

Diffuse Esophageal Spasm

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The purpose of this article is to review the clinical features, pathophysiology, diagnosis, and management of patients with diffuse esophageal spasm (DES). The PubMed database was searched with a focus on recent publications, using keywords "DES," plus "epidemiology," "prevalence," "diagnosis," "pathogenesis," "calcium channel blocker," "nitrates," "botulinum toxin," "antidepressants," "dilation," and "myotomy." The reference lists of papers identified in the initial PubMed search were reviewed for further relevant publications.

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INTRODUCTION

Retrosternal pain and dysphagia are common complaints in patients referred to gastroenterologists, either as a primary referral or via cardiologic consultation. After structural lesions have been excluded by endoscopy or radiography and a trial of acid suppression to exclude contributions from gastroesophageal reflux disease (GERD), the underlying diagnosis is usually presumed to be a "functional" or "motility" disorder, which may or may not be investigated further. If a decision is made to proceed with the investigation, esophageal manometry may reveal esophageal spasm. The question for the physician then becomes the clinical significance of the abnormalities demonstrated, and in particular, the relationship between these findings and the patient's symptoms.

The concept that chest pain may be due to disordered esophageal contractile activity was initially described by Osgood in 1889, who reported six patients with chest pain and dysphagia (1), and in 1892, Osler described "esophagismus" in a group of "hypochondriac" patients with unexplained chest pain (2). The first recorded description of the manometric features of DES was made by Creamer *et al.* in 1958 (3), who found simultaneous pressure waves in the distal third of the esophagus; these occurred repetitively and were of higher pressure and longer duration than the normal peristaltic waves.

Clinically, DES is often suspected in patients with intermittent chest pain and dysphagia. The symptoms of DES, however, are very variable, ranging in severity from mild to severe, lasting from seconds to minutes, occurring in a variety of locations, may be precipitated by solids or liquids, or can occur independently of eating (4). The variety of symptoms that have been attributed to DES and the lack of a "gold" diagnostic standard have resulted in a confusing literature.

Epidemiology of DES

Noncardiac chest pain (NCCP) is common, with a mean annual prevalence of 25% of the U.S. adult population. Many patients with NCCP respond to acid suppression, and are therefore presumably suffering from GERD (5). In the group of patients with non-GERD-related noncardiac chest pain referred to specialized centers, esophageal dysmotility (*e.g.*, DES, achalasia, vigorous achalasia, and nutcracker esophagus) accounts for less than 30% of the cases studied (6–8). Even in these specialized motility laboratories, the prevalence of DES generally ranges between only 0.6 and 2.8% in patients referred for evaluation of chest pain, between 3.3 and 5.3% in patients referred for dysphagia, and 4–4.5% in those referred for combined chest pain and dysphagia (5, 7, 8). Ambulatory manometry does not seem to increase the yield of investigation; as in a 24-h manometry study, the prevalence of DES was 4% of 390 patients referred with symptoms thought to arise from the esophagus (9). The incidence and prevalence of manometric abnormalities consistent with DES in asymptomatic subjects is not known; moreover, there is no agreement on a gold standard for diagnosis. As a result, the sensitivity and specificity of esophageal manometry in detecting DES cannot be determined. Indeed, the reported prevalence appears to depend on the group of patients being studied, with studies based in a single center with a motility interest showing a higher prevalence of all motility disorders as compared to studies involving a variety of centers.

There are no data on the impact of age, gender, or race on the prevalence of DES. A limited number of small studies have shown associations between DES and mitral valve prolapse (MVP) (10), obesity (11, 12), and psychiatric illness (13); but these could, at most, account for only a small proportion of cases.

