NIFEDIPINE AND ESOPHAGEAL DYSFUNCTION IN PROGRESSIVE SYSTEMIC SCLEROSIS

A Controlled Manometric Study

ANDRÉ KAHAN, BRUNO BOUR, DANIEL COUTURIER, BERNARD AMOR, and CHARLES J. MENKES

We evaluated the effect of the calcium channel blocking agent, nifedipine, on esophageal dysfunction in 15 patients with progressive systemic sclerosis, using a double-blind, randomized, crossover, placebo-controlled manometric study. Nifedipine significantly decreased lower esophageal sphincter pressure in these patients; this reduced lower esophageal sphincter pressure may cause gastroesophageal reflux. Thus, nifedipine may have detrimental effects on progressive systemic sclerosis patients.

The pathogenesis of esophageal dysfunction in progressive systemic sclerosis (scleroderma; PSS) has not been well elucidated (1,2). PSS is characterized by vascular and microvascular abnormalities (1–4), excessive fibroblastic activity (5,6), and collagen deposition in numerous organs (1,2,7). The possibility that the lesions in target organs are a reflection of a primary fibrous tissue overgrowth leading to secondary vascular compromise has not been ruled out. Nevertheless, a growing body of evidence based on studies of several organs involved in PSS suggests that the vascular system per se may be the primary target organ and that the lesions are a manifestation of focal ischemic injury resulting from functional, with or without accompanying structural, vascular disease (1–4,8–14).

Nifedipine, a calcium channel blocking agent, is effective in the treatment of coronary vasospasm (15–18). We (19–21) and others (22–25) have shown that nifedipine is effective in the treatment of idiopathic Raynaud's phenomenon and Raynaud's phenomenon occurring with progressive systemic sclerosis. Thus, if a microvascular abnormality is a contributor to the pathogenesis of scleroderma, nifedipine may be useful in the treatment of patients with early disease.

However, nifedipine may have detrimental effects caused by its direct action on the lower esophageal sphincter. The actions of nifedipine on smooth muscle cells are well documented (15–18). Several studies have shown that the drug decreases the lower esophageal sphincter pressure (LESP) in patients with achalasia (26,27). If nifedipine also decreases the LESP in patients with progressive systemic sclerosis, this could lead to gastroesophageal reflux.

In the present investigation, we used a controlled, double-blind, randomized, crossover manometric study to evaluate the effect of nifedipine on 15 patients with progressive systemic sclerosis and esophageal dysfunction. Our trial demonstrates that nifedipine significantly decreases the lower esophageal sphincter pressure in patients with PSS.

PATIENTS AND METHODS

Patients. Fifteen patients with progressive systemic sclerosis and diffuse scleroderma were studied. All patients satisfied the American Rheumatism Association preliminary criteria for classification of definite systemic sclerosis (28). None of the patients had the CREST syndrome variant (calcinosis, Raynaud's phenomenon, esophageal dysmo-

Presented in part at the 48th Annual Meeting of the American Rheumatism Association, Minneapolis, MN, June 1984.

From the Departments of Rheumatology and Gastroenterology, René Descartes University, School of Medicine, Hôpital Cochin, Paris, France.

André Kahan, MD: Department of Rheumatology; Bruno Bour, MD: Department of Gastroenterology; Daniel Couturier, MD: Department of Gastroenterology; Bernard Amor, MD: Department of Rheumatology; Charles J. Menkes, MD: Department of Rheumatology.

Address reprint requests to André Kahan, MD, Department of Rheumatology, Hôpital Cochin, 27 Rue du Fg Saint-Jacques, 75674 Paris Cedex 14, France.

Submitted for publication June 11, 1984; accepted in revised form December 20, 1984.

tility, sclerodactyly, telangiectasias) of PSS (29). The presence of the esophageal symptoms of heartburn and dysphagia was determined by direct questioning. All patients had abnormal results on basal esophageal manometric studies. Informed consent was obtained from all participants.

