

Chicago Classification Update (v4.0): Technical review on diagnostic criteria for distal esophageal spasm

Sabine Roman¹  | Geoff Hebbard² | Kee Wook Jung³  | Phil Katz⁴ | Radu Tutuian^{5,6} | Reuben Wong⁷ | Justin Wu⁸ | Rena Yadlapati⁹  | Daniel Sifrim¹⁰ 

¹Digestive Physiology, Hôpital E Herriot, Hospices Civils de Lyon and Lyon I University, Lyon, France

²Royal Melbourne Hospital, University of Melbourne, Parkville, Vic., Australia

³Department of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

⁴Weill Cornell Medicine, New York, NY, USA

⁵Clinic for Gastroenterology and Hepatology, Bürgerspital Solothurn, Solothurn, Switzerland

⁶University of Berne, Berne, Switzerland

⁷Yong Loo Lin of Medicine, National University of Singapore, Singapore, Singapore

⁸The Chinese University of Hong Kong, Hong Kong, Hong Kong SAR

⁹Division of Gastroenterology, Center for Esophageal Diseases, University of California San Diego, La Jolla, CA, USA

¹⁰Wingate Institute of Neurogastroenterology, Queen Mary University of London, London, UK

Correspondence

Sabine Roman, Digestive Physiology, Hôpital Edouard Herriot 5, place d'Arsonval 69437 Lyon Cedex 03, France. Email: sabine.roman@chu-lyon.fr

Abstract

Distal esophageal spasm (DES) is defined as a manometric pattern of at least 20% of premature contractions in a context of normal esophago-gastric junction relaxation in a patient with dysphagia or non-cardiac chest pain. The definition of premature contraction requires the measurement of the distal latency and identification of the contractile deceleration point (CDP). The CDP can be difficult to localize, and alternative methods are proposed. Further, it is important to differentiate contractile activity and intrabolus pressure. Multiple rapid swallows are a useful adjunctive test to perform during high-resolution manometry to search for a lack of inhibition that is encountered in DES. The clinical relevance of the DES-manometric pattern was raised as it can be secondary to treatment with opioids or observed in patients referred for esophageal manometry before antireflux surgery in absence of dysphagia and non-cardiac chest pain. Further idiopathic DES is rare, and one can argue that when encountered, it could be part of type III achalasia spectrum. Medical treatment of DES can be challenging. Recently, endoscopic treatments with botulinum toxin and peroral endoscopic myotomy have been evaluated, with conflicting results while rigorously controlled studies are lacking. Future research is required to determine the role of contractile vigor and lower esophageal sphincter hypercontractility in the occurrence of symptoms in patients with DES. The role of impedance-combined high-resolution manometry also needs to be evaluated.

KEYWORDS

chest pain, distal latency, dysphagia, spasm

1 | INTRODUCTION

Distal esophageal spasm (DES) is a major motility abnormality that can be associated with dysphagia and/or non-cardiac chest pain. The Chicago Classification (CC) v3.0 defined DES when liquid swallows are followed by at least 20% of premature contractions without impairment of esophago-gastric junction (EGJ) relaxation (normal integrated relaxation pressure (IRP)).¹ With the version 3.0, the distal latency (DL) between swallow and distal contraction was introduced as a new

parameter to analyze esophageal high-resolution manometry (HRM). It requires the localization of the contractile deceleration point (CDP) which is the inflexion point in the contractile front propagation velocity in the distal esophagus.² Premature contraction is thus defined by the DL measured as the interval from the start of relaxation of the upper esophageal sphincter (UES) to the CDP shorter than 4.5 s.³ The proposed definition of DES is purely manometric in the CCv3.0.

An international process began in 2019 to update the Chicago Classification based on new publications and the experience in using

the Chicago Classification. Refinement of the definition of DES was a priority of the update. First, DES is a rare diagnosis and when identified may represent a pattern along the spectrum of type III achalasia.³ At the same time, the manometric pattern of DES, considered initially as a major primary motility disorder, could also be associated with gastro-esophageal reflux disease (GERD) or in the setting of opioid use.^{4,5} These observations raised the clinical relevance of the manometric definition of DES. Further, the recent popularity of endoscopic treatment for esophageal motility disorders requires an accurate definition of DES in order to avoid inappropriate invasive procedures.⁶ Altogether, these arguments plead for an update of DES definition.

2 | METHODS

In the Chicago Classification version 4.0 (CCv4.0) process, one working group consisting of seven members was dedicated to DES (SR, DS, GH, KWJ, RW, JW, RT). This working group, led by two co-chairs, was tasked with developing statements regarding a conclusive clinical and manometric definition of DES, an inconclusive definition of DES, and testing that may support a clinical diagnosis of DES based on literature review and expert consensus. As detailed in the main CCv4.0 document, each proposed statement underwent two rounds of independent ranking according to the RAND UCLA Appropriateness Methodology to determine appropriateness of each statement.⁷ Statements with $\geq 85\%$ agreement as appropriate were considered strong recommendations, while those with 80% to 85%

agreement as appropriate were considered conditional recommendations. Statements nearly meeting criteria and/or those generating controversy were discussed at working group meetings. Additionally, statements that met criteria for inclusion in the final CCv4.0 underwent further independent evaluation to assess the level of supportive evidence, using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) process, when possible.⁸ Two experts (PK, RY) external to the working sub-groups independently evaluated the supportive literature provided by the sub-groups. Some statements were not amenable to the GRADE process, either because of the structure of the statement or lack of available evidence.

This technical review reports the statements raised by a group of experts assigned by the CCv4.0 Working group to update the definition of DES. We discuss also the rationale for the statements proposed in the CCv4.0 (Table 1).

