Towards better understanding of symptoms associated with disordered esophageal function
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JACKHAMMER ESOPHAGUS: OBSERVATIONS ON A EUROPEAN COHORT

Thomas V.K. Herregods, André J.P.M. Smout, Joanne L.S. Ooi, Daniel Sifrim, Albert J. Bredenoord

ABSTRACT

Background
With the advent of high-resolution manometry (HRM), a new diagnosis, jackhammer esophagus, was introduced. Little is known about this rare condition, and the relationship between symptoms and hypercontractility is not always straightforward. The aim of our study was to describe a large cohort of patients with jackhammer esophagus and to investigate whether manometric findings are associated with the presence of symptoms.

Methods
All patients from 06-2014 until 12-2015 seen at two tertiary centers with at least one hypercontractile swallow (distal contractile integral (DCI)>8000 mmHg·s·cm) on HRM were analyzed. Patients with ≥20% premature swallows, or patients with another diagnosis explaining their symptoms were excluded.

Results
Of the 34 patients identified with jackhammer esophagus, most suffered from dysphagia (67.6%) and/or chest pain (47.1%). The symptom chest pain was not associated with any of the manometric findings, while dysphagia was associated with the DCI of the hypercontractile swallows and with intrabolus pressure. In addition, all patients who had an isolated DCI of the LES zone > 2000 mmHg·s·cm had dysphagia. The differences in HRM and clinical characteristics between subgroups based on the contraction type (single- or multi-peaked) or based on meeting criteria of the Chicago Classification v3.0 and v2.0 were limited.

Conclusions
The symptom dysphagia is accompanied with strong contractions of the LES, signs of a possible outflow obstruction, and a very high DCI. The presence of a multi-peaked contraction seems to be of limited relevance, and caution is warranted in labeling patients with one hypercontractile swallow as normal.
INTRODUCTION

Ever since the introduction of esophageal manometry, researchers have observed and described a group of esophageal motor abnormalities which can be denoted as hypercontractile disorders. The group comprises entities that were labelled esophageal spasm, nutcracker esophagus, hypertensive lower esophageal sphincter (LES), and, more recently, jackhammer esophagus. The esophageal hypercontractile disorders have in common that one or more measures of contractile activity exceed the upper limit of normal and that it is assumed that the abnormal motility is causally related to the symptoms of chest pain and/or dysphagia. The pathophysiology is complex and incompletely understood, but it has been suggested that esophageal spasm could be related to an impaired deglutitive inhibitory reflex and spontaneous contractions could be generated by discharges of acetylcholine independent of swallows\(^1\). Other possible causes of hypercontractility could be an increase in esophageal muscle thickness\(^2\), or temporal asynchrony between the contractions of the circular and longitudinal muscle layers\(^3\).

Esophageal manometry tests are considered to be the best diagnostic tool for the study of the motor activity of the esophagus and LES\(^4\). Originally, hypertensive motility disorders were described using conventional manometry\(^5\). The clinical relevance of the commonly used term, nutcracker esophagus, was later questioned as hypertensive peristaltic contractions were also encountered in asymptomatic patients, and could persist despite the disappearance of symptoms\(^6\). Thus, the relationship between symptoms and hypercontractility is not always that straightforward. This is supported by a study in which 24-hour ambulatory manometry did not always find an association between motility abnormalities and the symptoms\(^7\). With the advent of high-resolution manometry (HRM), a new metric was used to assess contractility, namely distal contractile integral (DCI)\(^8\). This metric takes into account the amplitude, duration and the length of the contractile segment.

