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Influence of esophageal motility impairment on upper and lower esophageal sphincter pressure in Chagas disease

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HIGHLIGHTS

- Chagas disease changes esophageal motility, causing failed or non-peristaltic esophageal contractions and partial or absent lower esophageal sphincter relaxation. However, these esophageal motility alterations are not present in all patients affected by the disease.
- Upper and lower esophageal sphincter basal pressure could be influenced by changes in esophageal motility.
- No differences were observed in upper or lower esophageal sphincter basal pressure between controls and Chagas disease patients with absent or mild radiologic esophageal involvement.
- Chagas disease patients with constipation had decreased lower esophageal sphincter pressure compared to patients without constipation.

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ABSTRACT – Background – Chagas disease causes digestive anatomic and functional changes, including the loss of the myenteric plexus and abnormal esophageal radiologic and manometric findings. **Objective** – To evaluate the association of abnormal esophageal radiologic findings, cardiac changes, distal esophageal contractions, and complaints of dysphagia and constipation in upper (UES) and lower (LES) esophageal sphincter basal pressure in Chagas disease patients. **Methods** – The study evaluated 99 patients with Chagas disease and 40 asymptomatic normal volunteers. The patients had normal esophageal radiologic examination (n=61) or esophageal retention without an increase in esophageal diameter (n=38). UES and LES pressure was measured with the rapid pull-through method in a 4-channel water-perfused round catheter. Before manometry, the patients were asked about dysphagia and constipation and submitted to electrocardiography and chest radiography. **Results –** The amplitude of esophageal distal contraction decreased from controls to chagasic patients with esophageal retention. The proportion of failed and simultaneous contractions increased in patients with abnormal radiologic examination (P<0.01). There were no significant differences in UES and LES pressure between the groups. UES pressure was similar between Chagas disease patients with cardiomegaly (n=27, 126.5±62.7 mmHg) and those without it (n=72, 144.2±51.6 mmHg, P=0.26). Patients with constipation had lower LES pressure (n=23, 34.7±20.3 mmHg) than those without it (n=76, 42.9±20.5 mmHg, P<0.03). **Conclusion** – Chagas disease patients with absent or mild esophageal radiologic involvement had no significant changes in UES and LES basal pressure. Constipation complaints are associated with decreased LES basal pressure.

Keywords – Chagas disease; esophageal achalasia; deglutition disorders; esophageal sphincter, upper; esophageal sphincter, lower.

INTRODUCTION

Chagas disease, also known as American trypanosomiasis, is a neglected tropical disease consequent to an infection with the protozoan *Trypanosoma cruzi,* endemic to Latin America[1,2] and, mostly due to immigration, present also in North America, Europe, and Asia[1-3].

The disease was described in 1909 by the Brazilian physician Carlos Ribeiro Justiniano das Chagas[2,4], with the most frequent clinical manifestations affecting the heart[4,5] and the digestive tract[6-8].

In the esophagus, the disease impaired the myenteric plexus, thus affecting esophageal motility. Its radiologic and manometric images are similar to those of idiopathic achalasia: loss of esophageal peristalsis, partial or absent relaxation of the lower esophageal sphincter (LES) with swallows, increased esophageal diameter (megaesophagus), causing dysphagia and food retention, which is associated with regurgitation[6,7]. Despite the similarities in esophageal changes between idiopathic and chagasic achalasia, there are also differences[9] – although the clinical conditions are very similar. The involvement of the enteric nervous system also affects the large intestine, resulting in megacolon and constipation[6,7].

The loss of esophageal myenteric plexus is not equally intense in all Chagas disease patients[10]. Some of them do not have significant esophageal myenteric plexus impairment and may be asymptomatic, whereas others have intense esophageal plexus destruction and megaesophagus[10,11]. This is likely due to differences in inflammatory lesions and/or immune responses to the protozoan infection[5,12].

Previous investigations have described that the upper esophageal sphincter (UES) pressure is higher in patients with normal esophageal radiologic findings than in controls and that it is the same in controls in patients with more abnormal radiologic findings[13,14]. Their LES pressure is the same or lower than in normal controls[15], possibly due to an imbalance between excitatory and inhibitory esophageal innervation impairments[16]. As seen in idiopathic achalasia[17], esophageal manometry is heterogeneous among patients with Chagas disease[7], as not all patients have achalasia[11].