3 | RECOMMENDED STATEMENTS IN THE CCV4.0 REGARDING DISTAL LATENCY AND DISTAL ESOPHAGEAL SPASM

3.1 | Conclusive diagnosis

3.1.1 | Manometric consideration

Recommendation: A conclusive manometric diagnosis of DES is defined as presence of at least 20% of premature contractions (Low GRADE, Strong Recommendation).³

Distal Esophageal Spasm			
Recommended statement	Percent agreement	Strength of recommendation	Level of evidence
A conclusive manometric diagnosis of DES is defined as presence of at least 20% of premature contractions	86%	Strong	Low
Esophageal contractile activity must be distinguished from other causes of pressure rise in the distal esophagus such as intrabolus pressure and/or artifact.	100%	Strong	Very Low
The CDP might be difficult to identify. In this setting, alternative methodologies need to be considered to diagnose DES	86%	Strong	
A clinically relevant diagnosis of DES requires both clinically relevant symptoms and a conclusive manometric diagnosis of DES	84%	Conditional	Low
Clinically relevant symptoms for DES include dysphagia and non-cardiac chest pain		Accepted clinical observation	
The presence of at least 20% of premature contractions (DL < 4.5 s) but with a DCI < 450 mmHg-s-cm is inconclusive for a manometric diagnosis of DES	81%	Conditional	Low

TABLE 1 Recommended statements with strength of recommendation, percent agreement, and level of evidence

Compared with the previous iteration of the CC, the definition of premature contraction (esophageal contraction with a DL shorter than 4.5 s, in the setting of a distal contractile integral (DCI) of 450 mmHg-s-cm or greater⁹) remains unchanged (Figure 1; Table 2). The literature on the effects of nitric oxide (NO) agonism and antagonism supports the use of the DL as a marker of inhibition to define premature contraction and thus DES. It clearly indicates a role for deglutitive inhibition in the peristaltic-“progression” of the contractile wave down the esophagus.¹⁰ DL measures end of inhibition (nitroergic) and post-inhibition after contraction. The neurotransmitter involved in the aftercontraction is more controversial. Spastic contractions can be generated by reducing NO with hemoglobin,¹¹ but there is also a central vagal cholinergic component with impact on the timing and strength of contraction.¹² The only new literature about this since 2015 is the literature on opiate use. It seems that there are both acute and chronic effects of opiates which may indicate other pathways (although maybe still via NO inhibition as the final effector).^{4,5}

The threshold of a DL of 4.5 s to define DES was determined according to observation in healthy controls and in patients.^{3,9} However, in some conditions the threshold of 4.5 s may not be relevant. For example, in case of large hiatal hernia, the esophagus can be shortened and as a consequence the DL can be shorter in patients with large hernia compared to those without.¹³ Interestingly large hernia patients with premature contractions do not exhibit evidence of DES after hernia repair without myotomy. Some complementary maneuvers during HRM might be discussed in borderline cases (see below).

The threshold of 20% premature contractions to define DES was translated from the classification of motility disorders in conventional manometry.¹⁴ Clinical observations reveal that true DES has many premature contractions. This suggests that the higher number of premature contractions is, the higher confidence of true DES is. Collaborative studies are required to confirm the impact of the number of premature contractions on the relevance of the diagnosis.

Recommendation: Esophageal contractile activity must be distinguished from other causes of pressure rise in the distal esophagus such as intrabolus pressure and/or artifact. (Very Low GRADE, Strong Recommendation).^{3,13}

Confusion between intrabolus pressure and premature contractions is certainly responsible for overdiagnosis of DES. Therefore, the definition of what is intrabolus pressure and what is the manometric signature of a contraction is important as DES is defined based on premature contractile activity. By examining Clouse plots, intrabolus pressure can appear more homogeneous than the pressure generated by the contractile activity. The isobaric contour can be used to identify intrabolus pressure (Figure 2). As intrabolus pressure comes at varied pressure levels (above intragastric pressure), having a fixed threshold to define intrabolus pressure is questionable. Indeed, by definition intrabolus pressure is the pressure transmitted equally throughout a fluid filled cavity and hence must be equal (after accounting for pressure measurement drift) at two or more sensors. Intrabolus pressure should be greater than intragastric pressure (to distinguish from background intrathoracic pressures, which would also fulfill this definition). Contraction pressure by contrast requires occlusion of the lumen

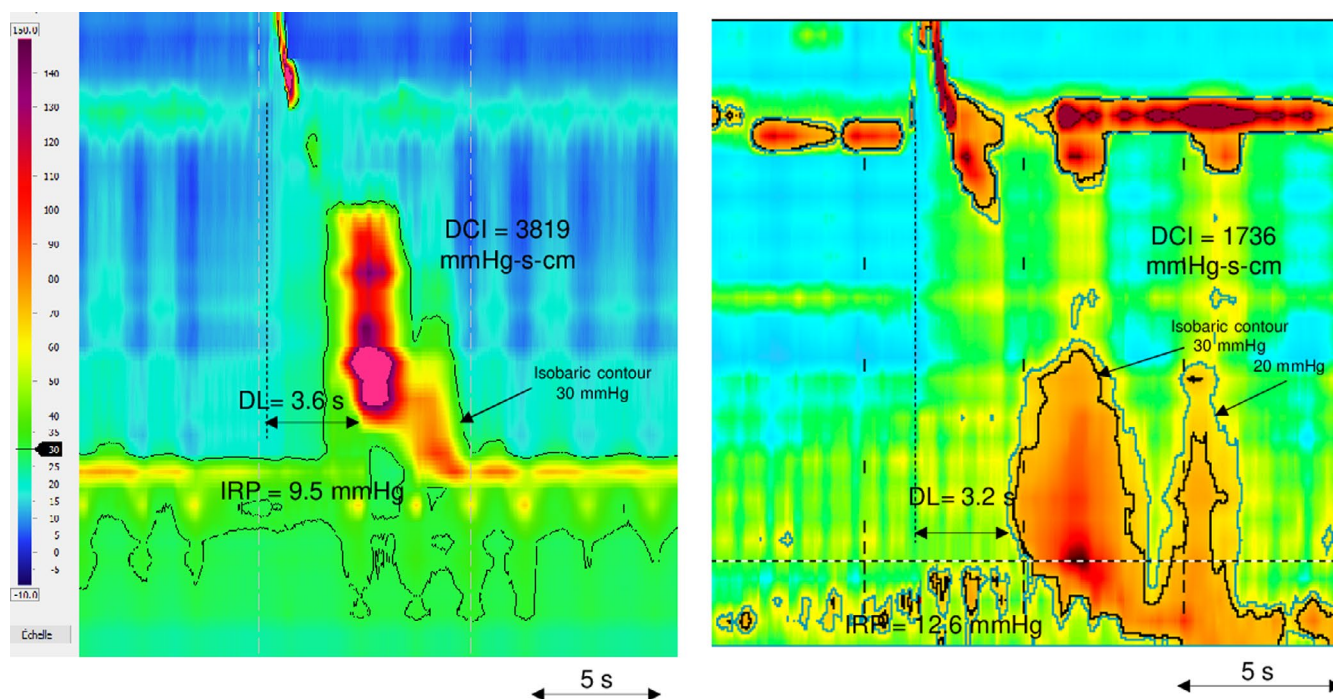


FIGURE 1 Conclusive diagnosis of distal esophageal spasm (DES). Premature contraction is defined as a contraction with a distal contractile integral (DCI) > 450 mmHg-s-cm, a distal latency (DL) < 4.5 s and a normal integrated relaxation pressure (IRP). Panel A is a premature contraction with the Medtronic system and Panel B with the Diversatek system

TABLE 2 What is new?