In the Chicago Classification version 2.0\(^9\), the diagnosis “jackhammer esophagus” was introduced, and defined as the presence of at least one swallow (≥10% of swallows) with a DCI > 8000 mmHg·s·cm with a single-peaked or multipeaked contraction. This definition was created as this hypercontractile feature had never been seen in normal individuals. Multipeaked contractions can be synchronized with respiration or not\(^10\) and can be located in either of the distal two contractile segments and occasionally in the LES. The most frequent location of the multipeaked contraction is in the third contractile segment\(^9\). In the latest version of the Chicago Classification\(^11\), the requirement for jackhammer esophagus (synonym: hypercontractile esophagus) was modified. Henceforth ≥20% of swallows with a DCI > 8000 mmHg·s·cm are required instead of ≥10%\(^11\). Additionally, it was accepted that the hypercontractility can involve the LES and even be restricted to the LES. As in certain cases excluding the LES could result in a fail to detect the abnormality, the new version proposes to
incorporate the LES into the DCI measurement in those instances. The authors argue that the degree by which the normal LES pressure exceeds 20 mmHg will not influence the DCI significantly. It has subsequently become apparent that hypercontractile esophagus can occur along with other abnormalities such as esophagogastric junction (EGJ) outflow obstruction, gastroesophageal reflux disease (GERD), or eosinophilic esophagitis.

As little is known thus far about this newly defined condition, the aim of our study was to describe a large cohort of patients with jackhammer esophagus in detail using HRM and to investigate whether certain manometric findings are associated with the presence of symptoms.

METHODS

Patients
All patients referred to the Academic Medical Center (AMC) of Amsterdam, the Netherlands, and the Royal London Hospital in London, United Kingdom, who underwent diagnostic testing using HRM between June 2011 and December 2015, were retrospectively analyzed. All patients were required to fulfill the criteria for jackhammer esophagus of either the Chicago Classification v2.0 or v3.0, and be 18 years of age or older. Patients who had previous esophageal or gastric surgery, eosinophilic esophagitis, or who already had a diagnosis with explanation of their symptoms such as an identified mechanical obstruction, scleroderma, achalasia or distal esophageal spasm, were excluded. The presence of symptoms was assessed by retrospectively reviewing the referral letter and clinician notes. The study proposal was submitted to the local institutional review board of the Academic Medical Center in Amsterdam, the Netherlands, and formal evaluation was waived according to Dutch law.

Ambulatory pH-impedance monitoring
Twelve subjects (35.3%) underwent 24-hour esophageal pH-impedance monitoring according to routine clinical protocol off acid suppressive therapy. Patients were instructed to discontinue proton pump inhibitors for at least 7 days, and histamine-2 receptor antagonists, antacids and prokinetic agents for at least 3 days prior to the study. The catheter consisted of six impedance segments and one ion-sensitive field effect transistor pH electrode (Unisensor AG, Attikon, Switzerland) for pH monitoring. The catheter was positioned with the pH electrode 5 cm above the manometrically localized lower esophageal sphincter (LES). The impedance recording segments were located at 2-4, 4-6, 6-8, 8-10, 14-16, and 16-18 cm above the upper border of the LES. The pH and impedance signals were both stored on a digital datalogger (Ohmega, Medical Measurement Systems [MMS], Enschede, the Netherlands), using a sampling
frequency of 1 Hz and 50 Hz respectively. Patients were told to restrict their intake to 3 meals and 4 beverages at standardized times throughout the 24 hours. They were also instructed to consume their meals and drinks within 30 and 15 minutes respectively and mark these times in the diary. Furthermore, they were encouraged to maintain their normal daily activities throughout the measurement. Moreover, patients were instructed to mark the period spent in the supine position and were shown how to promptly activate the event marker button on the pH datalogger when they experienced symptoms. These symptoms were also written down in the diary.

Stationary high-resolution manometry
All patients with at least one hypercontractile swallow (DCI > 8000 mmHg·s·cm) were analyzed. If there were ≥20% premature swallows, or patients fulfilled the criteria of achalasia, they were excluded. In all subjects stationary esophageal HRM studies were performed using a solid-state HRM system (Given Imaging, Yoqneam, Israel). The solid-state HRM catheter comprised 36 pressure channels spaced at 1-cm intervals. Prior to the study, subjects had fasted for 4 hours. The HRM catheter was placed transnasally and positioned to record from the hypopharynx to the stomach. Following this, patients were placed in the supine position and were asked to perform a series of 10 swallows of 5 mL of water. Subsequently, patients were asked not to swallow during 30 seconds, allowing a landmark recording to place the anatomical markers during analysis. The HRM signals were recorded using a sampling frequency of 37 Hz, and the pressure tracings were calibrated at 0 and 300 mmHg before the onset of the measurement.