Esophageal motor disorders, in general, have been associated with the thickening of the esophageal muscle wall (see

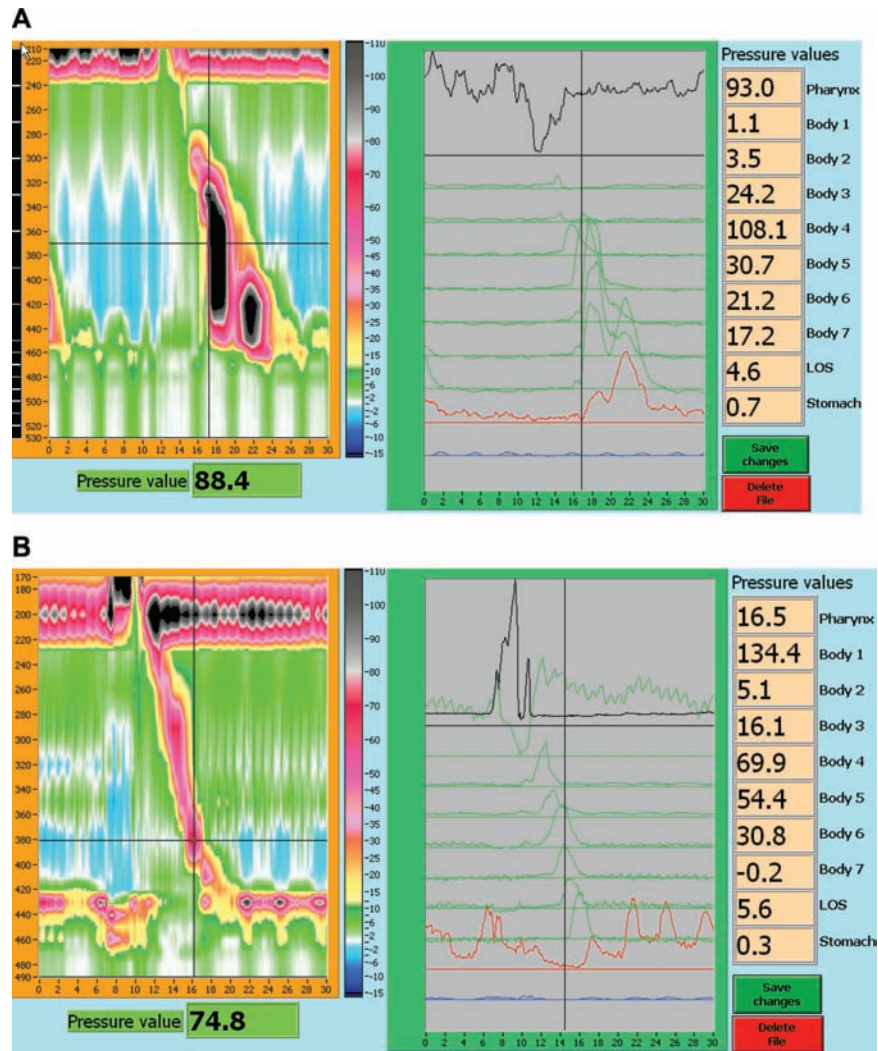


Figure 1. Manometric appearance of a synchronous contraction (A) in spatiotemporal and line plot and normal comparison (B).

below), and also with the presence of “epiphrenic diverticula” in the distal esophagus. The prevalence of wall thickening in DES is uncertain; however, the prevalence of DES in a group of patients admitted for evaluation of epiphrenic diverticula ranged between 7% and 24% (14–18).

UNRESOLVED ISSUES

Despite a sizeable literature, the definition, diagnostic criteria, pathogenesis, and effective management of DES remain significant unresolved issues.

Definition

As a general concept, DES is a disease characterized by simultaneous contractions of the distal esophageal smooth muscle with clinical manifestations of dysphagia and chest pain. The problem has been in translating this concept into a formal operational definition. According to a recent American Gastroenterological Association (AGA) review (19), DES can

be defined on the basis of manometric criteria in patients with a consistent clinical presentation (chest pain and/or dysphagia) (19). A number of manometric definitions of DES have been developed; however, the primary diagnostic feature of esophageal manometry is the presence of simultaneous contractions of the distal esophageal smooth muscle, manifested as “synchronous” pressure waves (>8 cm/sec propagation) (20, 21) with a minimum amplitude of 30 mmHg (21). In most definitions, these are required on $\geq 20\%$ of 10 swallows, and some “normal” peristaltic waves must also be present (20, 22–25). Figure 1 shows a typical example of synchronous contraction. Confusion may arise with other causes of synchronous pressure waves, which are not due to the synchronous contractions, but rather due to the nonocclusive contractions causing isobaric or “common cavity” pressure waves due to increased resistance to flow at the lower esophageal sphincter (LES). Many of these pressure waves are <30 mmHg in amplitude, but others may be of sufficient amplitude to cause diagnostic problems. In addition, although manometric abnormalities may be observed at rou-