Thirteen of the 15 patients were women. The mean age (±SD) was 47.4 ± 12.1 years (range 18–67). The duration of disease ranged from 2–24 years (mean ± SD, 11.5 ± 7.6 years). All 15 patients had Raynaud's phenomenon, and 8 had a history of digital ulcers. All patients had normal serum creatinine concentrations (76 ± 13 μmoles/liter, mean ± SD). Three patients had associated Sjögren's syndrome. Four patients had pulmonary involvement (abnormal forced vital capacity, lung diffusion capacity, or chest roentgenogram results); none of the patients had evidence (auscultation, electrocardiographic, roentgenographic, or echocardiographic) of significant pulmonary hypertension (1,2). Six of the 15 PSS patients reported a history of dysphagia with solid foods, 5 of them also had heartburn, i.e., a retrosternal burning pain radiating into the neck, with sour and bitter regurgitation.

Evaluation of esophageal dysfunction. The methods we used have been described in detail previously (30–32). In summary, patients were evaluated in the fasting state and in a supine position, using a triple-lumen assembly (inside diameter of each lumen, 1.1 mm) with radially oriented side ports (diameter, 1 mm) spaced 5 cm apart. Radial side-hole recording orifices were used to minimize the effects of LESP asymmetry as a source of recording error between pull-throughs. The polyvinyl catheters were perfused with distilled water (22°C) at 0.6 ml/minute, using a low-compliance pneumohydraulic capillary system (32). Occlusion of any orifice caused a rise in the recording pressure to >800 cm H_2O/second. Polyvinyl catheters were connected in series with Statham transducers (model P 23ID) and pressure tracings were recorded on a Beckman polygraph (model R 511A). The manometric system was calibrated in cm H_2O, with end-expiratory gastric pressure set at 0 as a reference point.

For manometry, the catheter assembly was passed via the mouth. The LESP was recorded by the conventional station pull-through technique and by a rapid pull-through technique (31). The station pull-through technique consisted of withdrawal of the radial recording tips through the LES in 0.5-cm increments, with a pause of 20 seconds or longer at each station; we assessed resting LESP by measuring peak LESP at the pressure inversion point. The rapid pull-through technique featured continuous manual withdrawal of the recording sensors through the LES at an approximate rate of 0.5–1.0 cm/second during a 10–15-second interval of suspended respiration. In our study and in those of others (30,31), LESP values measured by the rapid pull-through technique were similar to those determined by the station pull-through technique.

We averaged the pressure values obtained from the 3 radial recording sites to obtain a representative LESP value. At least 3 pull-throughs were performed. Using this method, reproducible LESP were obtained in normal subjects. LESP between 10–30 cm H_2O were considered normal. We also assessed LES relaxation following deglutition (several dry swallows were obtained in each patient).

To record esophageal peristalsis, the recording sensors were stationed in the distal esophagus, 1, 6, and 11 cm, respectively, above the LES. Waves were recorded from each lumen in response to 3 dry swallows (spaced 30 seconds apart). Waves were analyzed for amplitude and duration by averaging, respectively, the height from the mean esophageal baseline to the peak and the width from the extrapolated onset of the rapid upstroke to the return to baseline. In the distal esophagus, peristaltic waves of 40–80 cm H_2O lasting 2–4 seconds were considered normal. Speed of contraction propagation was calculated in cm/second by dividing the 5-cm distance between 2 pressure orifices by the time required for the pressure front of the contractile wave to travel this distance.

Finally, the amplitude and duration of waves were recorded in the upper esophagus (5 cm below the upper esophageal sphincter).

The tracing was read by 2 of the authors, who were unaware of the patient's symptoms.