Data analysis
HRM analyses were performed according to a previously described method\textsuperscript{12}. The DCI was measured by multiplying the amplitude, duration and length of the distal esophageal contraction exceeding 20 mmHg. In instances of a possible hypercontractile swallow, the DCI was not only measured from the transition zone to the proximal margin of the LES (DCI\textsubscript{+LES}), but an additional measurement was performed in which the DCI box included the LES (DCI\textsubscript{-LES}). Both values were noted if one of the values exceeded 8000 mmHg·s·cm. Furthermore, for each of these hypercontractile swallows, additional measurements were done. The maximum DCI was measured with and without inclusion of the LES (maximum DCI\textsubscript{+LES} and maximum DCI\textsubscript{-LES} respectively). Moreover, the DCI of the LES zone was calculated (DCI LES zone). The extent of the DCI box included the entire hypercontractile segment. Additionally, the maximum amplitude was measured at 3, 5 and 7 cm above the LES for all hypercontractile contractions. For the measurement of the location of highest amplitude, if two locations were equally present, then the location with highest overall amplitude was chosen. Moreover, if the pressure in the LES was above 100
mmHg, the LES was noted to participate in the esophageal contraction. Multiple-peaked contractions were defined according to previous criteria\textsuperscript{10,13}; i) at least 2 peaks are present, ii) pressure trough between the peaks is greater than zero, iii) the peak of least amplitude is at least 10 mmHg greater than the inter-peak trough, and iv) the pressure peaks are separated by at least one second. Additionally, the synchrony of the pressure peaks with respiration was evaluated. A multiple-peaked contraction was considered to be synchronous with respiration if the pressure troughs occurred during inspiration (identified by diaphragmatic contraction and/or an increase of the abdominal pressure corresponding with a decrease of the intra-esophageal pressure). If in a patient there were an equal number of multiple-peaked and single-peaked contractions, then this was considered to be single-peaked. Moreover, if there was an equal number of synchronous and asynchronous multiple-peaked contractions, then this was deemed to be asynchronous.

GERD was defined as a percentage acid exposure time >6% on 24-hour pH-impedance measurement and/or the presence of esophagitis on gastroscopy. Hypersensitive esophagus was defined as a normal acid exposure time (<6% total time with a pH<4) and a positive symptom-reflux association (symptom index (SI) ≥50\textsuperscript{14} and/or symptom association probability (SAP) ≥95\textsuperscript{15}). Esophagitis was classified using the LA Classification\textsuperscript{16}.

\textbf{Statistical analysis}
Statistical analyses were performed using SPSS version 23 (SPSS, Inc, Chicago, IL, USA). HRM metrics are expressed as median (interquartile range). The correlations between the different metrics were tested using the Spearman's Rank correlation. Categorical variables were described using frequencies and percentages. Associations between the symptoms and HRM metrics were tested using logistic regression. The Kruskal-Wallis test was used to compare the three different multiple-peaked groups. When comparing two groups, the Mann-Whitney U-test was used. The Fisher's exact test was used to compare the patients who did not meet the Chicago Classification v3.0 criteria to the patients who did meet the criteria. We considered p<0.05 statistically significant.

\textbf{RESULTS}

\textbf{Study patients}
Thirty-four patients (19 females, median age 57) were included in the study of which 14 patients were included in the Royal London Hospital. All patients underwent a HRM measurement. Thirty-three patients (97.1%) met the jackhammer esophagus criteria for the Chicago Classification v2.0 (CC v2.0), while 27 patients (79.4%) met the criteria for the Chicago Classification v3.0 (CC v3.0). None of the patients had a history of previous esophageal or gastric surgery. The main patient characteristics are presented
in Table 1. Most patients suffered from dysphagia (67.6%) and/or chest pain (47.1%). The majority of the patients (73.5%) had more than one symptom, and 6 patients (17.6%) had neither chest pain nor dysphagia. At upper endoscopy, reflux esophagitis was found in 2 patients (5.8%), one of whom had Los Angeles grade D esophagitis and the other Los Angeles grade A. The latter patient also had a pathological acid exposure time on pH-impedance measurement. The patient with Los Angeles grade D esophagitis had a repeat endoscopy which showed no signs of esophagitis and a barium swallow which was normal. The HRM was done after these investigations. Twelve of the patients underwent a 24-hour pH-impedance measurement and in 18 patients a barium swallow was performed. Seven patients (20.6%) ended up with a concomitant diagnosis of esophagogastric junction (EGJ) outflow obstruction. Two patients (5.9%) had an additional diagnosis of GERD while four (11.8%) had an additional diagnosis of hypersensitive esophagus.