tine manometry, patients are often not experiencing their typical symptoms at that time, so it is difficult to postulate that the abnormalities observed are the cause of their symptoms. Other features that may be observed on routine manometry (and are supportive of, but are not required for the diagnosis) include high amplitude, spontaneous, repetitive, or multiphased contractions (20, 21). High amplitude contractions alone (nutcracker esophagus) may cause chest pain, but are peristaltic rather than synchronous in nature. Similarly, dysfunction of the LES (hypertensive or delayed/incomplete relaxation) (4, 20, 26, 27) may be seen, but the relationship of these findings to the symptoms has not been established. Because of the difficulties in making a definitive diagnosis of DES, a number of supportive diagnostic features, including solid swallows (28, 29), 24-h manometry (9, 30, 31), or provocative testing using balloon distension (32) or edrophonium (33–35), have been described, although these have not been well characterized and are used only at a limited number of centers. There is, as yet, no definitive, widely accepted definition of the characteristics of the contraction pattern required for the diagnosis of DES, nor is it known whether the different patterns observed within this group define specific subgroups of patients. Tutuian *et al.* examined the relationship between manometric abnormalities and symptoms in a group of DES patients, finding that patients with predominant chest pain had higher esophageal contraction amplitudes than those with dysphagia-predominant symptoms (36); however, this issue remains largely unexplored.

The new techniques of high-resolution manometry (HRM) and spatiotemporal analysis may aid in the diagnosis of DES. Clouse *et al.* (37) compared the diagnostic accuracy between conventional (5 channel) manometry and HRM (21 channels) in 212 consecutive patients referred for esophageal studies, and found a diagnostic disagreement in 12% of the cases. Conventional manometry missed one case of DES and misdiagnosed DES in four cases, which on HRM proved to be achalasia or aperistalsis. In a case series of HRM findings in patients with endoscopy negative dysphagia, Fox *et al.* (38) reported cases of symptomatic esophageal dysmotility missed or not appreciated on conventional manometry (seven channel with sleeve). These included focal midesophageal spasm, low-pressure segmental spasm, and vigorous achalasia with “LES pseudorelaxation” due to gross shortening of the tubular esophagus.

Contrast radiology is more widely available than manometry and barium swallow may be suggestive of DES (either with the classic appearance of the corkscrew esophagus or with an area of focal spasm/retrograde flow); however, these changes are somewhat observer dependent, do not provide a definitive diagnosis of DES, and the sensitivity and specificity of these findings have not been defined.

Pathogenesis

DES occurs in the smooth muscle of the lower esophagus, and is believed to be due to dysfunction of the intrinsic neural

regulation of contraction. Normal peristalsis almost always remains intact in the upper third of the esophagus, which is composed of striated muscle with somatic innervations.

HISTOPATHOLOGY AND *IN VIVO* IMAGING. Structural changes found in the muscular wall of the esophagus in DES patients are, in contrast to achalasia, inconsistent and non-specific; although, endoscopic ultrasound imaging has shown that, on average, patients with DES have a thicker esophageal muscularis propria and LES than healthy subjects (39, 40). Gross thickening of the muscular wall of the esophagus, found in patients undergoing surgery for this condition, is due to hyperplasia and not due to hypertrophy of the smooth muscle (41). Moreover, a recent study was unable to demonstrate pathologic changes in the myenteric plexus of a small number of patients with DES (42). These findings suggest that muscle wall thickening may not be the primary cause of DES, but rather a response to increased resistance to bolus passage through the esophagus and gastroesophageal junction.

PERISTALTIC FUNCTION. Human and animal studies have shown that nitric oxide (NO) mediates LES and esophageal body relaxation (43, 44), and over the past 15 yr, the hypothesis that altered endogenous NO synthesis and/or degradation is involved in the pathogenesis of DES has gained acceptance. In 1992, Yamato *et al.* (45) showed in an animal model that the administration of L-N-nitro-L-arginine methyl ester (NAME), an NO synthase inhibitor, significantly increased the velocity of peristalsis. Further evidence that the velocity of conduction of the contraction wave along the esophagus may be related to NO was provided by Sifrim *et al.* (46), who showed in 1994 that the degree of inhibition of the esophageal body was inversely correlated with the propagation velocity such that absent inhibition was associated with synchronous contraction.

