SEQUENTIAL SWALLOWS HAVE NO INFLUENCE ON ESOPHAGEAL CONTRACTIONS OF PATIENTS WITH IRON DEFICIENCY ANEMIA

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ABSTRACT – ***Background*** – An experimental study showed that thyropharyngeal, cricopharyngeal and cervical esophageal muscles of rabbits with iron deficiency anemia had morphological changes similar to those observed in muscular dystrophy, causing myastenic changes in muscles involved in swallowing. Our hypothesis is that patients with iron deficiency anemia may have a decrease in esophageal contractions with successive swallows. ***Patients and Method*** – We studied the esophageal motility of 12 women with iron deficiency anemia aged 31 to 50 years (median 36 years) with serum iron from 11 to 40 µg/dL (median 21 µg/dL), and 13 asymptomatic women aged 26 to 49 years (median 35 years) with serum iron over 60 µg/dL. We used the manometric method with continuous perfusion. The esophageal contractions were measured at 3, 9 and 15 cm from the upper margin of a sleeve that straddled the lower esophageal sphincter. Each subject performed 10 swallows of a 2 mL bolus of water alternated with 10 swallows of a 7 mL bolus, with an interval of 30 seconds between swallows. We measured the amplitude, duration, velocity and area under the curve of contractions. ***Results*** – There was no difference between the swallows of a 2 mL or 7 mL bolus. The amplitude, duration and area under the curve were lower in patients with iron deficiency than in asymptomatic volunteers, mainly in the proximal and middle esophageal body. There was no difference in velocity. Sequential swallows did not change contraction amplitude, duration, velocity or area under curve in patients and volunteers. ***Conclusion*** – Although the power of esophageal contractions was decreased in patients with iron deficiency anemia, sequential swallows did not cause further impairment.

HEADINGS – Deglutition. Esophagogastric junction. Anemia, iron-deficiency.

INTRODUCTION

An experimental study showed that the thyropharyngeal, cricopharyngeal and cervical esophageal muscles of rabbits with iron deficiency anemia had morphological changes similar to those observed in progressive muscular dystrophy, leading to the conclusion that iron deficiency may cause myastenic changes in muscles that pertain to swallowing[7]. In myastenia gravis the pharynx undergoes progressive worsening of function upon repeated swallows[2]. Oculopharyngeal muscular dystrophy predominantly affects the striated pharyngeal muscles and the palpebral levator. The esophageal smooth muscle in the disease also shows dysfunction characterized by nonpropulsive, simultaneous, retrograde and failed activity[1, 11].

Iron deficiency causes reduction of the constricting power of the pharyngeal muscle for propulsion of bolus into the esophagus[7]. In the study of the esophagus in patients with iron deficiency anemia we found a decrease in esophageal contractions[5, 6] and an increased esophageal transit duration[6].

Our hypothesis is that with the morphological alterations of muscles involved in swallowing there is the possibility of a decrease in esophageal contraction with repeated swallows in patients with iron deficiency anemia.

PATIENTS AND METHODS

We studied 12 female patients aged 31 to 50 years (median 36 years) with serum iron from 11 to 40 µg/dL (median 21 µg/dL). The normal range for serum iron in women is

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49 to 151 µg/dL. The patients had hemoglobin levels below 11µg/dL and hematocrit below 30%. The duration of the symptoms attributed to anemia ranged from 2 months to 22 years (median 6 years). Two patients complained of dysphagia. The cause of anemia was hypermenorrhea. The patients did not have any systemic disease that could influence esophageal motility and none had been submitted to previous gastrointestinal surgical treatment. Endoscopic examination was performed in all patients, with normal results. None of the patients had malnutrition or was underweight.

As a control group we studied 13 asymptomatic female volunteers aged 26 to 49 years (median 35 years) with normal hematologic evaluation and serum iron over 60 µg/dL. Informed consent was obtained from each volunteer and patient. The study was approved by the Human Research Committee of the University Hospital of Ribeirão Preto, SP, Brazil.