Chicago v3.0	Chicago v4.0	Changes
DES is a major disorder of peristalsis	DES is a disorder of peristalsis	The notion of major and minor disorders is no longer present in the new iteration
DES is defined as normal median IRP, $\geq 20\%$ premature contractions with DCI > 450 mmHg·s·cm Some normal peristalsis may be present	A conclusive manometric diagnosis of DES is defined as presence of at least 20% of premature contractions	The manometric diagnosis of DES remained unchanged
Premature contraction is contraction with DCI > 450 mmHg·s·cm and DL (interval between UES relaxation and CDP) < 4.5 s	The presence of at least 20% of premature contractions (DL < 4.5 s) but with a DCI < 450 mmHg·s·cm is inconclusive for a manometric diagnosis of DES	
	A clinically relevant diagnosis of DES requires both clinically relevant symptoms and a conclusive manometric diagnosis of DES	The diagnosis of DES requires relevant symptoms (in addition of a conclusive manometric diagnosis)
	Clinically relevant symptoms for DES include dysphagia and non-cardiac chest pain	
The CDP represents the inflexion point in the contractile front propagation velocity in the distal esophagus. It is localized within 3 cm of the proximal margin of the LES	The CDP might be difficult to identify. In this setting alternative methodologies need to be considered to diagnose DES	The definition of CDP remains unchanged but the difficulty to identify CDP is acknowledged
	Esophageal contractile activity must be distinguished from other causes of pressure rise in the distal esophagus (intrabolus pressures, artifact)	Caution is warranted to distinguish esophageal contraction and intrabolus pressure

Abbreviations: CDP, contractile deceleration point; DCI, distal contractile integral; DES, distal esophageal spasm; DL, distal latency; IRP, integrated relaxation pressure; LES, lower esophageal sphincter; UES, upper esophageal sphincter.

and direct contact of the wall to the catheter and so shows spatial variation. Once the top and bottom boundaries of the bolus are defined at a specific point in time, the next point can be examined until the pressure equivalency between sensors is lost and the intrabolus pressure event ends. This will define a two-dimensional "intrabolus pressure event."

Recommendation: The CDP might be difficult to identify. In this setting alternative methodologies need to be considered to diagnose DES (Strong Recommendation).

The CDP is an important physiologic landmark demarcating the 2 phases of the peristaltic wave (slow and fast contractile front velocity (CFV)). An accurate identification is important to define DL, and previously, CFV calculation.² CDP is easy to identify in normal swallow. It is being used to define the return of contractile activity in the lower esophageal body as a marker of loss of inhibition but is difficult to define where peristalsis is abnormal (weak peristalsis is by definition already excluded, and if intrabolus pressure can also be identified and excluded that will eliminate some confusion).

To facilitate the CDP location, a horizontal line can be drawn 2-3 cm above the proximal aspect of the pre-swallow EGJ high-pressure zone) (Figure 3). The DL can be determined by the duration of time from the start of the UES relaxation to the intersection at the contractile wave-front. It is important that this horizontal line is extended to the contraction and not to the

pressurization front that can be compartmentalized ahead of the peristaltic contractile wave-front. A more sophisticated method is the "tML method," named because the necessity of finding the time of maximal length (tML) of concurrent contraction.¹⁵ An algorithm finds the time during peristalsis at which a maximal length of the distal esophagus is contracting concurrently and the CDP is at the intercept between the leading edge of the 30-mmHg isobaric contour of the contraction and the time of maximal contracting segment length.

Another alternative method might be to drop the term CDP and define this physiological parameter as the occurrence of an identifiable contractile event in the triangle bounded by the upper border of the lower esophageal sphincter (LES), the pharyngeal swallow (at the UES) and 4.5 s after the swallow at the level of the upper border of the LES. This would be a "triangle of expected inhibition" and contractile activity within that would indicate loss of the expected degree of inhibition. It would encompass the current definition and also more sporadic contractile activity (but that would need to be distinguished from artifact and have some requirements for a DCI equivalent). Another suggestion would be a polygon with the top defined as a particular distance above the LES. A swallow normalization process was proposed when DL was defined and can be refined to identify the inhibition zone.⁹

FIGURE 2 Adjusting the isobaric contour (IBC) helps to differentiate pressurization from contraction. The blue line is 20-mmHg IBC, the black line 30-mmHg IBC, and the white dashed line the 40 mmHg IBC. Increasing the IBC to 40 mmHg identifies clearly the contraction