Experimental inhibition of NO function in humans is also associated with significant disruption of esophageal function. Following infusion of recombinant human hemoglobin (an NO scavenger), healthy subjects showed simultaneous and high-pressure contractions with retrosternal pain during swallowing (44), and the infusion of L-NG-monomethyl-L-arginine (NMMA), an NO synthase blocker, resulted in increased velocity of propagation of contractions; an effect that was reversed by infusion of L-arginine (47). Congruent with this concept, infusion of glyceryl trinitrate, an NO donor, (100–200 $\mu\text{g}/\text{kg}$ IV) prolonged latency in DES patients after swallowing, converted simultaneous into propagated contractions, decreased mean contraction amplitudes significantly, and alleviated symptoms (48). Similarly, administration of sildenafil, a phosphodiesterase type 5 blocker, which inhibits the degradation of NO, significantly reduced pressure amplitudes and conduction velocity in the distal esophagus in healthy volunteers as well as in patients with motility disorders. Together, these studies provide strong evidence that

endogenous NO is involved in the physiological regulation of motility patterns of the distal esophageal body and that loss of inhibitory control results in a pattern of contractions similar to that observed in DES. The mechanism by which the loss of the inhibitory motor function leads to muscle hypertrophy has not been clarified, but it may relate to unopposed stimulation by excitatory neurotransmitters.

The translation of the concept of loss of inhibitory neural function into improved therapy remains problematic and is based on small case series, although preliminary reports suggest that treatment aimed at potentiating the effect of NO may improve esophageal motility and relieve symptoms. Eherer *et al.* reported manometric improvement on sildenafil in 9/11 patients with hypertensive esophageal disorders, including 5/6 patients with hypertensive “nutcracker” esophageal contractions and/or esophageal spasm. Of these, 3/6 patients had a symptomatic response to treatment; however, ongoing treatment was limited by side effects (dizziness, headache) (49). In contrast, Fox *et al.* (50) reported that sildenafil treatment was well tolerated, and provided effective relief of symptoms in two patients with severe, refractory symptoms related to DES. Treatment suppressed esophageal contractions almost completely for water swallows and reduced synchronous contractions for solid bolus, restoring almost normal esophageal motility.

ETIOLOGY OF PAIN IN DES. The reason why patients with DES suffer from chest pain is not understood. Pain is presumably related to the abnormal contractions; however, the mechanism(s) through which simultaneous contractions cause pain is speculative. The amplitude of the contraction may be relevant. Tutuian *et al.* demonstrated that symptoms were reliably associated with esophageal spasm with pressures higher than 300 mmHg. Such powerful contractions may cause pain due to the increase in wall tension or, if prolonged, due to the muscle wall ischemia. Esophageal manometry is most sensitive in detecting circular muscle contractions; however, studies using high-frequency endoscopic ultrasound suggest that contractions in the longitudinal muscle also cause discomfort (51, 52). This may provide a partial explanation for the unsatisfactory relationship between routine manometric findings and symptoms as longitudinal muscle contractions do not increase intraesophageal pressure and are difficult to appreciate on routine manometry, although shortening of the esophagus is seen on HRM. Chest pain, consistent with DES, may respond to acid suppression, suggesting that GERD is involved in the pathogenesis of pain, although whether this is GERD alone or GERD-inducing secondary esophageal spasm has not been adequately evaluated. Hypersensitivity may also contribute to the perception of symptoms in some patients. Handa *et al.* examined the effects of antidepressant treatment in patients with DES. Anxiety and depression scores were higher for the DES patients than the control group of healthy volunteers, and five of the nine DES patients were diagnosed as having major psychiatric disorders (53).

Treatment improved symptoms without altering esophageal motility; however, it is unclear whether this effect was due to reduced visceral sensitivity or improved mental state.