Esophageal manometry was performed using an eight-lumen manometric catheter assembly incorporating a 6-cm sleeve device at its distal end. Side-hole recording orifices were cut at the distal and proximal margins of the sleeve. Five additional side-hole recording orifices were cut at 3 cm intervals along the assembly, starting 3 cm proximal to the sleeve (Arndorfer Specialties Inc, Greendale, WI, USA). The catheter assembly was connected to external pressure transducers, which in turn were connected to a PC Polygraph HR (Synectics Medical, Stockolm, Sweeden). The manometric signals were stored in a computer. During manometric recordings, a minimally compliant pneumohydraulic pump (JS Biomedicals Inc, Ca, USA) perfused distilled water at 0.5 mL/min through the sleeve and the side holes.

Each subject was studied after an overnight fast. The catheter assembly was passed through the nose and positioned so that the 6-cm long sleeve straddled the lower esophageal sphincter (LES). The contractions in the esophageal body were registered by the side holes localized at 3, 9 and 15 cm from the upper margin of the sleeve. All volunteers and patients were studied in the supine position. They performed 10 swallows of a 2 mL bolus of water at roam temperature alternated with 10 swallows of a 7 mL bolus of water. Using the computer Polygram Upper GI software version 6.4 (Gastrosoft, Inc) we measured the amplitude, duration, area under curve (AUC) and velocity of the peristaltic contractions.

For statistical analysis we used the unpaired *t*-test, calculating the one-tailed *P* value and analysis of variance. The swallows of the 7 mL bolus were analyzed. The Kolmogorov and Smirnov method showed that the data were sampled from populations that followed Gaussian distribution. The results are reported as mean ± SEM unless otherwise indicated.

RESULTS

There was no difference between the swallows of a 2 mL or 7 mL bolus.

The contraction amplitude (Figure 1), duration (Figure 2) and AUC (Figure 3) were lower in patients with iron deficiency than in asymptomatic volunteers for most of the swallows, mainly in the proximal and middle esophageal body. There was no difference in peristaltic contraction velocity.

The contraction amplitude duration, AUC and velocity did not change significantly with sequential swallows. There was no difference between the mean of the initial five swallows and the mean of the final five swallows (Tables 1, 2) in volunteers or patients.