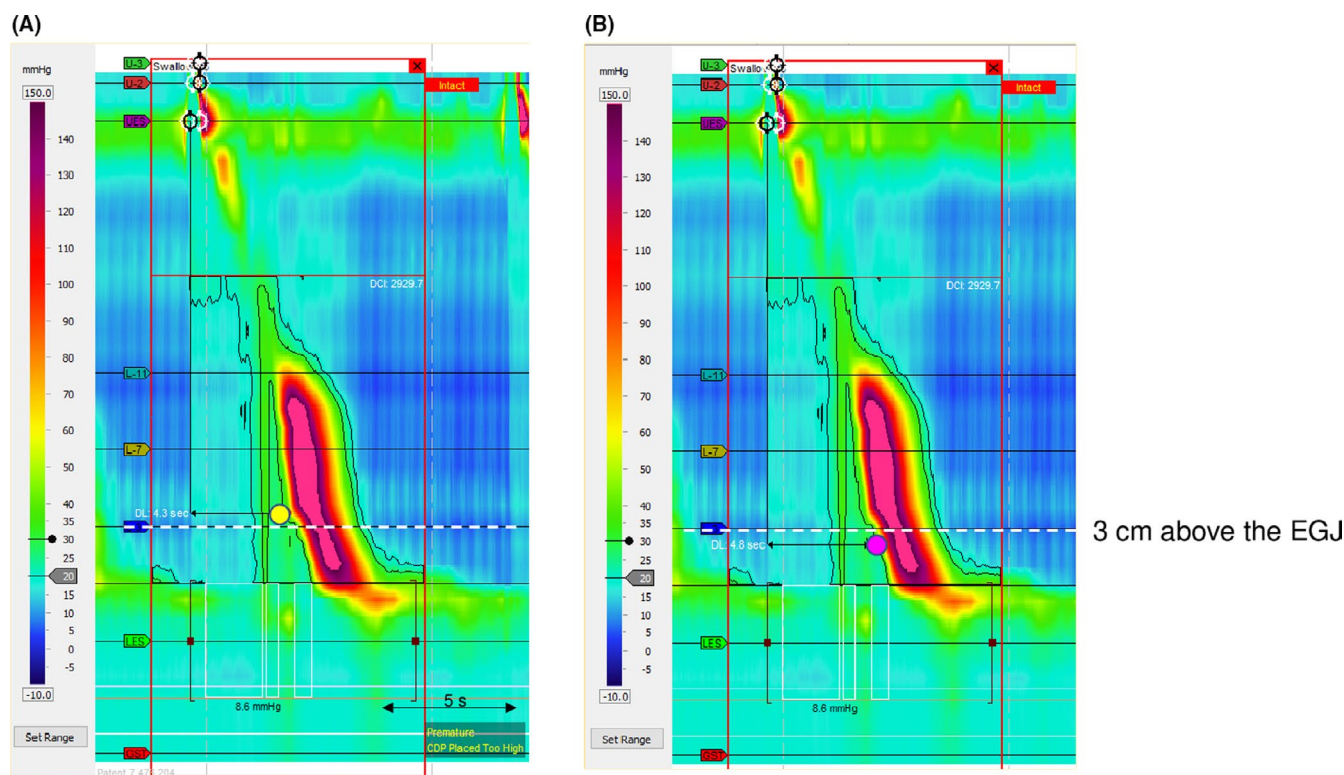
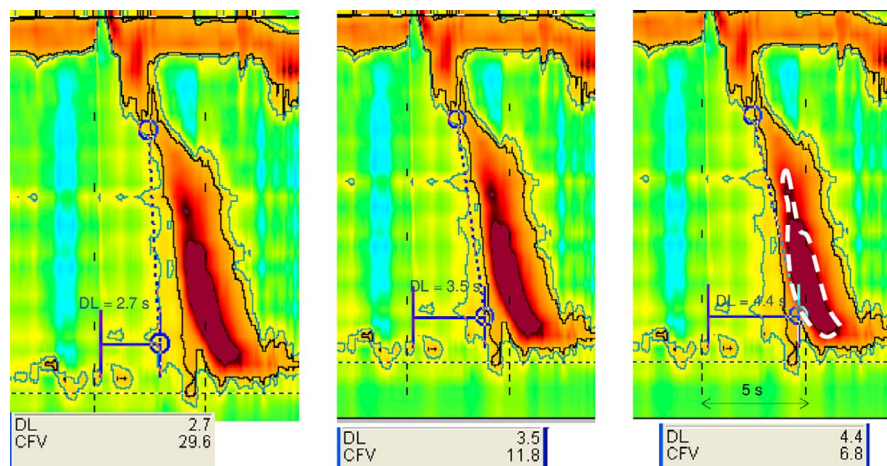


FIGURE 3 The contractile deceleration point (CDP) is located within the 2 to 3 cm above the esophago-gastric junction (EGJ). The CDP (yellow dot, Panel A) is located too high (above the dashed white line represented the line 3-cm above the EGJ) leading to a distal latency (DL) of 4.3 s. The correct placement of the CDP (pink dot on Panel B) is leading to a normal distal latency 4.8 s)

3.1.2 | Clinical consideration

Within the update of the CC, it appears that clinical information was important, and the Working Group recognized the importance of the presence of both esophageal symptoms and manometric pattern to diagnose DES.

Recommendation: A clinically relevant diagnosis of DES requires both clinically relevant symptoms and a conclusive manometric diagnosis of DES (Low GRADE, Conditional Recommendation).³

Recommendation: Clinically relevant symptoms for DES include dysphagia and non-cardiac chest pain (Accepted Clinical Observation).

The diagnosis of DES made on manometry may carry little or no clinical relevance if the patients has no related symptoms. The use of DL criterion resulted in decrease of sensitivity and increase of specificity of the diagnosis.³ However, the manometric diagnosis of DES can be incidental, during a preoperative evaluation for antireflux surgery for example. In this situation, questions arise whether DES is the consequence of the abnormal acid exposure

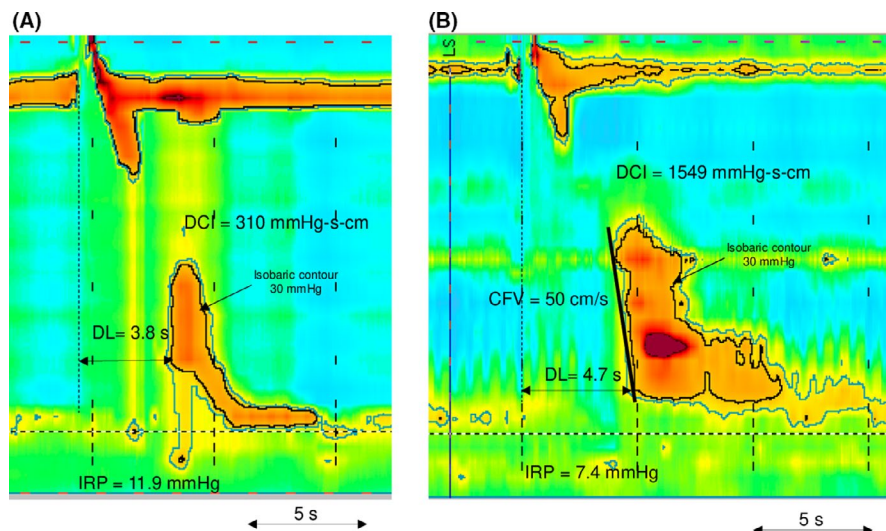


FIGURE 4 Inconclusive diagnosis of distal esophageal spasm (Diversatek system). Panel A represents a contraction with low distal contractile integral (DCI) and short distal latency (DL). Panel B exhibits a contraction with a normal DL, a normal DCI but a rapid contractile front velocity (CFV)

in the distal esophagus or if DES is independent of GERD contributing on their own to symptoms. To date, there are no known differences in amplitude (DCI) or time-line characteristics (DL) of spastic contractions in patients with DES in the presence or in the absence of GERD.