The UES is composed of the cricopharyngeus and thyropharyngeus muscles, inferior pharyngeal constrictor, and craniocervical esophagus smooth muscle. The most important of these is the cricopharyngeus muscle[18,19], which receives neural motor fibers from the pharyngo-esophageal and superior laryngeal branches of the vagus nerve[18]. Considering that the central nervous system is not significantly involved in Chagas disease[20], it is unlikely to affect UES basal pressure – although the bolus transit through the pharyngo-esophageal transition is slower[14,21], which may reflect a partial UES opening.

The LES is located at the esophageal-gastric transition. Its tone is controlled by smooth muscle cells, neurons, and interstitial cells of Cajal[22], and the latter two are affected by Chagas disease[10,23], which may impair LES tone.

This investigation aimed to evaluate how abnormal esophageal radiologic findings, cardiac changes, decreased distal esophageal contractions, and complaints of dysphagia and constipation influence UES and LES basal pressure in Chagas disease patients with absent or mild esophageal radiologic involvement. The hypothesis was that these patients' UES and LES basal pressure may be changed in association with abnormal esophageal radiologic and manometric findings, cardiac involvement, dysphagia, and constipation.

METHODS

All patients with a serologic diagnosis of Chagas disease (including asymptomatic ones) between 2000 and 2005, most of them had volunteered to donate blood, treated at the tertiary University Hospital, were investigated for esophageal and cardiac changes associated with the disease. This investigation included both individuals with normal esophageal radiologic examination and with delayed esophageal transit and esophageal retention of liquid bolus, without an increase in esophageal diameter. This retrospective investigation was approved by the Human Research Committee of the University Hospital of Ribeirão Preto.

The radiologic examination followed the university hospital's esophageal radiologic method. All individuals had an anteroposterior radiograph taken from the same distance 10 seconds after swallowing 100 mL of 100% liquid barium sulfate. Results were considered normal if no barium remained in the esophagus,

and abnormal (Grade I) if barium sulfate was retained, with an esophageal distal diameter of less than 4 cm – which means no increase in esophageal diameter[24].

Manometry was performed with a round eight-lumen polyvinyl catheter with an outer diameter of 4.5 mm and an inner diameter in each lumen of 0.8 mm (Arndorfer Specialities, Inc, Greendale, Wisconsin, USA). The four distal lateral openings of the catheter, used to measure sphincter pressures, were at the same level at 90º angles. The amplitude of distal esophageal contraction was measured at 5 cm, and contraction propagations 10 cm to 5 cm from the LES. They were connected to external pressure transducers (pvb Medizintechnik Gmb H, Kirchseeon, Germany), which in turn were connected to a PC Polygraph HR (Synectics Medical, Stockholm, Sweden). During the manometric recordings, a minimally compliant pneumohydraulic pump (JS Biomedicals, Ventura, CA, USA) perfused distilled water at 0.5 mL/min through each lumen.

All individuals were studied in the supine position after 12 hours of fasting. The catheter was introduced through the nose, and its four distal openings were positioned in the stomach. After locating the four distal openings of the catheter inside the LES and one proximal opening 10 cm and the other 5 cm from the LES, the subject swallowed 10 times a 5-mL bolus of water at room temperature, with an interval between successive swallows of at least 30 seconds. Then, the LES and UES pressure were measured with the rapid pull-through technique at the end of expiration.

For LES pressure, the four distal pressure sensors were located inside the stomach, and, at the end of expiration, the catheter was pulled by hand at 1 cm/s. LES pressure was recorded in triplicate, with the intragastric pressure as a reference. For UES pressure, the four sensors were located at the proximal esophagus, and, also at the end of expiration, the catheter was pulled by hand at 1 cm/s. The UES pressure was also measured in triplicate. Due to the asymmetrical pressure inside the UES and LES[25,26], there were four different pressure-measurement sensors in each sphincter. The pressures were evaluated from the higher (UES1 and LES1) to the lower (UES4 and LES4) values of each sphincter. Individual results were the mean of the three measurements in each of the four pressure sensors.

