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New Method for Quantitative Evaluation of Esophageal Sensibility

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A method for quantitating esophagus sensibility by an electric stimulation test is described. Square stimulus waveform at different voltages and durations were transmitted to the esophagus, three series of electric stimuli being used in successive durations (0.5, 1, 2, 4, 8 and 16 ms); in each series the voltage discharge was increased progressively from 0 mV, until the subject noted the first sensation. This procedure was carried out at all esophageal levels. The following parameters were analyzed: a) sensitive threshold along the esophagus; b) the relation of threshold sensibility (mV) duration of stimulus (ms), and c) reobase and cronaxia for each esophageal level. At all esophageal levels, the sensitive threshold was regular and coherent; in the middle esophagus a zone was found having higher sensitive threshold than the proximal and distal esophageal zones. The relationship between sensitive threshold and inverse of the stimulus duration indicated that esophageal sensibility follows the basic law of excitation of WEISS, at least with this type of stimulus, reobase and cronaxia being representative of the sensibility threshold along the esophagus. Quantitative esophageal sensibility, therefore is concluded to be particulary suited to evaluation by electric stimulation.

Key words: Esophageal electric stimulation, Esophageal sensibility.

The esophagus has an important sensory capacity, as demonstrated by a series of clinical and experimental data, esophageal disorders being accompanied by unmistakable symptoms such as pyrosis, disphagia and restrosternal pain; these symptoms can also be induced by experimental manoeuvres. Pyrosis is suffered by patients with reflux esophagitis, during acid perfusion (5) and also when certain foods come into direct contact with the inflamed esophageal mucosa (27). Retrosternal pain, found in esophageal motor disorders, can be reproduced by the administration of cholinergic drugs

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(20, 21), as well as by sudden esophageal distension with an intraesophageal balloon, thereby provoking retrosternal pain in subjects not affected by esophageal disorders (17, 25). It is, therefore, evident that there are structures sensitive to various stimuli, having symptomatic responses similar to those of esophageal disorders.

On the other hand, histologic studies undertaken using animal or human esophagus have shown the large number of nerve endings possibly having a sensitive function (3, 8, 15, 29-31), as demonstrated by experimental models and electrophysiological studies (2, 10, 14, 19). These investigations indicate the functional existence of mechanical, chemical and thermic sensitive receptors.

Clinical and experimental data thus confirm an evident esophageal sensory capacity, that in man is very difficult to analyze due to lack of a proper methodology. This study presents an orginal method carried out by our laboratory (6, 18, 22), consisting of electrical stimulation of the esophagus by rectangular stimulus waveform at different voltages and durations of time with the registering of the receptive sensitive thresholds.

Material and Methods

Healthy volunteers, 11 men and 3 women, either medical students or hospital personnel, having a mean age of 23 ± 6 years (range 18-39), participated in this study. None presented esophageal symptoms or systemic disease and radiological study of the esophagus was normal in all; esophageal manometry (4) and acid perfusion test (5) demonstrated no abnormality.

An Electrical Intraesophageal Stimulation Test (E.I.S.T.) was carried out in all subjects, the following equipment being used (fig. 1): Multifunction solid-state square wave stimulator model 588 (Gras Medical Instruments). An isolation stimuli unit SIU 5. An electrode-sound Plastimed 8F of 10 electrodes (5 pairs) in circles of 2 mm in height, with separations of 18 mm between each. A simple circuit having a light and a conventional switch connected to the system.

Procedure. After overnight fasting, the electrode-sound was fitted in subjects' mouths to the upper limit of the lower esophageal sphincter (L.E.S.) (distance previously known by manometric study).

The ends of the sound were connected to the isolating unit and this to the stimulator.

Three series of electrical stimuli were used in successive durations of 0.5, 1, 2, 4, 8 and 16 ms; in each series, the voltage discharged progressively increased from 0 mV until the subject noted the first sensation, at which moment he would press the cut-out switch, as previously instructed. The voltage applied in the stimulus was then recorded on the corresponding data sheet.

The esophagus was divided into 12 conventional levels (0-A / A-B / B-C / and so on, till L-M), the distance between pairs of electrodes always being 18 mm and level 0 corresponding to the upper limit of L.E.S. Exploration of the esophagus was divided into three arbitrary sections: Distal third, placing the electrode-sound as cited above and working successively with the pairs 1(+)/3(—); 3(+)/5(—); 5(+)/7(—); 7(+)/9(—). The response obtained for the first pair was referred to as level 0 and successively for the like until the fourth pair (level C). Medial third, corresponding to levels D, E, F and G, obtained by withdrawing the electrode-sound at 7.2 cm (18 mm×4). Proximal third, corresponding to levels H, K, L and M, after withdrawing the sound another 7.2 cm and proceeding with the same method.