**High-resolution manometry characteristics**

The various HRM parameters are summarized in Table 2, while Table 3 summarizes the HRM parameters of the hypercontractile swallows. In 22 patients (64.7%) the LES participated in the hypercontractile swallows. Figure 1a illustrates a hypercontractile swallow in which the LES is not involved while Figure 1b shows a hypercontractile

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total patients</th>
<th>Median age (years)</th>
<th>Female gender</th>
<th>Symptoms</th>
<th>24-hour pH-impedance measurement</th>
<th>Barium swallow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>34</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median age (years)</td>
<td>57</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td>19 (55.9%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
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<tr>
<td>Dysphagia</td>
<td>23 (67.6%)</td>
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<td></td>
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</tr>
<tr>
<td>Chest pain</td>
<td>16 (47.1%)</td>
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<tr>
<td>Heartburn</td>
<td>14 (41.2%)</td>
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<tr>
<td>Regurgitation</td>
<td>12 (35.3%)</td>
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<tr>
<td>Globus</td>
<td>5 (14.7%)</td>
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<tr>
<td>Belching</td>
<td>3 (8.8%)</td>
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<tr>
<td>Vomiting</td>
<td>2 (5.9%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-hour pH-impedance measurement</td>
<td>12 (35.3%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>7 (58.3%)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>GERD</td>
<td>1 (8.3%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hypersensitive esophagus</td>
<td>4 (33.3%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Barium swallow</td>
<td>18 (52.9%)</td>
<td></td>
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</tr>
<tr>
<td>Normal</td>
<td>8 (44.4%)</td>
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</tr>
<tr>
<td>Tertiary contractions</td>
<td>4 (22.2%)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Stasis of contrast</td>
<td>4 (22.2%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diverticula</td>
<td>2 (11.1%)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
swallow in which the LES is involved. The highest DCI measured when including the LES was 70996 mmHg·s·cm, while this was 59438 mmHg·s·cm when excluding the LES. In the hypercontractile swallows, the location of the highest amplitude was 3 cm above the LES in 16 patients (47.1%), 5 cm above the LES in 14 patients (41.2%) and 7 cm above the LES in 4 patients (11.8%).
We found that the DCI did not correlate significantly with the integrated relaxation pressure (IRP) of all wet swallows ($r=0.281$, $p=0.107$), yet it did correlate with the IRP of the hypercontractile swallows ($r=0.344$, $p=0.046$) and with the intrabolus pressure (IBP) ($r=0.389$, $p=0.023$). In addition, the DCI of the LES zone correlated significantly with the IRP ($r=0.523$, $p=0.002$) and with the IBP ($r=0.637$, $p<0.001$). The IRP also correlated with the IBP ($r=0.718$, $p<0.001$). The presence of a hiatus hernia also correlated significantly with the IRP ($p=0.038$).

**Symptom characteristics**

The presence of the symptom chest pain was not associated with a specific location of peak amplitude, with DCI or with the number of swallows with a DCI > 8000 mmHg·s·cm. However, a trend was found towards an association between the presence of dysphagia and the DCI ($B=0.0003$, $p=0.065$). Interestingly, all patients who had an isolated DCI of the LES zone > 2000 mmHg·s·cm had dysphagia. In addition, the presence of dysphagia showed a trend towards an association with the DCI of the LES zone ($B=0.001$, $p=0.070$). A significant association was found between dysphagia and the DCI of the hypercontractile swallows ($B=0.001$, $p=0.019$) and then with the DCI of the hypercontractile swallows. In addition, dysphagia was significantly associated with the IBP ($B=0.342$, $p=0.018$), but not with the IRP ($B=0.079$, $p=0.180$). Absence of both the symptom chest pain and dysphagia (observed in 6 patients) was not associated with any of the manometric findings. Therefore, no association was found