Protocol. Our protocol for manometry required that the patient take no medication (including alcohol, coffee, or cigarettes) for 48 hours before the study. After a baseline manometric recording, each patient received a single oral dose of 20 mg nifedipine or placebo; the manometric study was done 90 minutes after each drug or placebo administration. Nifedipine and placebo were assigned on a random, double-blind basis and were administered at the same time at 3-day intervals.

Statistical methods. The Student's *t*-test for paired data was used to evaluate the significance of the differences between the values at baseline and those obtained after placebo or nifedipine administration. P values <0.05 were considered significant.

RESULTS

Esophageal manometric findings. Results of the manometric studies are shown in Table 1. Baseline esophageal dysfunction was demonstrated by decreased or absent distal peristalsis in all 15 PSS patients. Eight patients had distal aperistalsis; 7 patients had a decrease in esophageal contraction amplitude, 5 of whom also had an increase in the duration of waves. Ten patients had normal baseline LESP (group I), and 5 had low basal LESP (group II). Four of the 10 patients with normal baseline LESP and 4 of the 5 patients with low baseline LESP had distal aperistalsis. Two patients with low baseline LESP and distal aperistalsis had heartburn and a history of dysphagia. Two patients with normal baseline LESP and distal aperistalsis had dysphagia, 1 of whom also had heartburn. Two patients with normal baseline LESP and low-amplitude distal esophageal contractions had heartburn and dysphagia.

Twelve patients had normal baseline upper esophageal peristalsis; 3 patients had a decrease in amplitude of peristaltic contractions in the upper esophagus (5 cm below the upper esophageal sphincter).

Table 1. Manometric characteristics of 15 patients with progressive systemic sclerosis and diffuse scleroderma, at baseline and after placebo and nifedipine administration*

	n	Baseline	Placebo	Nifedipine
LESP				
All patients	15	13.9 ± 7.7	13.8 ± 8.3	10.2 ± 5.7†
Group I	10	18.0 ± 5.8	18.2 ± 6.3	12.9 ± 5.1‡
Group II	5	5.6 ± 2.0	5.0 ± 2.2	4.9 ± 2.2
Waves				
Amplitude, 1 cm above LES	15	7.7 ± 8.7	7.5 ± 8.4	7.0 ± 7.9
Amplitude, 6 cm above LES	15	7.7 ± 8.8	7.6 ± 8.7	6.6 ± 7.6
Amplitude, 11 cm above LES	15	8.1 ± 9.1	8.1 ± 9.0	8.5 ± 9.7
Duration, 1 cm above LES	7	5.1 ± 1.8	4.5 ± 1.2	5.4 ± 1.0
Duration, 6 cm above LES	7	4.8 ± 1.1	4.6 ± 1.1	4.8 ± 0.9
Duration, 11 cm above LES	7	4.4 ± 1.4	4.5 ± 1.4	4.2 ± 1.0
Amplitude, 5 cm below UES	15	48.1 ± 26.1	47.1 ± 25.8	49.4 ± 25.9
Duration, 5 cm below UES	14	2.5 ± 0.7	2.5 ± 0.6	2.6 ± 0.8

* Amplitude in cm H_2O; duration in seconds. Eight patients had distal esophageal aperistalsis; the amplitude of distal esophageal contractions in these 8 patients was considered to be 0, and was taken into account in calculating the mean amplitude of distal esophageal waves in all 15 patients. The mean duration of distal esophageal contractions was calculated using the values obtained in the other 7 patients. One patient had upper esophageal aperistalsis; the amplitude of upper esophageal contractions in this patient was considered to be 0, and was taken into account in calculating the mean amplitude of upper esophageal waves (5 cm below the upper esophageal sphincter [UES]) in all 15 patients. The mean duration of upper esophageal waves was calculated using the values obtained in the other 14 patients. Group I = 10 patients with normal baseline lower esophageal sphincter pressure (LESP), in cm H_2O; Group II = 5 patients with low baseline LESP. Values are mean ± SD.
† $P < 0.005$ versus placebo; $P < 0.0025$ versus baseline.
‡ $P < 0.0025$ versus placebo; $P < 0.0025$ versus baseline.