The amplitude of contraction was measured at 5 cm from LES, and peristaltic contractions were measured 10 cm to 5 cm from LES, having the esophageal basal pressure as a reference. Contractions whose upstrokes took less than 1 second between these two points were considered simultaneous. No esophageal response to 5 mL water swallows at 5 cm from LES was considered a failed contraction.

The investigation included 99 patients with Chagas disease and 40 asymptomatic volunteers as controls. The inclusion criteria in the Chagas disease group were a positive serologic test for the disease, epidemiologic history of living in a zone where the disease is endemic, and a normal esophageal radiologic examination or distal esophageal bolus retention without an increase in esophageal diameter. Exclusion criteria were esophageal dilatation, other associated diseases unrelated to Chagas disease, severe cardiac failure, and severe large bowel involvement (megacolon). The controls were asymptomatic volunteers who never lived in areas where the disease was endemic and did not have symptomatic cardiopathy or esophageal or colon diseases.

Before manometry, the patients were asked about dysphagia and constipation and submitted to electrocardiography (ECG) and chest radiography. ECG results were considered abnormal when there was bradycardia, extrasystoles, low voltage, left anterior fascicular block, electrically inactive zone, and increased dispersion of the QT interval[5]. Increased heart area in chest anteroposterior radiography, evaluated by a radiologist, was considered abnormal (cardiomegaly).

The statistical analysis was done by covariance (ANCOVA) test adjusted by sex and age. Amplitude, UES1, and LES1 were compared with dysphagia and constipation also with Mann-Whitney, using SAS 9.4. The results are shown as means, standard deviations, medians, and percentages, with P values ≤0.05 considered significant.

RESULTS

This retrospective investigation evaluated 99 individuals with positive serologic tests for Chagas disease and an epidemiologic history of living in areas where the disease is endemic (61 had normal eso-

phageal radiologic examinations [NER], and 38 had abnormal esophageal radiologic examinations [AER]) and 40 asymptomatic controls who never lived in areas where the disease is endemic.

The participants' mean age increased from the control group to patients with Chagas disease and normal esophageal transit and patients with Chagas disease and abnormal esophageal transit (TABLE 1, $P<0.01$). The proportion of men was higher than that of women in the chagasic groups (TABLE 1, $P=0.03$). Patients with abnormal esophageal radiologic examination had dysphagia and constipation more often than patients with normal radiography ($P<0.04$), but the frequency of abnormal ECG and cardiomegaly was not different (TABLE 1, $P>0.20$).

TABLE 1. Normal volunteers (controls, n=40), patients with Chagas disease with a normal esophageal radiologic examination (NER, n=61), and patients with Chagas disease with abnormal radiologic examination (AER, n=38), included in the investigation.

	Controls	NER	AER
Age: mean (SD), years	37.5 (14.3)	42.9 (12.7)	51.5 (11.1)*
Women: n (%)	20 (50.0)	15 (24.6)	16 (42.1)*
Men: n (%)	20 (50.0)	46 (75.4)	22 (57.9)*
Dysphagia: n (%)	-	13 (21.3)	27 (71.1)*
Constipation: n (%)	-	10 (16.4)	13 (34.2)*
Abnormal ECG: n (%)	-	46 (75.4)	31 (81.6)
Cardiomegaly: n (%)	-	14 (23.0)	13 (34.2)

ECG: electrocardiography; SD: standard deviation. *$P<0.04$ vs NER.

The amplitude of esophageal distal contraction decreased from the controls to chagasic patients with abnormal radiologic results. The proportion of failed and simultaneous contractions was higher in patients with Chagas disease ($P<0.01$) and abnormal radiologic examinations than in those with normal examinations (TABLE 2, $P<0.01$).

The highest UES pressure (UES1) was possibly the only difference in this measurement between patients with normal radiologic examinations and controls – higher in chagasic patients, although without a statistical significance (TABLE 3, $P=0.06$). The statistical analysis also demonstrated a lower pressure in LES2 (the second highest LES pressure) compared to controls (TABLE 4, $P=0.02$).