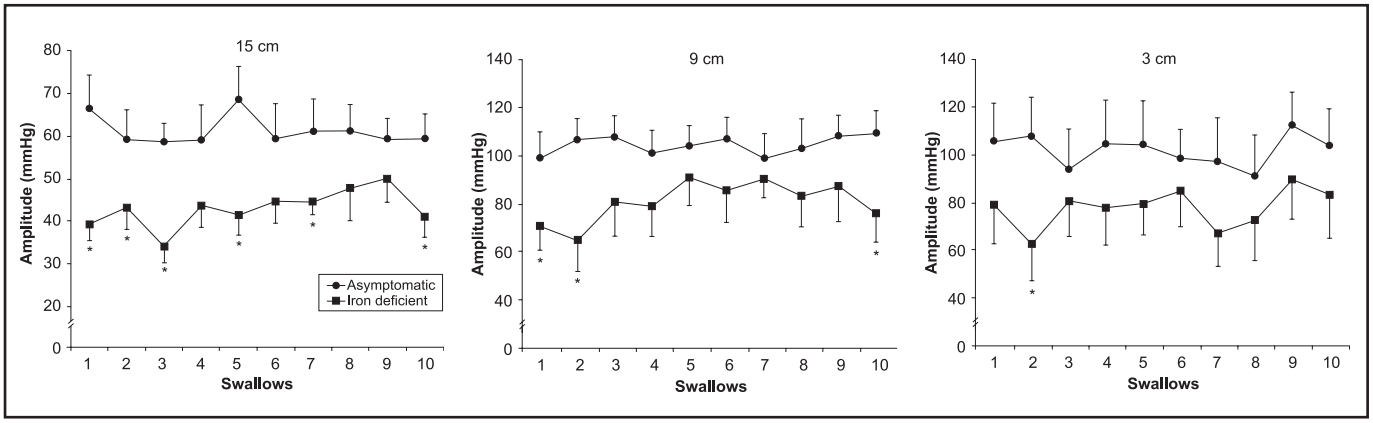

FIGURE 1 – Amplitude of esophageal contractions measured in 10 swallows of a 7 mL bolus of water at 3, 9 and 15 cm from the upper margin of the sleeve in asymptomatic volunteers (n = 13) (●) and patients with iron deficiency anemia (n = 12) (■). The results are shown as mean ± SEM. *$P < 0.05$

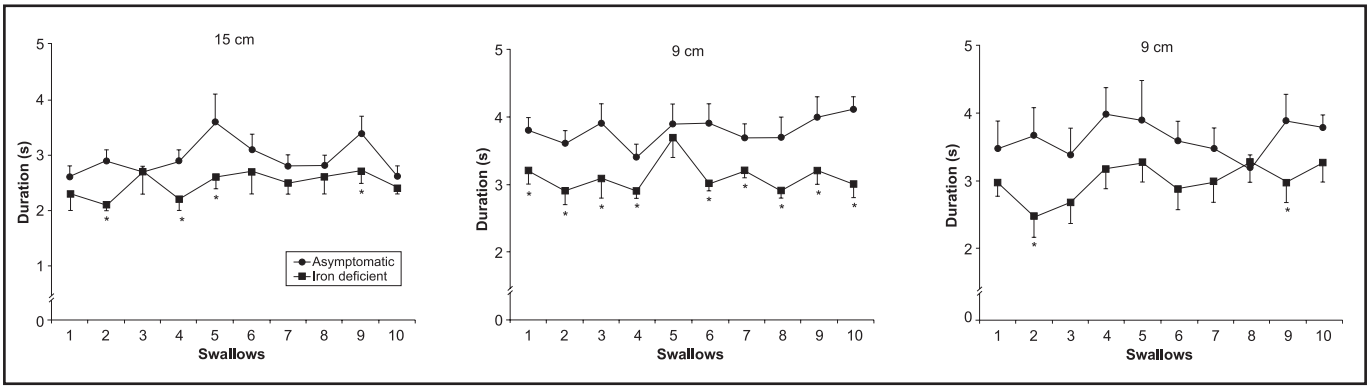

FIGURE 2 – Duration of esophageal contractions measured in 10 swallows of a 7 mL bolus of water at 3, 9 and 15 cm from the upper margin of the sleeve in asymptomatic volunteers (n = 13) (●) and patients with iron deficiency anemia (n = 12) (■). The results are shown as mean ± SEM. *$P < 0.05$