The mean (±SD) baseline LESP of the total group was 13.9 ± 7.7 cm H_2O; it was 13.8 ± 8.3 cm H_2O in the placebo-treated patients and 10.2 ± 5.7 cm H_2O in the nifedipine-treated patients (Figure 1 and Table 1). Nifedipine treatment significantly decreased LESP when compared with values at baseline ($P < 0.0025$) and after placebo treatment ($P < 0.005$). The mean LESP values at baseline and after placebo treatment did not differ significantly.

Nifedipine induced a 25–50% decrease in LESP in 6 of the 10 patients with normal baseline LESP (group I) and in 1 of the 5 patients with low baseline LESP (group II). In group I, nifedipine significantly decreased LESP (12.9 ± 5.1 cm H_2O, mean ± SD) when compared with placebo (18.2 ± 6.3 cm H_2O; $P < 0.0025$) and with baseline values (18.0 ± 5.8 cm H_2O; $P < 0.0025$) (Table 1).

Other manometric characteristics were not significantly changed in the treated patients (Table 1). Nifedipine did not significantly modify the amplitude, duration, or speed of waves in the distal esophagus, or the LES relaxation. The amplitude and duration of waves in the upper esophagus (5 cm below the upper esophageal sphincter) were similar at baseline and after placebo and nifedipine administration.

DISCUSSION

Esophageal involvement occurs in up to 90% of patients with progressive systemic sclerosis (1,2,7,33–44). Esophageal manometric studies often demonstrate abnormalities in the portion of the esophagus containing smooth muscle (the distal one-half to two-thirds), with diminished amplitude or absence of peristaltic waves. A decrease or absence of pressure in the lower esophageal sphincter is frequently noted (1,2,35–39,41–44). These abnormalities may lead to dysphagia, heartburn, and reflux esophagitis. Patients may have dysphagia secondary to either an esophageal stricture or to disturbed esophageal peristalsis. The incomplete functioning of the lower esophageal sphincter allows gastroesophageal reflux; weakened peristaltic contractions in the lower esophagus fail to clear this refluxed gastric acid, and acid remains in contact with the esophageal mucosa for a longer period of time, causing esophagitis (1,2,42–44).

Several reports have emphasized the possible vascular and microvascular pathogenesis of progressive systemic sclerosis (1–4). On histopathologic examination, the digital arteries of patients with scleroderma reveal striking intimal hyperplasia, leading in the majority of cases to severe attenuation of the arterial lumen (45). Similar histopathologic changes are evident in the small arteries of the gastrointestinal tract, lungs, and kidneys (4,7). Transient nonperfusion or Raynaud's phenomenon of the digits (1,2), kidneys (10,11), lungs (12,13), and heart (8,9) probably accounts for many of the morphologic changes observed in these organs (1,2).