NATURAL HISTORY OF DES. DES is generally not progressive and symptoms are often intermittent; however, there are no adequate longitudinal studies of large groups of patients with DES. A few case reports have suggested a transition from DES to achalasia in some patients (54–58); however, given the substantial difficulties in making a definitive diagnosis of DES, the significance of these observations is unclear. Recently, Khatami *et al.* (54) described a prospective cohort study observing the outcome of 32 patients with DES diagnosed between 1992 and 2003. Twelve patients agreed to participate and underwent second manometry 4.8 ± 3.4 yr later. Achalasia was diagnosed on follow-up manometry in one patient, seven patients continued to have DES, three had normal motility, and one had nutcracker esophagus. There were no predictors of progression to achalasia based on the initial manometry parameters. The manometric features of DES changed very little and the symptoms reduced over long-term follow-up. Spencer *et al.* (59) examined long-term outcome in a group of patients with abnormal esophageal manometry and found that patients with DES had an improvement in their symptoms over time, but only 39% found any treatment helpful; in particular, no patient felt that calcium channel blockers or nitrates were beneficial. These studies suggest that DES often runs a relatively benign course with improvement in symptoms to be expected over time.

TREATMENT

The literature regarding treatment of DES is inconsistent. Issues that complicate the investigation of this condition include low prevalence, lack of clear and well-accepted diagnostic criteria leading to heterogeneity in patient groups, and incomplete understanding of the pathophysiology. This has led to small, uncontrolled therapeutic trials with varying end points.

Providing a “diagnosis” to explain the patient’s symptoms, along with the reassurance that this is a non-life-threatening yet chronic condition that will probably remain stable or improve with time, is an important initial step in therapy. Dietary modification may be helpful in patients suffering from dysphagia, as liquids or soft foods often pass better than solids (Fig. 2).

Pharmacological

Various medications have been used to attempt to mitigate the symptoms of DES, none of which have been proven to be consistently successful.

ACID SUPPRESSION. It has been suggested that some cases of DES are due to GERD (60). Whether this is the case or not, some patients do respond to a trial of acid sup-

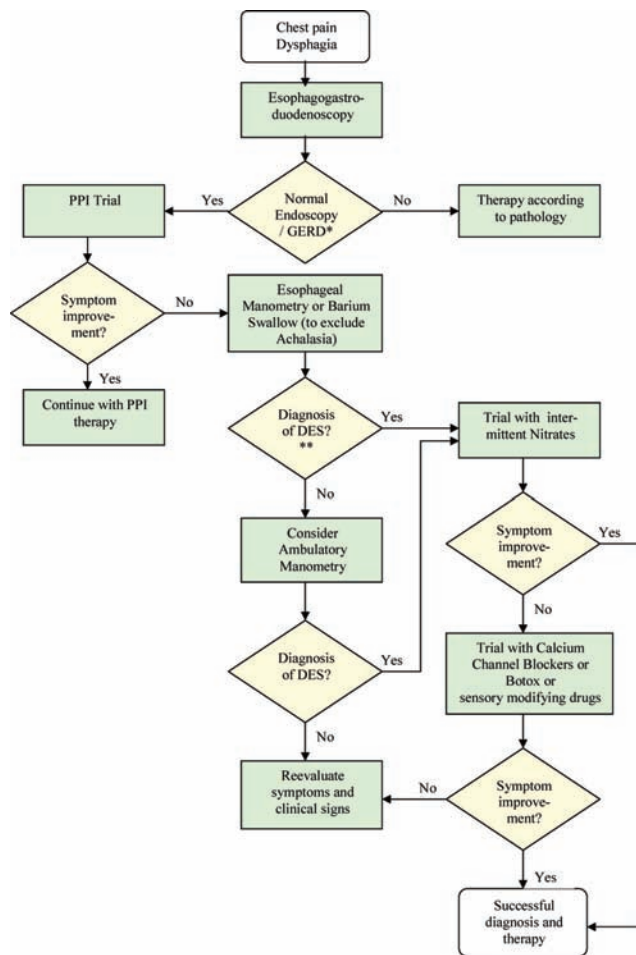


Figure 2. Suggested algorithm for diagnosis and treatment in suspected DES. *Take biopsies, if normal endoscopy, to rule out eosinophilic esophagitis in patients presenting with dysphagia. ** $\geq 20\%$ synchronous contraction in routine manometry testing with (5 mL) water swallows.

pression and may not require further investigation. Therefore, an initial trial of a proton pump inhibitor (PPI) is appropriate in patients suspected clinically of having DES (61).