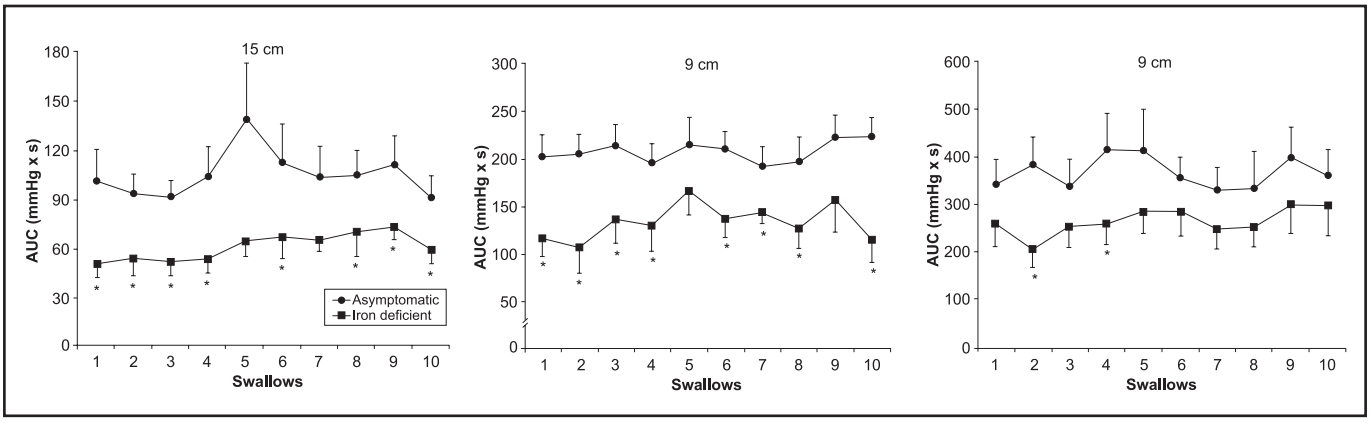

FIGURE 3 – Area under curve (AUC) of esophageal contractions measured in 10 swallows of a -7 mL bolus of water at 3, 9 and 15 cm from the upper margin of the sleeve in asymptomatic volunteers (n = 13) (●) and patients with iron deficiency anemia (n = 12) (■). The results are shown as mean ± SEM. *$P < 0.05$

DISCUSSION

Our results showed a decrease in the power of esophageal contraction, mostly in the middle and proximal esophagus, manifested in the amplitude, the duration and area under curve (amplitude x duration) of contractions in patients with iron deficiency. The comparison of the results of esophageal contractions between patients with iron deficincy and asymptomatic volunteers have been published in a previous paper[6].

Studies of the effect of iron deficiency on the skeletal muscle metabolism of the rat found metabolic changes that are consistent with either a reduction in supply of oxygen to the muscle cell or altered oxidative phosphorylation by the mitochondria[9]. The decreased mitochondrial activity is likely to be due either to a reduction in the numbers of mitochondrial or to decreased activity of the mitochondrial oxidative components[9]. A leakage of mitochondria in type I muscle fibers was found in rabbits with iron deficiency[7]. In humans with iron deficiency anemia of moderate to severe degree there was not evidence for a major mitochondrial oxidative defect[10].

Consequent to the description of alterations in muscles involved in swallowing in animals with iron deficiency[7,9], our hypothesis was that the esophageal contraction, mainly in the proximal esophagus, where there is a proportion of striated muscle, might be impaired. Since it has also been suggested that myastenic changes are found in muscles of iron deficient animals, sequential swallows might show a progressive decrease in the power of esophageal contractions. The

TABLE 1 – Amplitude and duration of esophageal contractions in asymptomatic volunteers (n = 13) and in patients with iron deficiency anemia (n = 12) measured at 3, 9 and 15 cm from the upper margin of the sleeve, after 10 swallows of a 7 mL bolus of water. Swallows 1 to 5 are the initial ones and 6 to 10 are the final ones (mean ± SEM)

	Amplitude (mm Hg)		
	3 cm	**9 cm**	**15 cm**
Volunteers			
Initial	143.1 ± 17.1	103.5 ± 9.4	62.4 ± 7.0
Final	140.2 ± 15.3	105.0 ± 10.0	60.1 ± 6.4
Iron deficiency			
Initial	116.1 ± 14.9	77.1 ± 12.4	40.4 ± 4.6*
Final	119.3 ± 16.0	84.1 ± 12.1	45.6 ± 5.3*
	Duration (seconds)		
	3 cm	**9 cm**	**15 cm**
Volunteers			
Initial	4.7 ± 0.4	3.7 ± 0.2	2.9 ± 0.3
Final	4.6 ± 0.3	3.9 ± 0.3	2.9 ± 0.2
Iron deficiency			
Initial	3.9 ± 0.3	3.2 ± 0.2	2.4 ± 0.2
Final	4.1 ± 0.3	3.1 ± 0.1*	2.6 ± 0.2

P < 0.05 *vs.* volunteers

TABLE 2 – Area under curve and velocity of esophageal contractions in asymptomatic volunteers (n = 13) and in patients with iron deficiency anemia (n = 12), measured at 3, 9 and 15 cm from the upper margin of the sleeve, after 10 swallows of a 7 mL bolus of water. Swallows 1 to 5 are the initial ones and 6 to 10 are the final ones (mean ± SEM)