Recent findings of an ultrastructural study of

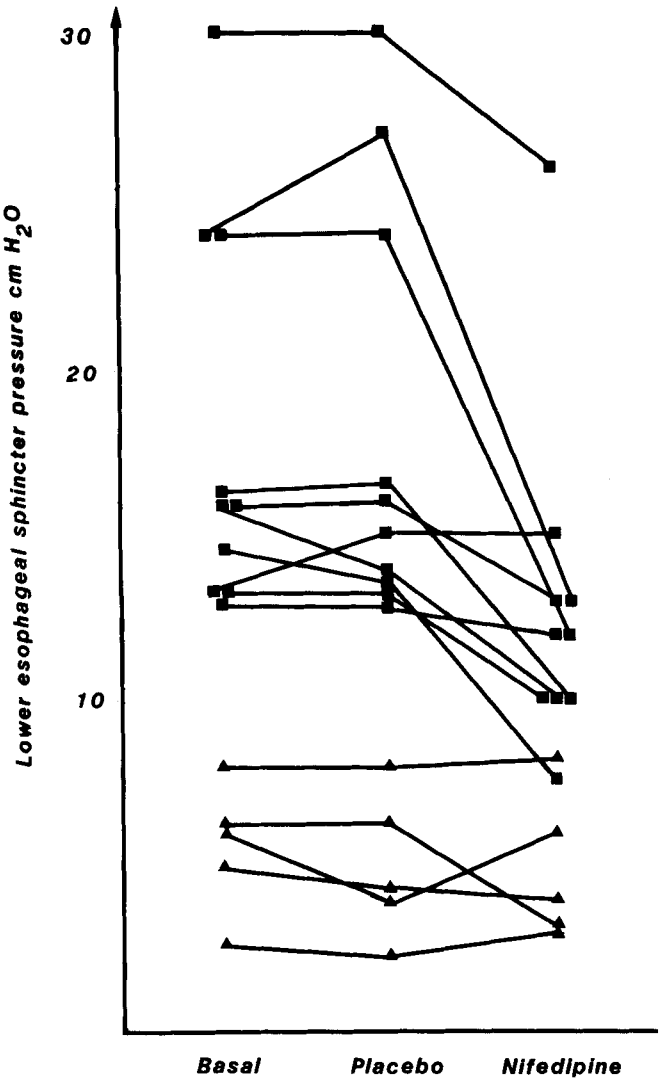

Figure 1. Effect of nifedipine on lower esophageal sphincter pressure (LESP) in 15 patients with progressive systemic sclerosis and diffuse scleroderma. Lower esophageal sphincter pressure in each individual patient is shown for the baseline state and after placebo and nifedipine administration. ■ = group I: 10 patients with normal baseline LESP; ▲ = group II: 5 patients with low baseline LESP.

the esophagus (46) also supported a primary vascular cause, rather than a neurogenic (47) or myopathic process, of esophageal dysfunction in progressive systemic sclerosis. Thus, a functional, with or without accompanying structural, vascular disease may be an important contributor to the pathogenesis of PSS. The calcium channel blocking agent, nifedipine, which causes vasodilation (15–25), may be effective in early stages of the disease in preventing some vasospastic events that could lead to the long-term damage often found in scleroderma; thus, we would recommend the use of nifedipine in the treatment of early PSS.

However, our manometric findings should be taken into account when nifedipine is being considered as a treatment for patients with scleroderma. The major observation in this study was that nifedipine significantly decreased the lower esophageal sphincter pressure in these patients. It should be emphasized that nifedipine-induced reduction in LESP was striking in patients with normal baseline LESP. This effect is probably due to the block of calcium transmembrane influx, which determines the LES tone, both under baseline conditions and after administration of some agonists (48,49).

Thus, nifedipine, which decreases the LESP, may have a detrimental effect on patients with progressive systemic sclerosis. An incompletely functioning lower esophageal sphincter fails to provide a barrier to reflux of gastric acid into the esophagus, which may cause esophagitis. Moreover, gastroesophageal reflux may be responsible for chronic aspiration; thus, nifedipine may also enhance chronic aspiration and pulmonary disease in PSS patients (50).

The effectiveness of cimetidine in the treatment of gastroesophageal reflux has been demonstrated in progressive systemic sclerosis patients (51). Thus, the use of an H-2 receptor antagonist may prevent some of the deleterious effects of nifedipine: in early scleroderma, when nifedipine can be an effective treatment for vascular features of the disease, an H-2 receptor antagonist may be used to minimize esophageal damage and the potential gastroesophageal reflux that may accompany ongoing pulmonary aspiration, pulmonary hypertension, and/or pulmonary fibrosis.