At all 12 levels indicated, electric stimuli were applied using the above-men-

tioned procedure; definitive, numeric data were then obtained, corresponding to the minimum voltage necessary for perception by subject at all levels and duration. The following parameters were then analyzed: a) sensitive threshold along the esophagus; b) relations of threshold sensibility (mV) — duration of the stimulus (ms); c) reobase and cronaxia for each level. All data were expressed as mean ± ± SEM.

Results

Sensitive thresholds. As shown in table I, the sensitive threshold at each level was regular and coherent, the voltage necessary for perception to be obtained decreasing as duration of the stimulus increased. The higher the esophageal level, the lesser the duration of stimulus which, in turn, meant that the dispersion of values was greater.

In the middle esophagus, a zone corresponding to levels D, E, F, G and H had a higher sensitive threshold than that found in the proximal and distal esophageal zones.

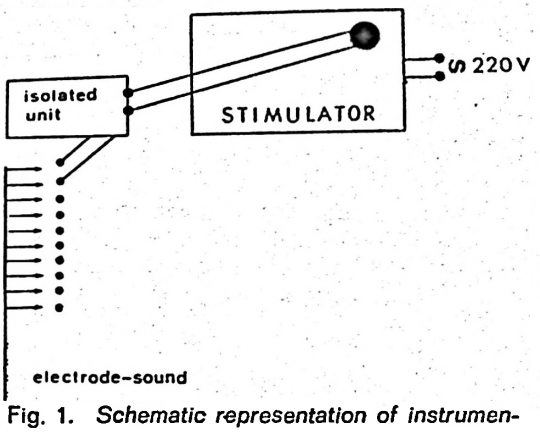

Fig. 1. *Schematic representation of instrumental used in the electrical intraesophageal stimulation test (E.I.S.T.).*

Relations between sensitive threshold (mv) and duration of stimulus (ms). As shown in table II, the sensitive thresholds at each level are correlated to the inverse of the electric stimulus durations ($p < 0.05$).

The relationship between sensitive threshold and the inverse of the stimulus duration indicated that, at least for this type of stimulus, the esophageal sensibility followed the basic law of excitation of WEISS (33).

Table I. *Sensitivity threshold (mV) in each duration (ms) and level.*

Level	Duration 0.5	1	2	4	8	16
M	36.5 ± 1.0	31.9 ± 1.3	30.2 ± 1.2	29.0 ± 0.9	23.6 ± 0.9	20.6 ± 0.9
L	40.4 ± 1.4	36.2 ± 1.9	32.0 ± 0.9	30.0 ± 0.8	24.9 ± 0.7	20.2 ± 1.0
K	41.2 ± 1.9	35.1 ± 1.8	32.8 ± 1.6	30.4 ± 1.6	26.2 ± 1.3	22.7 ± 1.6
H	45.0 ± 2.1	40.2 ± 2.0	36.7 ± 1.5	31.1 ± 1.6	28.4 ± 1.3	25.8 ± 1.4
G	55.1 ± 2.4	45.4 ± 1.9	42.1 ± 2.0	37.8 ± 1.4	32.5 ± 1.1	29.2 ± 0.9
F	57.9 ± 2.1	49.5 ± 1.6	43.6 ± 1.8	38.7 ± 2.0	35.1 ± 1.7	30.3 ± 1.0
E	57.9 ± 2.5	50.9 ± 2.8	44.6 ± 2.3	36.2 ± 3.4	35.7 ± 2.1	32.3 ± 1.6
D	55.3 ± 3.2	47.7 ± 3.2	41.7 ± 1.8	36.7 ± 1.5	33.1 ± 1.6	30.3 ± 1.7
C	50.5 ± 2.5	43.5 ± 2.0	39.2 ± 1.5	34.4 ± 1.1	30.5 ± 1.3	27.5 ± 1.1
B	51.0 ± 2.8	42.6 ± 2.4	36.9 ± 1.4	31.7 ± 1.3	30.1 ± 2.2	25.7 ± 1.3
A	47.6 ± 2.6	41.0 ± 2.3	36.1 ± 1.6	31.0 ± 1.7	27.7 ± 1.4	23.0 ± 1.1
0	44.9 ± 3.2	39.6 ± 3.2	35.2 ± 3.5	28.2 ± 2.2	24.5 ± 1.8	21.7 ± 1.8

Table II. *Equations of linear regression, reobases and cronaxias in each esophageal level.*

