,18], the results are also compatible with the possibility that Lyme disease might affect the brainstem. Indeed, given that the dorsal nucleus of the vagus nerve, the nucleus ambiguus, the nucleus tractus solitarius, and the spinal trigeminal nucleus, which give rise to or receive axons of the vagus nerve, are located in the medulla oblongata, these two possibilities are not mutually exclusive.

The causative *Borrelia* bacteria are able to undergo pleomorphic changes, including into a cystic form; indeed, it has been suggested that this may at least in part account for some cases of antibiotic resistance and recurrence of Lyme disease[19]. It may be that this cystic form is often to be found in the brainstem in affected patients. However, this is unlikely to be an explanation here because this is believed to occur only in chronic Lyme neuroborreliosis.

It should be noted that there was no evidence that the patients were suffering from other disorders, such as Epstein-Barr viral infection, which might have caused false-positive serological results.

Finally, from Table 1 it can be seen that the mean resting cardiac rate in the controls (63.7 min^{-1}) was slightly (but not statistically significantly) lower than that in the patients (72.0 min^{-1}), while the mean resting cardiac vagal tone (5.7) was slightly (but not statistically significantly) higher than that in the patients (4.7). These findings might reflect the fact that the control group, in contrast to the Lyme patient group, were more physically fit; eight of the control subjects regularly engaged in exercise (sports, gymnasium attendance, or regular walking).

COMMENTS

Background

Lyme disease or Lyme borreliosis is an arthropod-borne zoonosis caused by *Borrelia* spirochetes, the incidence of which has recently been increasing with the geographical spread of infected ticks and which was previously identified clinically in Europe as Garin-Bujadoux-Bannwarth syndrome and in the United States as Lyme arthritis.

Innovations and breakthroughs

Respiratory modulation of cardiac vagal tone is impaired in Lyme disease, which suggests that Lyme disease may directly affect the vagus nerve or the brainstem.

Applications

Cardiac vagal tone is reflexly generated through arterial baroreceptor stimulation, by the afferents of the latter facilitating cardiac vagal motoneuron discharge relaying through interneurons in the nucleus tractus solitarius, implying that Lyme disease may directly affect the vagus or brainstem.

Peer review

The topic is relatively new and there are few data about the topic of the study about (respiratory modulation of cardiac vagal tone in Lyme disease). This finding seems very interesting.

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