Recent studies (52) have shown that various mechanisms, such as transient complete LES relaxation, transient increase in intraabdominal pressure, or spontaneous free reflux associated with a low resting LESP, may cause gastroesophageal reflux in patients with symptomatic reflux esophagitis (without progressive systemic sclerosis). Further studies with continuous monitoring of LESP and esophageal pH (52) are needed to determine whether nifedipine can modify transient LES relaxation unrelated to swallowing in patients with early PSS.

In summary, when nifedipine is used in treating scleroderma patients, the physician should consider both the generalized potential effects on the disease and the local effects on the esophagus. On the one hand, since a vascular abnormality may be a contributor to the pathogenesis of progressive systemic sclerosis, nifedipine, which causes relief of artery spasm,

may be beneficial in the treatment of early scleroderma. However, our controlled manometric study does document that nifedipine has a deleterious effect on lower esophageal sphincter pressure, which could contribute to gastroesophageal reflux leading to esophagitis and chronic aspiration and pulmonary disease. Thus, it appears that the use of nifedipine for generalized scleroderma may be helpful if protective mechanisms, i.e., H-2 receptor antagonists, liquid antacids, and the use of postural esophageal drainage, are added. A long-term controlled study of nifedipine in patients with early PSS and esophageal dysfunction is warranted.

ACKNOWLEDGMENTS

We thank Drs. F. Delrieu and L. Saporta for encouraging their patients to participate in these studies and for helpful discussions and Magali Vallet-Amor for expert secretarial assistance.

REFERENCES

1. LeRoy EC: Scleroderma (systemic sclerosis), Textbook of Rheumatology. Edited by WN Kelley, ED Harris Jr, S Ruddy, CB Sledge. Philadelphia, WB Saunders, 1981, pp 1211–1230
2. Rodnan GP: Progressive systemic sclerosis (scleroderma), Arthritis and Allied Conditions. Ninth edition. Edited by DJ McCarty. Philadelphia, Lea & Febiger, 1979, pp 762–809
3. Campbell PM, LeRoy EC: Pathogenesis of systemic sclerosis: a vascular hypothesis. Semin Arthritis Rheum 4:351–368, 1975
4. Norton WL, Nardo JM: Vascular disease in progressive systemic sclerosis (scleroderma). Ann Intern Med 73:317–324, 1970
5. LeRoy EC: Connective tissue synthesis by scleroderma skin fibroblasts in cell culture. J Exp Med 135:1351–1362, 1972
6. Buckingham RB, Prince RK, Rodnan GP, Taylor F: Increased collagen accumulation in dermal fibroblast cultures from patients with progressive systemic sclerosis (scleroderma). J Lab Clin Med 92:5–21, 1978
7. D'Angelo WA, Fries JF, Masi AT, Shulman LE: Pathologic observations in systemic sclerosis (scleroderma): a study of fifty-eight autopsy cases and fifty-eight matched controls. Am J Med 46:428–440, 1969