TABLE 2. Amplitude of contractions at 5 cm proximal to LES, percentage of failed contractions at 5 cm from LES, and percentage of simultaneous contractions 10 cm to 5 cm proximal to LES, in normal volunteers (controls, n=40), patients with Chagas disease with normal esophageal radiologic examinations (NER, n=61), and patients with Chagas disease with abnormal radiologic examinations (AER, n=38). Mean (SD).

	Amplitude (mmHg)	Failed (%)	Simultaneous (%)
Controls	110.2 (43.3)*	2.0 (5.2)*	2.2 (8.0)*
NER	74.9 (51.0)+	6.1 (15.1)+	7.2 (17.4)+
AER	47.2 (38.2)	11.3 (23.6)	40.3 (42.5)

LES: lower esophageal sphincter; SD: standard deviation. *$P<0.01$ vs NER and AER +$P<0.01$ vs AER.

TABLE 3. Upper esophageal sphincter pressure (mmHg) of normal volunteers (controls, n=40), patients with Chagas disease with normal esophageal radiologic examination (NER, n=61), and patients with Chagas disease with abnormal radiologic examination (AER, n=38), measured in four directions of the sphincter. Mean (SD).

	UES			
	1	2	3	4
Controls	113.0 (46.0)	84.4 (42.5)	48.6 (26.3)	31.6 (14.2)
NER	142.6 (48.2)*	96.4 (40.8)	44.8 (25.6)	34.1 (23.3)
AER	134.3 (65.0)	93.5 (45.1)	39.3 (21.5)	27.0 (19.3)

UES: Upper esophageal sphincter; SD: standard deviation. *$P=0.06$ vs controls.

TABLE 4. Lower esophageal sphincter pressure (mmHg) of normal volunteers (controls, n=40), patients with Chagas disease with normal esophageal radiologic examination (NER, n=61), and patients with Chagas disease with abnormal radiologic examination (AER, n=38), measured in four directions of the sphincter. Mean (SD).

	LES			
	1	2	3	4
Controls	48.8 (19.1)	35.2 (15.0)	23.5 (11.1)	18.4 (10.8)
NER	39.7 (19.4)	26.6 (15.2)*	19.5 (12.0)	15.2 (11.0)
AER	43.1 (22.7)	28.1 (13.9)	20.1 (10.4)	13.9 (9.8)

LES: Lower esophageal sphincter; SD: standard deviation. *$P=0.02$ vs controls.

Considering the highest sphincter pressures (UES1 and LES1), Chagas disease patients with cardiomegaly had similar UES1 pressure (n=27, 126.5±62.7 mmHg) to patients without cardiomegaly (n=72, 144.2±51.6 mmHg) (*P*=0.26) (FIGURE 1). However, considering only patients with normal radiologic examinations, the UES1 pressure was lower in patients with cardiomegaly (median: 107.6 mmHg, n=14) than in those without cardiomegaly (median: 154.4 mmHg, n=47, *P*=0.03). Patients with constipation had lower LES1 pressure (n=23, 34.7±20.3 mmHg) than those without constipation (n=76, 42.9±20.5 mmHg) (*P*=0.03) (FIGURE 2). Age, sex, dysphagia, and abnormal ECG did not influence amplitude or UES1 or LES1 pressure in Chagas disease patients.

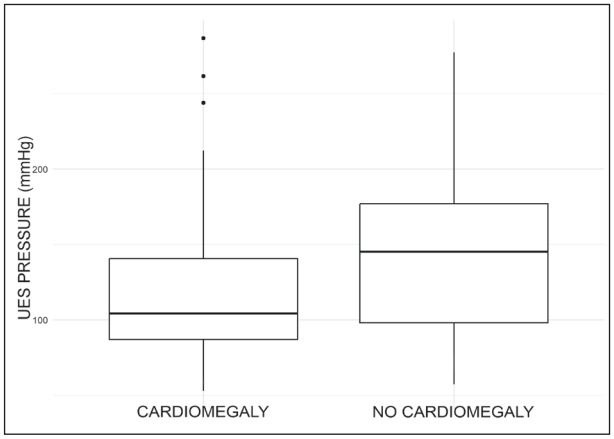

FIGURE 1. Upper esophageal sphincter (UES) pressure, in mmHg, measured in the place with the highest pressure (UES1) in Chagas disease patients with cardiomegaly (n=27) and without cardiomegaly (n=72). The box represents the first and third quartiles and the median. *P*=0.26.