![Figure 1](image.png)

*Figure 1.* Figure 1a illustrates a hypercontractile swallow in which the LES is not involved while Figure 1b shows a hypercontractile swallow in which the LES is involved. The red box is used to measure the DCI of the LES zone (DCI LES Zone). The area consisting of both the red and green box is used to measure the DCI +LES.
between the absence of both symptoms and the DCI (B=0.0002, p=0.296), DCI of
the LES zone (B=0.0004, p=0.311), or with the IRP (B=0.044, p=0.502).

**Single- versus multi-peaked contractions**

Figure 2 illustrates the three patterns of hypercontractile swallows: multi-peaked synchronous with respiration, multi-peaked asynchronous with respiration and single-peaked. These were present in 15 (44.1%), 15 (44.1%), and 4 patients (11.8%), respectively. Table 4 shows the HRM characteristics for the different subgroups. We found that the subgroups do not differ in most of the HRM characteristics. The only significant difference is that patients with multi-peaked synchronous contractions tend to have a higher DCI (p=0.024) and a higher maximum DCI_{LES} (p=0.04) when compared with patients with multi-peaked asynchronous contractions. A hiatus hernia was not more often present in a specific subgroup. No significant differences were found in clinical characteristics (age and symptoms) between the different subgroups.

**Chicago Classification v3.0 vs Chicago Classification v2.0**

Seven patients (20.6%) did not meet the criteria for the CC v3.0. Of the patients who did meet the criteria, five (14.7%) would not have met the criteria if the LES was not included in the measurement of the DCI. Table 5 compares the HRM characteristics of the patients not fulfilling the CC v3.0 criteria to the patients who do fulfill the criteria. As can be expected, the patients who met the criteria had a significantly higher DCI.

![Figure 2](image_url)

**Figure 2.** Illustrates the three patterns of hypercontractile swallows: multi-peaked synchronous with respiration (a), multi-peaked asynchronous with respiration (b) and not-multi-peaked (c). The white arrows indicate moments of inspiration while the black arrows indicate the pressure troughs.
### Table 4. High-resolution manometry parameters for the three patterns of hypercontractile swallows: multipeaked synchronous with respiration, multipeaked asynchronous with respiration and not-multipeaked.

<table>
<thead>
<tr>
<th></th>
<th>Multipeaked synchronized with respiration (n=15)</th>
<th>Multipeaked not synchronized with respiration (n=15)</th>
<th>Not multipeaked (n=4)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRP (mmHg)</td>
<td>12.2 (9.1-16.4)</td>
<td>10.9 (3.7-13.7)</td>
<td>13.7 (7.4-29.9)</td>
<td>0.297</td>
</tr>
<tr>
<td>DCI (mmHg·s·cm)</td>
<td>7309 (5639-11219)*</td>
<td>5583 (3582-6703)*</td>
<td>5995 (4782-22794)</td>
<td>0.074</td>
</tr>
<tr>
<td>CFV (cm/s)</td>
<td>3.9 (3.3-5.6)</td>
<td>4.6 (3.2-5.5)</td>
<td>3.8 (2.9-5.7)</td>
<td>0.752</td>
</tr>
<tr>
<td>DL (s)</td>
<td>6.8 (5.9-7.2)</td>
<td>6.2 (5.4-7.5)</td>
<td>6.7 (5.2-7.0)</td>
<td>0.837</td>
</tr>
<tr>
<td>IBP (mmHg)</td>
<td>4.7 (2-8.1)</td>
<td>4.3 (0.6-7)</td>
<td>7.5 (2.5-20.5)</td>
<td>0.498</td>
</tr>
<tr>
<td>DCI LES zone (mmHg·s·cm)</td>
<td>1916 (1326-2740)</td>
<td>963 (609-2718)</td>
<td>1276 (290-7085)</td>
<td>0.532</td>
</tr>
<tr>
<td>Maximum DCI LES (mmHg·s·cm)</td>
<td>16489 (14019-29674)*</td>
<td>11645 (9817-14225)*</td>
<td>11725 (10660-56244)</td>
<td>0.133</td>
</tr>
<tr>
<td>Maximum DCI +LES (mmHg·s·cm)</td>
<td>16237 (12160-28609)</td>
<td>10556 (8806-13416)</td>
<td>10787 (9234-47519)</td>
<td>0.157</td>
</tr>
</tbody>
</table>