3.2 | Inconclusive diagnosis, supportive testing, additional recommendations

Recommendation: The presence of at least 20% of premature contractions (DL < 4.5 s) but with a DCI < 450 mmHg-s-cm is inconclusive for a manometric diagnosis of DES (Low GRADE, Conditional Recommendation).

According to the Chicago classification v3.0, DL can be measured only if DCI is greater than 450 mmHg-s-cm (Figure 4). The seminal study of Pandolfino suggested that contractile fragments with low DCI could be rapid and associated with normal or weak peristalsis.³ The significance of contractile fragments with DCI < 450 and short DL was not evaluated. Some of them can be associated with achalasia. Further if contractions are «visible» and peristaltic, they are capable for liquid clearance. If these contractions are premature, they will not. Consequently, the relevance of DCI is uncertain unless there is no contraction at all.

Adjunctive testing (ie, multiple rapid swallows) might be useful to search for lack of deglutitive inhibition and provide an argument for a diagnosis of DES.¹⁶ The use of these tests was discussed but the statements did not reach agreement (see below).

Some additional testing may support diagnosis and predict response to treatment. Barium esophagogram can be in favor of DES in case of tertiary contractions, rosary bead or corkscrew esophagus.^{17,18} FLIP topography with repetitive retrograde contractions or sustained occluding contractions during response to distension is an abnormal pattern that can be encountered in patient with DES.¹⁹

3.3 | Statements that did not meet criteria for agreement with narrative text

Proposed Statement: In case of an inconclusive or borderline diagnosis of distal esophageal spasm, an interval follow-up manometry performed in a period when the patient is symptomatic may be of value

Data to support follow-up manometry are scarce. It can be useful in symptomatic patients with a DL within the borderline range (for example between 4.5 and 6 s) and reveal a distinct disease feature for the differential diagnosis of DL. However, it needs validation based on further studies to support its usefulness. The delay for the follow-up manometry remained to be determined.

Proposed Statement: The occurrence of at least 20% of contractions with normal DL and abnormal CFV (CFV > 8 cm/s) may be associated with spasm, but is inconclusive for the diagnosis of spasm

The CFV was dropped in Chicago 3.0 as it lacked specificity in identifying DES and in correlating with symptoms.¹ This resulted in a drop of sensitivity where symptomatic cases with clear DES like symptoms and an elevated CFV but normal DL get dropped and the diagnosis that would allow them treatment gets missed (Figure 4). A retrospective study demonstrated that patients with rapid CFV but normal DL had many features similar to DES defined on short DL.²⁰ Further synchronous contractions that are not premature can be associated with hold up of boluses. One caveat to use CFV is the occurrence of little or no break in peristalsis, to avoid an erroneous CFV calculation.

It is important to recognize that CFV corresponds to the measurement of the occurrence of lumen occlusion and not the true «contraction front.» The time from the beginning of the contraction to the occurrence of lumen occlusion depends on the strength of the contraction and luminal content. Hence, a weak contraction (or contractile area) may take longer to occlude the lumen (which is what provides the manometric event that we identify) and hence appear synchronous or even have a negative CFV when in fact the contraction is propagated. The contractions most likely to be misclassified

are those that are weak or have an intrabolus pressure component that is a synchronous pressure event, but not a synchronous contraction.

Proposed Statement: In a patient with GERD symptoms, the presence of at least 20% of premature contractions (DL < 4.5 s) is not in itself sufficient for the diagnosis of spasm and further tests are required to confirm that premature contractions are not secondary to GERD (GERD testing, follow up manometry on PPI)

Distal esophageal spasm can be diagnosed in patients referred for preoperative evaluation before fundoplication. This questions the relationship between acid exposure and DES occurrence.^{21,22} The hypothesis would be that acid exposure would modify the afferent component of the peristaltic peripheral pathway. In order to clarify the extent of the overlap between DES and GERD, a systematic search for GERD with pH-(impedance) monitoring might be of interest in patients diagnosed with DES. An alternative to GERD testing could be a trial of empiric treatment with PPI. In these patients, it would be also important to reassess the prevalence and frequency of spastic contractions especially in those who improved on PPI therapy. This approach will provide a better understanding whether symptoms are primarily related to GERD or to DES.

Proposed Statement: Abnormal inhibition defined by the persistence of peristaltic contractile activity in the distal esophagus during multiple rapid swallow (MRS) supports a manometric diagnosis of distal esophageal spasm

During MRS, the esophageal body remains inhibited until the last of the series of swallows and then a peristaltic contraction wave follows. A normal response to MRS requires integrity of both inhibitory and excitatory mechanisms and esophageal muscle. An inverse relationship was found between the degree of inhibition and the propagation velocity of deglutitive esophageal contractions: the less inhibition, the faster the propagation velocity, and in the extreme case of zero-inhibition the presence of simultaneous contractions.¹⁰ Therefore, there is evidence for the hypothesis that the spectrum of primary esophageal motility disorders is an expression of a progressively failing inhibition. In case of achalasia, there is an abnormal response to MRS.²³ Abnormal inhibition during MRS could be an argument in favor of the diagnosis of DES (Figure 5).²⁴ Performing MRS might help to confirm the diagnosis of DES in borderline cases.

Proposed Statement: Esophageal shortening and/or abnormal (premature, simultaneous) contractions during or after rapid drink challenge (RDC) supports a manometric diagnosis of distal esophageal spasm

Rapid drink challenge test (drinking 200-ml water as fast as possible) can detect EGJ obstruction.²⁵ Indeed the occurrence of pan-esophageal pressurization during RDC is in favor of EGJ obstruction and might be an adjunct test in case of suspected achalasia (Figure 6).

Esophageal shortening can be observed as well during and/or after RDC. It is encountered in patients with EGJ relaxation disorders or major disorders of peristalsis as defined by the Chicago Classification v3.0.²⁶ It might be also associated with adenocarcinoma of the cardia. When criteria of achalasia are not fulfilled, the

occurrence of esophageal shortening induced by RDC can be a sign in favor of atypical achalasia or major disorder of peristalsis. However, further complementary examinations should be performed to rule out an infiltrative process of the cardia.

Finally, an absence of inhibition might be observed in up to 30% of patients with DES or hypercontractile disorders.²⁷ Further persistent contractions or abnormal contractions after RDC might be a marker of DES and hypercontractile disorders.