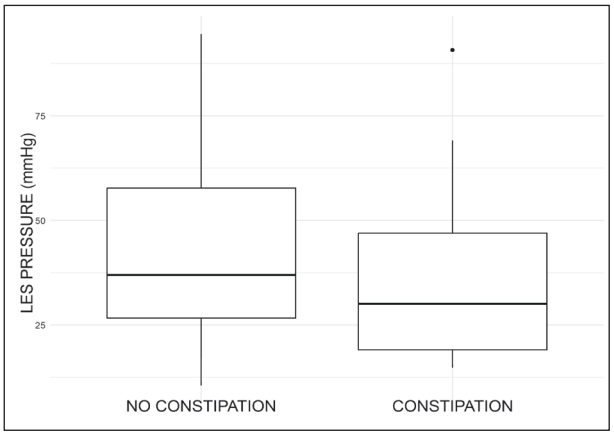

FIGURE 2. Lower esophageal sphincter (LES) pressure, in mmHg, measured in the place with the highest pressure (LES1) in Chagas disease patients without constipation (n=76) and with constipation (n=23). The box represents the first and third quartiles and the median. *P*=0.03.

DISCUSSION

Patients with more abnormal radiologic and manometric results and with complaints of dysphagia and constipation are older than patients with less intense esophageal changes, suggesting a possible increase in the intensity of esophagopathy caused by Chagas disease, as a consequence of progressive loss of esophageal neurons with the aging process[10,27,28].

The UES pressure in the group with normal esophageal radiologic examination may be different from that of controls only in the part with the highest pressure in the sphincter. The highest UES pressure is measured posteriorly[25], so this should be the place where the UES1 pressure was measured. During the measurement, the catheter movement increases the sphincter pressure[29]. The response of the sphincter muscle may be more intense in Chagas disease patients without a significant loss of esophageal innervation than in those with esophageal changes and healthy volunteers, possibly as a reflex to avoid regurgitation in patients with esophageal motility changes and preserved sensitivity. If esophageal sensitivity is lost, the reflex may not be present. Alteration of sensitivity is suggested to happen in patients with Chagas disease esophagopathy[30]. UES pressure increases when there is a stimulus inside the esophagus, as seen with liquid reflux in gastroesophageal reflux disease[31,32] and air infusion in patients with idiopathic achalasia[33].

Basal UES pressure decreases with age[34,35]. Therefore, UES pressure in Chagas disease patients was expected to decrease because of their higher mean age – which, however, was not confirmed by the results. Possibly, the UES pressure tended to be higher in the measurement of patients with chagasic esophagopathy, but the aging process had the opposite effect. Studies in patients with Chagas disease living in Europe found that 10% to 36% of them had hypertensive UES[36,37]. Functional alterations of UES function during swallow were described in patients with Chagas' disease[21,38] and patients with idiopathic achalasia[39].

Considering previous results[15], the LES pressure was expected to be lower in Chagas disease patients, which was found to be true only in patients with normal radiologic examinations and in a place

where the pressure was not the highest. The heterogeneous esophageal involvement due to the disease may cause different manifestations[11]. Although the results suggested the possibility of decreased LES pressure in Chagas disease, they do not confirm the previous conclusion[15].

Esophageal innervation loss in achalasia may impair more intensely either the excitatory (neurotransmitter - acetylcholine) or inhibitory (neurotransmitter - nitric oxide) innervation, or impair both similarly, influencing esophageal motility control and LES pressure[16]. The higher-than-normal LES pressure seen in patients with idiopathic achalasia may be due to the less intense impairment of the excitatory cholinergic LES innervation than that of the nonadrenergic, noncholinergic inhibitory nerves[40]. However, excitatory cholinergic and inhibitory nerves are seemingly impaired in Chagas disease[41]. Muscle action may be itself the main factor in maintaining the LES pressure in chagasic patients, with a less important participation of the cholinergic excitatory system. Cholinergic innervation impairment is also suggested by the lower LES pressure in patients with constipation than in those without it – which indicates cholinergic colon and esophageal innervation impairment. LES is circumferentially asymmetrical, as each quadrant has a different basal pressure[26]. Hence, innervation impairment may impact each quadrant of the sphincter differently.