Level	Equation* a	b	r	p	Reobase	Cronaxia
M	6.83	24.19	0.88	0.05-0.01	24.19	0.2823
L	8.80	24.88	0.89	0.05-0.01	24.88	0.3536
K	8.18	26.08	0.92	0.01-0.001	26.08	0.3136
H	9.29	28.49	0.93	0.01-0.001	28.49	0.3260
G	12.02	32.48	0.95	0.01-0.001	32.48	0.3703
F	12.94	34.05	0.95	0.01-0.001	34.05	0.3800
E	12.91	34.50	0.95	0.01-0.001	34.50	0.3742
D	12.25	38.81	0.96	0.01-0.001	38.81	0.3156
C	10.92	30.45	0.95	0.01-0.001	30.45	0.3586
B	12.10	28.44	0.97	< 0.001	28.44	0.4254
A	11.45	26.92	0.94	0.01-0.001	26.92	0.4253
0	20.72	23.98	0.81	0.05-0.01	23.98	0.8640

* Equation = $mV = a \cdot 1/t + b$.

Reobase and cronaxia. At all esophageal levels, reobase and cronaxia were obtained from the linear regression between sensitive threshold and duration of stimulus, these parameters being representative values of the sensibility threshold along the esophagus (table II).

Discussion

Clinical observations and sensory studies have provided information on visceral sensory capacity (16, 24). This principle could also be applied to the esophagus (3, 5, 9, 10, 14, 17-20, 22, 32).

The present studies demonstrate that there are well-defined areas of the esophageal wall that are sensitive to electrical stimulation and that responses are reproductive. A similar procedure has been described by FRIMODT-MOLLER (11) in a study on bladder sensibility.

Electrical stimuli have been frequently used for study of cutaneous (1, 23, 26) or mucosa (12, 13) sensibility, as well as to determine visceral sensitivity (6, 7, 11, 18, 22). Early studies by MARCOS (18) and BOTELLA *et al.* (6) showed electrostimulation to be an adequate method for study of esophageal sensitivity; subsequent investigations by MOLINA (22) confirmed these findings, concluding that this technique was capable of releasing esophageal sensations similar to pyrosis in patients with peptic esophagitis and included it among esophageal diagnostic procedures. According to this author, electrostimulation causes esophageal sensations by direct stimulation of the esophageal sensitive receptors; when esophageal manometry and electrostimulation were simultaneously recorded no changes in motility were observed.

Voltage threshold analysis along the esophagus showed the existence of a sensitive profile, with a zone in the mild third having low sensitivity. It should be noted that histologic studies on several species (28-31) have demonstrated that there is an area in the mid esophagus having fewer sensitive receptors. If these histologic findings are confirmed in the human esophagus, it would explain the

lesser sensitivity detected by electrostimulation in the medial esophagus.

As the present data correspond to the law of WEISS (33) at all esophageal levels and the coefficients of linear regression are statistically significant (table II), it can be stated that esophagus sensitivity follows the above law, suggesting that the threshold voltage decreases when duration of the stimulus increases.

Our findings are comparable to those of LIPKIN and SLEISSENGER (17), who produced esophageal pain by distension of an intraesophageal balloon and observed a direct relationship between stimuli intensity (pressure) and duration (seconds) which is similar to our data (hyperbolic curve). The similarity between observations from using different stimuli, indicates that visceral sensitivity, at least in the esophagus, follows the law of universal excitation of WEISS, having characteristics similar to those of cutaneous sensitivity.

Resumen

Se describe un nuevo método cuantitativo para estudiar la sensibilidad esofágica. Se han utilizado estímulos eléctricos («ondas rectangulares»), de duración creciente (0,5, 1, 2, 4, 8 y 16 ms) y en cada uno de ellos se incrementa el voltaje, comenzando por 0 mV, hasta que el sujeto perciba la primera sensación. Los datos, duración del estímulo y voltaje mínimo necesario para percibir la primera sensación, detectados en cada tramo esofágico son trasladados a una plantilla de recogida de datos. Las experiencias se han realizado en 14 sujetos sanos, estudiantes de Medicina y personal sanitario, que se prestaron voluntariamente a ello. Se han analizado los siguientes parámetros: umbral de sensibilidad a lo largo del esófago; relaciones entre umbral de sensibilidad (mv) y duración del estímulo (ms); y reobase y cronaxia en cada tramo esofágico. El umbral de sensibilidad en cada tramo esofágico es regular y coherente; en la zona media esofágica se detecta una elevación del umbral de sensibilidad con respecto a las zonas proximal y distal esofágicas. La relación entre umbral sensitivo esofágico y el inverso de la duración del estímulo eléctrico indica que la sensibilidad esofágica sigue, al menos para este tipo de estímulo, la ley de excitación de Weiss. La reobase y la cronaxia son representativas del umbral sensitivo esofágico a lo largo del esófago. Se concluye que la estimulación eléctrica esofágica, según el método propuesto, es una técnica especialmente indicada para el estudio cuantitativo de la sensibilidad esofágica.