Proposed Statement: The presence of at least 20% of premature contractions (DL < 4.5 s) in a patient with chest pain UNRELATED to eating is not sufficient for the diagnosis of spasm

As symptoms (dysphagia, chest pain) observed in DES are supposed to be related to impaired esophageal bolus clearance, the relevance of symptoms occurring in absence of eating are questionable. Using solid test meal (STM) during HRM might be helpful to determine whether the manometric pattern is associated with symptoms while the patient is eating. Further some patients demonstrate DES only during solid swallow test or test meal. Indeed the sensitivity and specificity of DES diagnosis is increased by inclusion of a solid test meal (STM) in HRM studies.^{28,29} It has been reported that additional cases of DES and hypercontractile motility can be detected with STM and up to 80% of these individuals reported symptoms during the STM study. Conversely, patients with DES or absent motility during single water swallows have restoration of normal esophageal motility with STM included. In contrast to patients with DES during STM, most individuals with DES detected only during single water swallows had no symptoms.²⁸

Another option is to perform a follow up HRM at 12 months or earlier in case of typical symptoms in patients who fulfill DES manometric criteria but have no or atypical symptoms. If the diagnosis of DES is confirmed, it is likely that the manometric pattern has evolved.

3.4 | Clinical considerations of when to intervene and therapeutic options

The analysis of recent literature and a better knowledge of DES raised different questions among the group of experts. DES can be part of type III achalasia spectrum or associated with opiates treatment. Different phenotypes might exist. The indications of invasive treatment might depend on the clinical presentation and complementary examinations. An important consideration is the evaluation of response to treatment.

3.4.1 | Is type III achalasia and DES part of the same spectrum of diseases?

According to the Chicago Classification v3.0, the only difference between DES and type III achalasia was the IRP (normal in case of DES and elevated in case of type III achalasia). Thus, the IRP was the

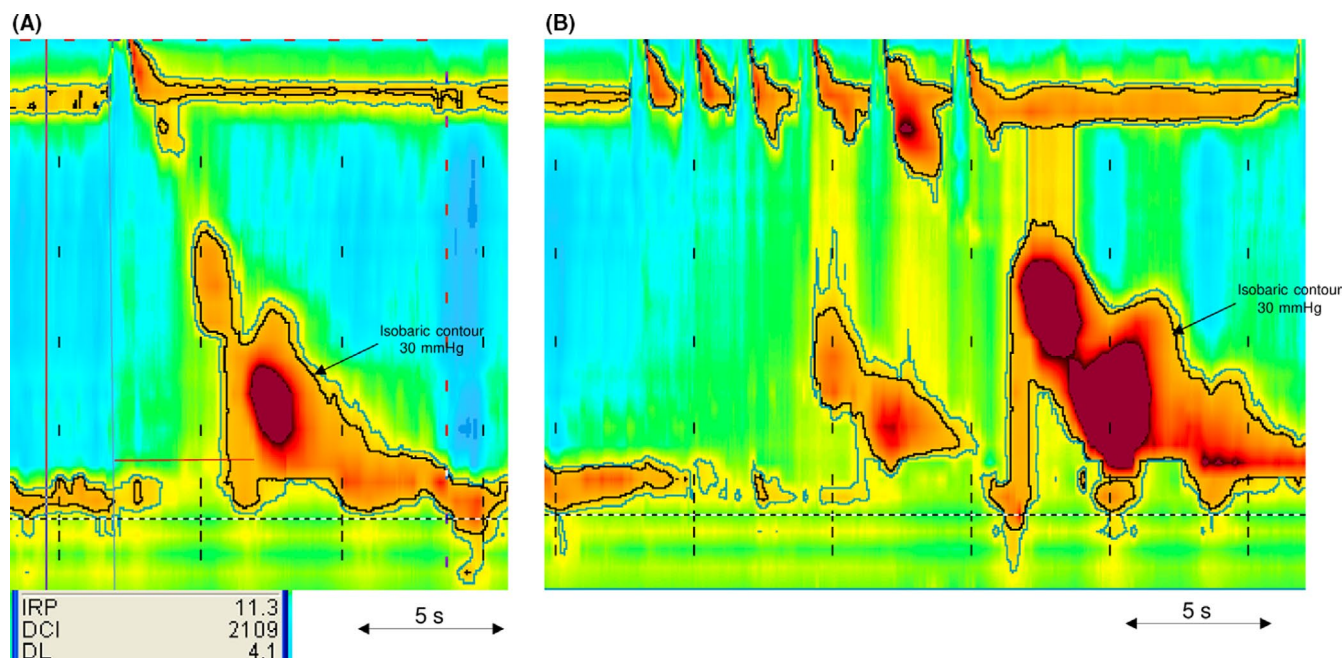


FIGURE 5 Premature contraction (A) and lack of inhibition on multiple rapid swallows (B). The third swallow of the multiple rapid swallow (MRS) test is followed by an esophageal contraction that demonstrates a lack of inhibition

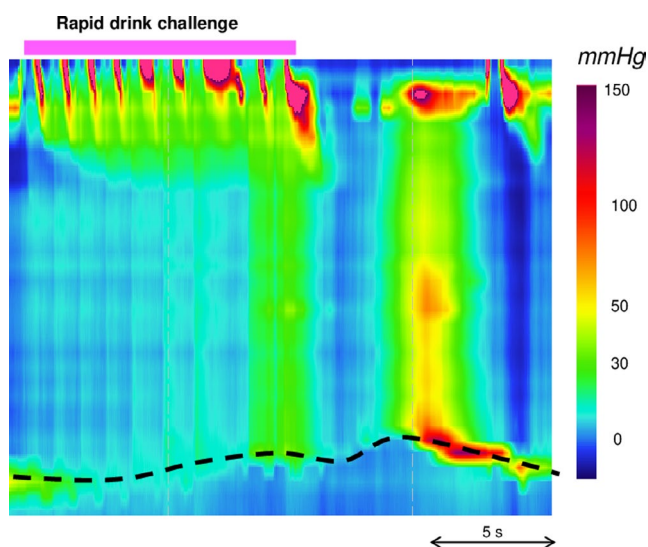


FIGURE 6 Rapid drink challenge is followed by pan-esophageal pressurization and esophageal shortening. The black dashed line represents the level of the esophago-gastric junction

only criterion to distinguish between type III achalasia and DES in a patient with 100% premature contractions. However, sometimes, the IRP based on manometry testing is equivocal or not clear-cut and the discrimination between DES and achalasia type III difficult. With the Chicago Classification v4.0, type III achalasia definition encompass an absence of peristalsis while some instance of normal peristalsis can be encountered in patients with DES.³⁰ That is important as IRP is no longer the only distinction between type III achalasia and DES.