	Area under curve (mm Hg x sec)		
	3 cm	**9 cm**	**15 cm**
Volunteers			
Initial	378.1 ± 66.6	206.3 ± 23.7	106.6 ± 18.8
Final	357.1 ± 57.9	210.5 ± 22.3	105.6 ± 18.0
Iron deficiency			
Initial	250.4 ± 42.4	131.2 ± 24.5*	55.4 ± 8.9*
Final	276.8 ± 50.5	136.5 ± 22.0*	68.0 ± 10.3*
	Velocity (cm/sec)		
	15 ➞ 9 cm		**9 ➞ 3 cm**
Volunteers			
Initial	2.7 ± 0.2		3.1 ± 0.3
Final	2.6 ± 0.1		3.1 ± 0.3
Iron deficiency			
Initial	2.8 ± 0.3		3.1 ± 0.3
Final	2.7 ± 0.3		3.2 ± 0.3

P < 0.05 *vs.* volunteers

present results confirm the possibility that the esophagus of subjects with iron deficiency has an impaired contraction power, but did not confirm the possibility that sequential swallows cause progressive impairment of contractions.

The alterations observed in muscles involved in swallowing should affect the pharyngeal phase. A decrease in the power of pharyngeal contractions[7] and a slower bolus penetration into the proximal esophagus was detected in humans[6]. The loss of the power of pharyngeal contractions affects the opening of the upper esophageal sphincter[3]. In the present study, we detected a lower amplitude of contractions in the proximal esophagus of patients compared to asymptomatic subjects.

Our results showed that the esophageal motility of patients with iron deficiency resembled the digestive motor impairment seen in muscular dystrophy but not in myastenia gravis.

In oculopharyngeal muscular dystrophy, muscle biopsies have demonstrated changes in levator, pharyngeal and vastus lateralis muscles, suggesting that the disorder may be a manifestation of mitochondrial myopathy[2]. It is a myopathy affecting almost exclusively the bulbar muscles and the levator muscle of the eyes. The major differential diagnoses are myastenia gravis and mitocondrial myopathies. The disease also affects esophageal motility[1, 11], which is associated with delayed esophageal isotope clearance[2].

Myastenia gravis is characterized by destruction of acetylcholine receptors at neuromuscular junctions. The musculature controlled by the cranial nerves is almost always involved. Diagnosis is confirmed by detecting acetylcholine receptor antibodies, which are present in 85% of the cases[2]. The pharyngeal radiographic examination shows diffuse functional abnormalities with progressive worsening on repeated swallows, with improvement after parenteral injection of neostigmine[8].

The comparison of the initial group of swallows (1 to 5) with the final one (6 to 10) did not show significant differences. We previously described the same results in normal volunteers, patients with Chagas' disease and patients with idiopathic achalasia[4]. These previous results and the present ones show that with an interval of 30 seconds between sequential swallows there is no change in amplitude, duration or velocity of peristaltic contractions. It is possible that in patients with iron deficiency sequential swallows performed within a shorter time interval cause progressive impairment of contractions.

In conclusion, although there is impairment of contractions in patients with iron deficiency anemia, sequential swallows do not change the contractions, with the changes in esophageal motility showing some similarity to those of muscular dystrophy.

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Dantas RO, Miranda ALM. Deglutições não modificam as contrações esofágicas de pacientes com anemia ferropriva. Arq Gastroenterol 2004;41(1):27-32.