8. Bulkley BH, Ridolfi RL, Salyer WR, Hutchins GM: Myocardial lesions of progressive systemic sclerosis: a cause of cardiac dysfunction. Circulation 53:483–490, 1976
9. Alexander EL, Firestein GS, Leitl G, Wagner HN, Hochberg MC, Heuser RR, Stevens MB, Weiss J, Becker L: Scleroderma heart disease: evidence for cold-induced abnormalities of myocardial function and perfusion (abstract). Arthritis Rheum (suppl) 24:S58, 1981
10. Kovalchik MT, Guggenheim SJ, Silverman MH, Robertson JS, Steigerwald JC: The kidney in progressive systemic sclerosis: a prospective study. Ann Intern Med 89:881–887, 1978
11. Cannon PJ, Hassar M, Case DB, Casarella WJ, Sommers SC, LeRoy EC: The relationship of hypertension and renal failure in scleroderma (progressive systemic sclerosis) to structural and functional abnormalities of the renal cortical circulation. Medicine (Baltimore) 53:1–46, 1974
12. Furst DE, Davis JA, Clements PJ, Chopra SK, Theofilopoulos AN, Chia D: Abnormalities of pulmonary vascular dynamics and inflammation in early progressive systemic sclerosis. Arthritis Rheum 24:1403–1408, 1981
13. Wise RA, Wigley F, Newball HH, Stevens MB: The effect of cold exposure on diffusing capacity in patients with Raynaud's phenomenon. Chest 81:695–698, 1982
14. Kahaleh MB, Sherer GK, LeRoy EC: Endothelial injury in scleroderma. J Exp Med 149:1326–1335, 1979
15. Antman EM, Stone PH, Muller JE, Braunwald E: Calcium channel blocking agents in the treatment of cardiovascular disorders. I. Basic and clinical electrophysiologic effects. Ann Intern Med 93:875–885, 1980
16. Stone PH, Antman EM, Muller JE, Braunwald E: Calcium channel blocking agents in the treatment of cardiovascular disorders. II. Hemodynamic effects and clinical applications. Ann Intern Med 93:886–904, 1980
17. Henry PD: Comparative pharmacology of calcium antagonists: nifedipine, verapamil and diltiazem. Am J Cardiol 46:1047–1058, 1980
18. Braunwald E: Mechanism of action of calcium-channel-blocking agents. N Engl J Med 307:1618–1627, 1982
19. Kahan A, Weber S, Amor B, Saporta L, Hodara M, Degeorges M: Etude contrôlée de la nifédipine dans le traitement du phénomène de Raynaud. Rev Rhum Mal Osteoartic 49:337–343, 1982
20. Kahan A, Weber S, Amor B, Menkes CJ, Saporta L, Hodara M, Degeorges M: Nifedipine for Raynaud's phenomenon (letter). Lancet 1:131, 1983
21. Kahan A, Amor B, Menkes CJ: Nifedipine treatment for Raynaud's phenomenon (letter). Arthritis Rheum 27:959–960, 1984
22. Smith CD, McKendry RJR: Controlled trial of nifedipine in the treatment of Raynaud's phenomenon. Lancet 2:1299–1301, 1982
23. Rodeheffer RJ, Rommer JA, Wigley F, Smith CR: Controlled double-blind trial of nifedipine in the treatment of Raynaud's phenomenon. N Engl J Med 308:880–883, 1983
24. Winston EL, Pariser KM, Miller KB, Salem DN, Creager MA: Nifedipine as a therapeutic modality for