Patients with normal esophageal radiologic examination and cardiomegaly had lower UES pressure than those without cardiomegaly. The pathogenetic mechanisms of Chagas heart disease are autonomic nervous system derangements, microvascular disturbances, parasite-dependent myocardial aggression, and immune-mediated myocardial injury[4,5]. The mechanisms of the combined cardiac/esophageal impairment are unknown, but the disease may lead to autonomic nervous system derangements in the proximal digestive system, possibly not intense enough to cause important symptoms, but affecting the pharynx and UES function during swallowing, as observed in the longer transit time through the pharynx[14] and a slower bolus transit through the UES[21].

In some physiological aspects, the cricopharyngeus acts more like a cardiac than a striated muscle[18]. In Chagas disease, there is an association between left ventricular systolic dysfunction and longer scintigraphic esophageal transit time, which suggests simultaneous disorders of gastrointestinal and cardiac functions[42].

This investigation has limitations. It is a retrospective study of examinations performed a long time ago. The manometry method used (water perfusion) is not the best one for esophageal manometry nowadays, which is now the high-resolution manometry. However, it was used and accepted for a long time in esophageal motility assessments. Fortunately, thanks to public health system interventions and social evolution, the prevalence of Chagas disease in the country's population has decreased significantly. Hence, these patients' digestive tract is assessed less often and more difficultly than decades ago. Nevertheless, the disease is still prevalent in some areas of the country[43], with new cases occurring worldwide[2].

CONCLUSION

The results indicated that, in Chagas disease patients with absent or mild esophageal radiologic involvement, esophageal motility does not clearly influence UES and LES basal pressure. Also, constipation complaints are associated with decreased LES basal pressure.

Authors' contribution

The author Dantas RO participated in the design of the study, data acquisition and interpretation, manuscript writing, and approval of the final version for submission.

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Dantas RO. Influência do comprometimento da motilidade do esôfago nas pressões do esfíncter superior e inferior do esôfago na doença de Chagas. Arq Gastroenterol. 2024;61:e23174.

RESUMO – Contexto – Doença de Chagas compromete principalmente o coração e o aparelho digestivo. No esôfago ocorre destruição do plexo mientérico, com alterações radiológicas e manométricas semelhantes às da acalásia idiopática. **Objetivo –** Avaliar a influência do comprometimento radiológico do esôfago, alterações cardíacas, contrações esofágicas distais e queixas de disfagia e constipação na pressão dos esfíncteres superior (EES) e inferior (EEI) do esôfago. **Métodos –** Foram avaliados 99 pacientes com exame sorológico positivo para doença de Chagas, com exame radiológico do esofâgo normal (n=61) ou retenção esofágica sem dilatação (n=38), e 40 voluntários normais. A pressão do esfíncter superior e inferior foi medida em triplicata pelo método da retirada rápida do cateter com perfusão de água, em quatro direções dos esfíncteres. Os pacientes foram questionados sobre disfagia e constipação, e foram realizados eletrocardiograma e radiografia de tórax. **Resultados** – A amplitude da contração distal foi de maior valor dos controles para pacientes com retenção esofágica; a proporção de contrações falhas e simultâneas aumentou em pacientes com exame radiológico anormal (P=0,01). Não houve diferença entre os grupos nas pressões do EES e do EEI. Pacientes com cardiomegalia apresentaram pressão do EES similar (n=27, 126,5±62,7 mmHg) a pacientes sem cardiomegalia (n=72, 144,2 ±51,6 mmHg, P=0,26). Pacientes com constipação apresentaram menor pressão do EEI (n=23, 34,7±20,3 mmHg) do que pacientes sem constipação (n=76, 42,9±20,5 mmHg, P<0,03). **Conclusão –** Os pacientes com doença de Chagas avaliados não apresentaram alteração significativa na pressão basal do EES e do EEI. Houve associação da queixa de constipação com diminuição da pressão basal do EIE.

Palavras-chave – Doença de Chagas; acalásia esofágica; transtornos da deglutição; esfíncter esofágico superior; esfíncter esofágico inferior.

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