Other tests, including the endoluminal functional probe (FLIP) along the EGJ or timed barium esophagography with a solid bolus, might be helpful if a doubt on EGJ relaxation exists. It is important to note that DES with normal EGJ relaxation is rare. Some data demonstrated that DES could evolve to achalasia.³¹ Thus, we can wonder whether DES and type III achalasia are the same disorder and differ in severity on the same spectrum. Some prospective follow-up studies are needed to determine the natural history of DES.

3.4.2 | Should we include a category of opioids induce spastic contraction?

Opioids affect esophageal motility and can be associated with increased IRP, increased DCI and shortened DL.^{4,5,32} The concept of DES might need to be categorized in the era of opioid induced esophageal motility disorders.

The previously described papers regarding DES might have missed or overlooked the detailed history of medications, especially opioid medications. If patients diagnosed as having DES underwent manometry with chronic opioid medication, follow-up manometry, after discontinuation of the opioid medication should be recommended. Moreover, before considering irreversible procedures, including POEM, in patients with DES, detailed history taking of opioid medications should be performed.

This would not be changing the definition of the manometric abnormalities, but the cause and management would perhaps be clearer, so more of clinical significance than manometric, unless we can define specific features (they seem to be rather nonspecific at present). If needed, the subcategorization into opioid-related or idiopathic DES might be considered in the future.

3.4.3 | What are the clinical phenotypes of DES and how do these differ manometrically?

Symptoms associated with DES are dysphagia, regurgitation and non-cardiac chest pain. Furthermore, DES is observed in patients evaluated for reflux symptoms such as heartburn/regurgitation. It is unknown if the symptoms, the percentage of premature contractions or the association with other patterns affect the natural history of the disease and the outcome.

Different clinical phenotypes might be described:

- Patients with dysphagia/regurgitation (who also often have chest pain that is either milder and probably part of the dysphagia albeit described as pain, or due to obstruction and a more significant pain)
- Patients with dominant chest pain that may be unrelated to eating
- Patients with DES presenting with heartburn/regurgitation and in whom reflux disease (defined by either endoscopy or abnormal acid exposure time) is present.

The first group fit best with the premature or non premature synchronous contraction pattern. It is difficult to see how a premature contraction of normal DCI is likely to be causing severe intermittent chest pain which may be an issue in combining the clinical groups into a single manometric diagnosis. Diagnosing patients with chest pain alone (without dysphagia) as DES only on the basis of a couple of premature contractions might not be sufficient. We may wonder whether it would be useful to require markers of a disordered inhibition with other symptoms or at different times. With regard to the 3rd group (DES in patients with reflux disease) it still remains to be clarified if normalizing acid exposure in the distal esophagus reverses or not the frequent premature contractions.

3.4.4 | What are the manometric criteria to select patients for POEM?

The treatment of DES is challenging. Medical treatment including nitrates and calcium channel blockers may have some efficacy.³³⁻³⁵

Endoscopic treatment might be an option when medical treatment failed. Randomized studies evaluated the efficacy of botulinum toxin injection versus placebo.^{36,37} The efficacy if any is limited.

More recently, the popularity of POEM in achalasia treatment led to propose it to treat DES. The procedure is effective, even if the response rate might be lower to the one observed in achalasia.^{38,39} We can wonder whether there is any manometric criteria to indicate good candidacy for POEM. A systematic review of eight observational studies with 179 patients reported that weighted pool rates for clinical success of POEM for type III achalasia, DES and hypercontractile (jackhammer) esophagus were 92%, 88%, and 72%, respectively.⁴⁰ There was no significant difference in success rates

between type III achalasia and DES. It was speculated that extreme contractility of esophageal body in patients with jackhammer esophagus contributed to the inferior outcome. In a recently published international study including 50 patients with non-achalasia disorders, Khasab et al report similar clinical success rates in patients with EGJ outflow obstruction (OO) (93.3%/n = 15), DES (94.1%/n = 17) and jackhammer esophagus (75.0%/n = 18) following POEM.⁴¹ Given the high success rates and low incidence of DES (17 patients in 11 centers in almost 3 years) it was not possible to identify manometric or impedance criteria that predict good clinical outcome after POEM in DES. Sham controlled trials are awaited.

3.4.5 | To what extent should we “diminish” / “abolish” simultaneous contractions for the patient to become asymptomatic?

There is still a lack of understanding on the manometric criterion that defines a successful treatment response in DES. Filicori et al collected preoperative and 6-month postoperative symptom scores, HRM, pH testing, and timed barium swallow data in 40 patients undergoing POEM for non-achalasia motility disorders.³⁸ They noticed a significant improvement in the Eckardt score (pre-POEM 5.02 vs. post-POEM 1.12; $p < 0.001$) in 90% of patients with significant improvements in chest pain (1.02–0.36, $p = 0.001$) and dysphagia (2.20 vs. 0.40, $p = 0.001$). With regard to the objective criteria significant improvements in LES pressures and esophageal emptying on timed barium swallow were observed across groups. Unfortunately, the study provides no details on changes in contraction vigor and distal latency as well as how they correlate with symptom improvement. Further studies with impedance manometry are needed to correlate the change in manometric measurements with bolus transit and symptom improvement. The increased interest in POEM for non-achalasia motility disorders will increase even more the challenge on collecting and analyzing these data in the near future.

3.5 | Future needs and research

Different areas require future research to better understand the pathophysiology of DES and improve the diagnosis.

3.5.1 | Is high DCI relevant for the diagnosis of DES?

“Traditionally” a diagnosis of DES was supported by high amplitude and repetitive contractions, but that “diagnosis” has now been separated on the basis of increased DCI. Nevertheless, there remains a group of patients who have both premature / synchronous contractions and high (but maybe not “abnormal”) DCI. It remains to be determined whether these constitute a separate group clinically, perhaps with more chest pain or if it is in the normal spectrum of DES.