Raynaud's phenomenon. Arthritis Rheum 26:1177–1180, 1983
25. Sauza J, Kraus A, González-Amaro R, Alarcón-Segovia D: Effect of the calcium channel blocker nifedipine on Raynaud's phenomenon: a controlled double blind trial. J Rheumatol 11:362–364, 1984
26. Bortolotti M, Labo G: Clinical and manometric effects of nifedipine in patients with esophageal achalasia. Gastroenterology 80:39–44, 1981
27. Gelfond M, Rozen P, Gilat T: Isosorbide dinitrate and nifedipine treatment of achalasia: clinical, manometric and radionuclide evaluation. Gastroenterology 83:963–969, 1982
28. Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee: Preliminary criteria for the classification of systemic sclerosis (scleroderma). Arthritis Rheum 23:581–590, 1980
29. Rodnan GP, Jablonska S, Medsger TA Jr: Classification and nomenclature of progressive systemic sclerosis (scleroderma). Clin Rheum Dis 5:5–13, 1979
30. Dodds WJ: Instrumentation and methods for intraluminal esophageal manometry. Arch Intern Med 136:515–523, 1976
31. Dodds WJ, Hogan WJ, Stef JJ, Miller WN, Lydon SB, Arndorfer RC: A rapid pull-through technique for measuring lower esophageal sphincter pressure. Gastroenterology 68:437–443, 1975
32. Arndorfer RC, Stef JJ, Dodds WJ, Linehan JH, Hogan WJ: Improved infusion system for intraluminal esophageal manometry. Gastroenterology 73:23–27, 1977
33. Stevens MB, Hookman P, Siegel C, Esterly JR, Schulman LE, Hendrix TR: Aperistalsis of the esophagus in patients with connective tissue disorders and Raynaud's phenomenon. N Engl J Med 270:1218–1222, 1964
34. Poirier TJ, Rankin GB: Gastrointestinal manifestations of progressive systemic scleroderma based on a review of 364 cases. Am J Gastroenterol 58:30–44, 1972
35. Treacy WL, Baggenstoss AH, Slocumb CH, Code CF: Scleroderma of the esophagus: a correlation of histologic and physiologic findings. Ann Intern Med 59:351–356, 1963
36. Atkinson M, Summerling MD: Oesophageal changes in systemic sclerosis. Gut 7:402–408, 1966
37. Saladin TA, French AB, Zarafonetis CJD, Pollard HJ: Esophageal motor abnormalities in scleroderma and related diseases. Dig Dis Sci 11:522–535, 1966
38. Garrett JM, Winkelmann RK, Schlegel JF, Code CF: Esophageal deterioration in scleroderma. Mayo Clin Proc 46:92–96, 1971
39. Turner R, Lipshutz W, Miller W, Rittenberg G, Schumacher HR, Cohen S: Esophageal dysfunction in collagen disease. Am J Med Sci 265:191–199, 1973
40. Orringer MB, Dabich L, Zarafonetis CJD, Sloan H: Gastroesophageal reflux in esophageal scleroderma: diagnosis and implications. Ann Thorac Surg 295:120–130, 1976
41. Clements PJ, Kadell B, Ippoliti A, Ross M: Esophageal motility in progressive systemic sclerosis (PSS): comparison of cineradiographic and manometric evaluation. Dig Dis Sci 24:639–644, 1979
42. Atkinson M: Oesophageal motor changes in systemic disease. Clin Gastroenterol 5:119–133, 1976
43. Mukhopadhyay AK, Graham DY: Esophageal motor dysfunction in systemic diseases. Arch Intern Med 136:583–588, 1976
44. Myers AR: Progressive systemic sclerosis: gastrointestinal involvement. Clin Rheum Dis 5:115–129, 1979
45. Rodnan GP, Myerowitz RL, Justh GO: Morphologic changes in the digital arteries of patients with progressive systemic sclerosis (scleroderma) and Raynaud's phenomenon. Medicine (Baltimore) 59:393–408, 1980
46. Russell ML, Friesen D, Henderson RD, Hanna WM: Ultrastructure of the esophagus in scleroderma. Arthritis Rheum 25:1117–1123, 1982
47. Cohen S, Fisher R, Lipshutz W, Turner R, Myers A, Schumacher R: The pathogenesis of esophageal dysfunction in scleroderma and Raynaud's disease. J Clin Invest 51:2663–2668, 1972
48. Fox JE, Daniel EE: The role of Ca^{++} in the genesis of lower esophageal sphincter tone and contraction (abstract). Gastroenterology 74:1035, 1978
49. Rattan S, Goyal RK: Influence of verapamil on the stimulated lower esophageal sphincter pressure (abstract). Gastroenterology 74:1082, 1978
50. Denis P, Ducrotte P, Pasquis P, Lefrançois R: Esophageal motility and pulmonary function in progressive systemic sclerosis. Respiration 42:21–24, 1981
51. Petrokubi RJ, Jeffries GH: Cimetidine versus antacid in scleroderma with reflux esophagitis: a randomized double-blind controlled study. Gastroenterology 77:691–695, 1979
52. Dodds WJ, Dent J, Hogan WJ, Helm JF, Hauser R, Patel GK, Egide MS: Mechanisms of gastroesophageal reflux in patients with reflux esophagitis. N Engl J Med 307:1547–1552, 1982