RESUMO – ***Racional*** – Estudo experimental encontrou que os músculos tirofaríngeo, cricofaríngeo e do esôfago cervical de coelhos com anemia ferropriva têm alterações morfológicas semelhantes às encontradas na distrofia muscular, provocando alterações miastênicas em músculos envolvidos com a deglutição. Nossa hipótese é de que pacientes com anemia ferropriva têm diminuição das contrações esofágicas com uma seqüência de deglutições sucessivas. ***Objetivo*** – Avaliar as contrações esofágicas em pacientes com anemia ferropriva. ***Pacientes e Método*** – Estudou-se a motilidade do esôfago de 12 mulheres com anemia ferropriva, com idades entre 31 e 50 anos (mediana 36 anos) com ferro sérico de 11 a 40 µg/dL (mediana 21 µg/dL), e 13 mulheres assintomáticas, com idades entre 26 e 49 anos (mediana 35 anos) com ferro sérico acima de 60 µg/dL. Foi utilizado o método manométrico com perfusão contínua. As contrações no esôfago foram medidas a 3, 9 e 15 cm da margem superior de sensor longo ("sleeve") colocado no esfíncter inferior do esôfago. Cada pessoa fez 10 deglutições de 2 mL de água, alternadas com 10 deglutições de 7 mL, com intervalo de 30 segundos entre as deglutições. Mediram-se a amplitude, duração, velocidade e área sob a curva das contrações. ***Resultados*** – Não houve diferença entre as deglutições dos volumes de 2 mL e 7 mL. A amplitude, duração e área sob a curva foram menores nas pacientes do que nas voluntárias assintomáticas, principalmente em partes proximal e média do esôfago. Não houve diferença na velocidade. A seqüência de deglutições não modificou a amplitude, duração, velocidade e área sob a curva das contrações nas pacientes e nas assintomáticas. ***Conclusão*** – Embora as contrações esofágicas estejam diminuídas em pacientes com deficiência de ferro, a seqüência de deglutições não provocou modificações nessas contrações.

DESCRITORES – Deglutição. Junção esofagogástrica. Anemia ferropriva.

REFERENCES

1. Castell JA, Castell DO, Duranceau A, Topart P. Manometric characteristics of the pharynx, upper esophageal sphincter, esophagus, and lower esophageal sphincter in patients with oculopharyngeal muscular dystrophy. Dysphagia 1995;10:22-6.
2. Cook IJ. Disorders causing oropharyngeal dysphagia. In: Castell DO, Richter JE, editors. The esophagus. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 1999. p.165-84.
3. Cook IJ, Dodds WJ, Dantas RO, Massey B, Kern M, Lang IM, Brasseur JG, Hogan WJ. Opening mechanisms of the human upper esophageal sphincter. Am J Physiol 1989;257:G748-59.
4. Dantas RO. Effect of successive swallows on esophageal motility of normal volunteers, patients with Chagas' disease, and patients with idiopathic achalasia. Neurogastroenterol Motil 2003;15:57-62.
5. Dantas RO, Villanova MG. Esophageal motility impairment in Plummer-Vinson syndrome. Correction by iron treatment. Dig Dis Sci 1993;38:968-71.
6. Miranda ALM, Dantas RO. Esophageal contractions and oropharyngeal and esophageal transits in patients with iron deficiency anemia. Am J Gastroenterol 2003;98:1000-4.
7. Okamura H, Tsutsumi S, Inaki S, Mori T. Esophageal web in Plummer-Vinson syndrome. Laryngoscope 1988;98:994-8.
8. Ott DJ. Radiology of the oropharynx and esophagus. In: Castell DO, Richter JE, editors. The esophagus. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 1999. p.45-87.
9. Thompson CH, Green YS, Ledingham JG, Radda GK, Rajagopalan B. The effect of iron deficiency on skeletal muscle metabolism of the rat. Acta Physiol Scand 1993;147:85-90.
10. Thompson CH, Kemp GJ, Taylor DJ, Radda GK, Rajagopalan B. No evidence of mitochondrial abnormality in skeletal muscle of patients with iron-deficient anaemia. J Intern Med 1993;234:149-54.
11. Tiomny E, Khilkevic O, Korczyn AD, Kimmel R, Hallak A, Baron J, Blumen S, Asherov A, Gilat T. Esophageal smooth muscle dysfunction in oculopharyngeal muscular dystrophy. Dig Dis Sci 1996;41:1350-4.

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