References

1. Adrian, E. D.: *J. Physiol.*, **53**, 70-85, 1919.
2. Andrew, B. L.: *J. Physiol. (London)*, **134**, 729-740, 1956.
3. Andrew, B. L.: *J. Physiol. (London)*, **135**, 54-55, 1957.
4. Benages, A., Paris, F., Ridocci, M. T., Tarazona, V., Molina, R., Mora, F., Canto, A., Lloret, M. and Garrido, G.: *Ann. Thorac. Surg.*, **26**, 574-580, 1978.
5. Bernstein, L. M. and Baker, L. A.: *Gastroenterology*, **34**, 760-781, 1958.
6. Botella Solana, S., López Merino, V., Insa Pérez, L., Llopis Llombart, R., Merino Sesma, J., Ferrero Cabedo, J. A., Morell Cabedo, S.: *Rev. esp. Cardiol.*, **32**, 11-19, 1979.
7. Boyden, E. A. and Riggler, L. G.: *J. Clin. Invest.*, **13**, 833-851, 1934.
8. Cecio, A. and Califano, G.: *Z. Zellforsch.*, **83**, 30-39, 1967.
9. Clerc, N. and Mei, N.: *J. Physiol.*, **336**, 487-498, 1983.
10. El Ouazzani, T. and Mei, N.: *Gastroenterology*, **83**, 995-1001, 1982.
11. Frimodt-Moller, C.: *Scand. J. Urol. Nephrol.*, **6**, **suppl. 15**, 135-142, 1972.
12. Goetzl, F. R., Burrill, D. J., Ivy, A. C.: *Quart. Bull. Northw. Univ. Med. Sch.*, **17**, 280-291, 1943.
13. Harris, S. C. and Blockus, L. E.: *J. Pharmacol.*, **104**, 135-148, 1952.
14. Iggo, A.: *Acta Neuroveget. (Wien)*, **28**, 121-134, 1976.
15. Jabonero, V.: *Acta Neuroveget. (Wien)*, **17**, 308-355, 1958.
16. Leek, B. F.: In «Handbook of sensory physiology enteroreceptors» (Neil, E., ed.), Springer-Verlag. Berlin, 1972, vol. III/1, pp. 114-160.

17. Lipkin, M. and Sleisenger, M. H.: *J. Clin. Invest.*, **38**, 28-34, 1957.
18. Marcos Buscheck, C.: Tesina de Licenciatura. Facultad de Medicina. Valencia, 1977.
19. Mei, N.: *Exp. Brain Res.*, **11**, 502-514, 1970.
20. Mellow, M. H.: *Gastroenterology*, **73**, 237-240, 1977.
21. Mellow, M. H.: *Gastroenterology*, **83**, 364-370, 1982.
22. Molina, R.: Tesis Doctoral. Facultad de Medicina. Valencia, 1981.
23. Notermans, S. L. H.: *Neurology*, **16**, 1071-1086, 1966.
24. Paintal, A. S.: *Physiol. Rev.*, **53**, 159-227, 1973.
25. Payne, W. W. and Poulton, E. P.: *Quart. J. Med.*, **17**, 53-72, 1928.
26. Pfeiffer, F. A.: *Med. Biol. Eng.*, **6**, 637-651, 1968.
27. Price, S. F., Smithson, K. W. and Castell, D. O.: In «Gastrointestinal Motility in Health and Disease» (Duthie, H. L., ed.), Press Ltd., Lancaster, 1978, pp. 441-445.
28. Rodrigo, J., Hernández, C. J., Pedrosa, M. A., Vidal, M. A. and Pérez-Antón, J. A.: *Trab. Inst. Capal Invest. Biol.*, **65**, 177-198, 1973.
29. Rodrigo, J., Nauta, B. E., Pedrosa, M. A. and Hernández, C. J.: *Bull. Ass. Anat.*, **58**, 696, 1974.
30. Rodrigo, J., Hernández, C. J., Vidal, M. A. and Pedrosa, M. A.: *Acta Anatomica (Basel)*, **92**, 79-100, 1975.
31. Rodrigo, J., Hernández, C. J., Vidal, M. A. and Pedrosa, M. A.: *Acta Anatomica (Basel)*, **92**, 242-258, 1975.
32. Siegel, C. I. and Hendrix, T. R.: *J. Clin. Invest.*, **42**, 686-695, 1963.
33. Weiss, G.: *Soc. Biol.*, **53**, 253-254, 1901.