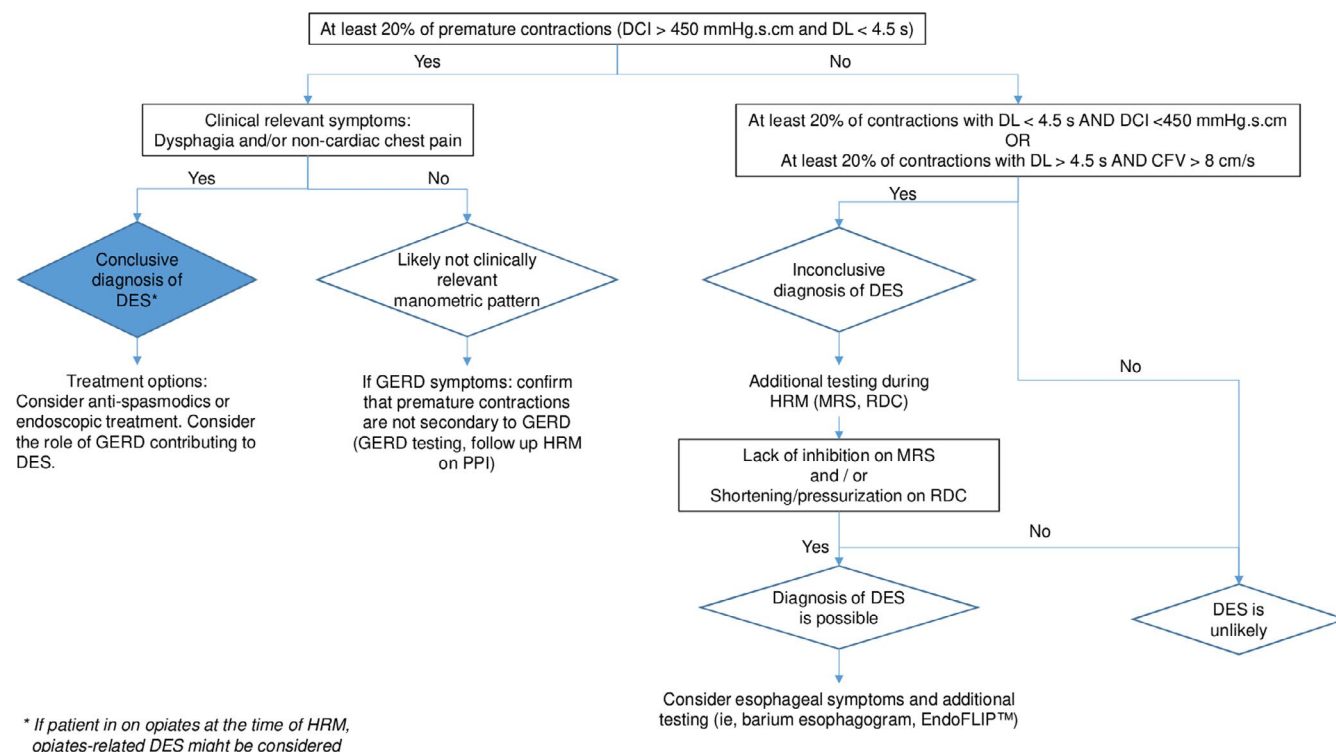


FIGURE 7 Clinical algorithm for the diagnosis of distal esophageal spasm (DES)

3.5.2 | Is LES spasm a specific entity of DES?

Isolated distal contractile fragment or esophageal shortening associated with LES contraction or hypercontractile LES can be observed. Should we consider these entities as part of DES spectrum? Should we use metric similar to esophago-gastric junction—contractile integral (EGJ-CI) to evaluate LES contractility? By definition this “condition” must be associated with “normal” LES relaxation—or it would fit into the achalasia/EGJOO group so is unlikely to be associated with significant obstruction to flow. The physiology is also not clear, is it an excessive contraction as inhibition must be present for the LES relaxation? Nevertheless, there are some patients where there is what seems to be significant LES contraction associated with (sometimes marked) esophageal shortening and often not focal pressure increases in the lower esophagus. Whether these are the patients described by Mittal et al with predominantly longitudinal muscle “spasm” remained to be determined.⁴²

3.5.3 | Is the adjunction of impedance measurement useful for the diagnosis of DES?

Studies performed with conventional manometry associated with impedance demonstrated that DES was a heterogeneous disorder and some DES features were associated with normal bolus transit.⁴³ Due to this potential heterogeneity of DES, we can wonder whether we should advocate a test to confirm failed bolus transit for documenting clinically significant DES. Combined impedance manometry might

be useful to evaluate relationship between esophageal contraction and bolus clearance. However, the yield of combined impedance-manometry was demonstrated for patients without a major motility disorder but not for patients with major disorders.⁴⁴ Interestingly, impedance measurement (esophageal impedance integral (EII) ratio in particular) can help to distinguish patients with dysphagia from those without. Impedance measurement might be of interest to assess correlation with symptoms. If the patient indicates that he or she has symptoms of dysphagia and if there is demonstrated bolus holdup on that swallow it is more powerful evidence that the manometric abnormality is causative.

3.5.4 | Can we use dry swallows to define DES?

Dry swallows are not really “dry” and do involve a small volume of saliva, so it is in essence a “mini-wet” swallow. They could be a harbinger of DES disorder but should be confirmed on proper standard liquid bolus swallows as the clinical significance of spontaneous synchronous contractions or isolated premature/synchronous contractions with dry swallows is unknown. There is no recent literature on this topic.

It is not uncommon when interpreting manometry in patient who have a diagnosis of one of the hypercontractile disorders to see spontaneous contractions of the lower esophagus and the significance of these is unclear. Observing this phenomenon might require extra test such as provocative test (eg, viscous or solid swallows, MRS or RDC) to bring out an abnormality that might not be appreciated on water swallows.

4 | CONCLUSION

According to the version 4.0 of the Chicago Classification, the diagnosis of distal esophageal DES requires both relevant esophageal symptoms (dysphagia, non-cardiac chest pain) and manometric pattern of at least 20% premature contraction in a context of normal EGJ relaxation. Caution is made to localize accurately the contractile deceleration point and to differentiate contractile activity from intrabolus pressure. Some adjunctive tests as multiple rapid swallows are useful to evidence the lack of inhibition which the pathophysiologic characteristic of DES (Figure 7). Questions are raised regarding the pathophysiology of the disease and its particularity according to the clinical presentation or to manometric parameters such as DCI or LES hypercontractility. Due to its rarity, it is difficult to evaluate the response to treatment in large studies and to determine the factors associated with response. Collaborative studies are necessary to better understand this disorder and to determine the best therapeutic approach.

CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

All authors equally contributed to this work.

ORCID

Sabine Roman  <https://orcid.org/0000-0002-7798-7638>

Kee Wook Jung  <https://orcid.org/0000-0002-3771-3691>

Rena Yadlapati  <https://orcid.org/0000-0002-7872-2033>

Daniel Sifrim  <https://orcid.org/0000-0002-4894-0523>

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