SMOOTH MUSCLE RELAXANTS. Smooth muscle relaxants such as anticholinergics, calcium channel blockers, and long-acting nitrates can decrease high-amplitude contraction, but do not consistently relieve chest pain. Especially with calcium channel antagonists, the frequency and severity of chest pain are no better than following the administration of placebo (62–64). A comparison of different calcium channel antagonists showed that nifedipine was more potent than diltiazem in inhibiting smooth muscle contraction (65), but also had more side effects (66). Agents that increase the availability of NO (e.g., sildenafil) may have a role in the treatment of DES, although controlled trials are required to determine the degree of benefit.

Recently, botulinum toxin injections in the lower esophagus and at the level of the gastroesophageal junction have been reported to have a beneficial effect in patients suffer-

ing from DES. A series of small, uncontrolled studies have shown positive outcomes (67–69). Storr *et al.* (69) injected botulinum toxin at multiple sites along the esophagus wall into endoscopically visible contraction rings. Symptoms improved immediately in seven of the nine patients after one injection session. After 4 wk, eight (89%) patients were in remission with a decrease in total symptom score from a median of 8, before treatment, to 2 (after 1 day and 1 month, $P < 0.01$). After 6 months, all eight patients with a response at 1 month still had a symptom score of 3 or less without further treatment. Subsequently, four patients required reinjection 8, 12, 15, or 24 months after the initial treatment with similarly good results.

A larger study by Miller *et al.* included 29 patients (70) treated with 100 U of botulinum toxin injected around the Z-line. Forty-eight percent had complete symptom relief, which lasted on average over 7 months. Controlled trials are required, however, before this treatment can be recommended for routine use.

PSYCHOTROPICS. Antidepressants can reduce the discomfort experienced and the patient's reaction to pain, although without any significant influence on esophageal motility. Trazodone, a serotonin reuptake inhibitor, is the most studied antidepressant in this regard. In a double-blind, placebo-controlled study, including patients with chest pain and manometric contraction abnormalities (only some with DES), low-dose trazodone (100–150 mg/dL) improved overall symptoms of spastic disorders of the esophagus to a greater degree than placebo (71), and in a comparative study it was superior to isosorbide dinitrate in relieving symptoms in DES patients (13).

Bougienage and Pneumatic Dilation

Bougienage and pneumatic dilation have been used in patients with intractable symptoms not responding to pharmacological therapy; however, the evidence for this approach is weak and there are no recent studies.

Surgical

Operations for motor dysfunction of the esophagus have been performed for more than 50 yr with variable outcomes. The surgical management of DES is based on esophagomyotomy, with the length of the myotomy related to the extent of manometric abnormalities. In addition, most authors recommend extending the myotomy through the LES onto the gastric cardia (72). Failed medical therapy usually precedes the referral of these patients for surgical intervention (73), and they are a particularly challenging group to treat. Not surprisingly, outcomes are variable and there are no controlled studies of surgical approaches to the treatment of DES, with the literature limited to a number of isolated case reports and small series showing some benefit in manometric findings and occasionally in symptoms (30, 74–80), but failure is frequent and patients may suffer postoperatively from reflux disease.

CONCLUSIONS

DES is an uncommon motility disorder probably related to the dysfunction of the inhibitory motor neurons of the esophagus causing dysphagia and/or chest pain.

The diagnosis of DES is made on the basis of manometric findings of synchronous contractions in the distal esophagus in patients with a consistent clinical presentation.

Therapeutic options are limited, but reassurance that the patients are not suffering from ischemic cardiac disease is important. An initial trial of acid suppression with a PPI is appropriate to suppress acid reflux that may be associated with DES (or at least cause similar symptoms) in some patients. Current treatments for esophageal spasm, including calcium channel blockers (e.g., nifedipine) and nitrate donors (e.g., isosorbide mononitrate), are limited by poor efficacy and side effects. In patients that fail to respond, visceral analgesics (antidepressants), a therapeutic trial of sildenafil (expensive!), or botulinum toxin injection into the lower esophagus may be trialed. Surgery should be approached with caution.

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CONFLICT OF INTEREST

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