Data are presented as median (IQR). The Kruskal-Wallis test was used to compare the different subgroups and the p-value is shown. LES, lower esophageal sphincter; CFV, contractile front velocity; DCI, distal contractile integral; DL, distal latency; IRP, integrated 4-s relaxation pressure; IBP, intrabolus pressure. * p < 0.05 for the comparison between the multipeaked synchronized with respiration and the multipeaked not synchronized with respiration.

### Table 5. Comparison of the HRM characteristics of the patients not fulfilling the Chicago Classification v3.0 criteria to the patients who do fulfill the criteria

<table>
<thead>
<tr>
<th></th>
<th>Patients not fulfilling the CC v3.0 criteria (n=7)</th>
<th>Patients fulfilling the CC v3.0 criteria (n=27)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRP (mmHg)</td>
<td>3.7 (0.2-13.8)</td>
<td>12.5 (9.1-14.9)</td>
<td>0.073</td>
</tr>
<tr>
<td>DCI (mmHg·s·cm)</td>
<td>3582 (3450-4704)</td>
<td>7214 (5639-10245)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CFV (cm/s)</td>
<td>5.3 (4.4-6.2)</td>
<td>3.9 (3.2-5.3)</td>
<td>0.136</td>
</tr>
<tr>
<td>DL (s)</td>
<td>5.8 (5.4-6.9)</td>
<td>6.6 (5.9-7.2)</td>
<td>0.107</td>
</tr>
<tr>
<td>IBP (mmHg)</td>
<td>0 (0-5.4)</td>
<td>4.8 (2.0-8.1)</td>
<td>0.100</td>
</tr>
<tr>
<td>DCI LES zone (mmHg·s·cm)</td>
<td>646 (129-3205)</td>
<td>1841 (792-2718)</td>
<td>0.131</td>
</tr>
<tr>
<td>Maximum DCI +LES (mmHg·s·cm)</td>
<td>11639 (8926-12610)</td>
<td>14290 (11273-25112)</td>
<td>0.018</td>
</tr>
<tr>
<td>Maximum DCI -LES (mmHg·s·cm)</td>
<td>8806 (8432-11763)</td>
<td>12575 (9811-22221)</td>
<td>0.020</td>
</tr>
</tbody>
</table>

Data are expressed as median (IQR). LES, lower esophageal sphincter; CFV, contractile front velocity; DCI, distal contractile integral; DL, distal latency; IRP, integrated 4-s relaxation pressure; IBP, intrabolus pressure.
In addition, a trend was found towards a higher IRP in patients who fulfill the criteria compared to those who do not \((p=0.073)\). No significant differences were found in clinical characteristics between both groups.

## DISCUSSION

The major objective of this study was to characterize a large cohort of patients with jackhammer esophagus and to investigate the manometric findings in detail. Jackhammer esophagus is a rare diagnosis, and its clinical presentation is diverse. In our study, dysphagia was the most frequent symptom which was present in 67.6% of the patients, followed by chest pain in 47.1%. In contrast to what was expected, we found no association between the symptom chest pain and any of the manometric findings. In particular, a high DCI is not more likely to result in chest pain in this patient population. In addition, the location of peak amplitude did not influence the presence of chest pain. The lack of association between any of the manometric findings and the symptom chest pain suggests that chest pain is not clearly linked to the finding of jackhammer esophagus, which in turn could explain why some patients do not respond to treatment such as nitrates and calcium channel blocker. Another potential explanation is that chest pain could be the result of other factors such as ischemia\(^{17}\) or an increased muscle thickness which is not visualized using HRM.

Our results do show an association between dysphagia and the DCI of the hypercontractile swallows. This association was also found when looking at the DCI in which the LES is excluded, suggesting that the association is not the result of a hypercontractile LES. This suggests that despite the normal distal latency seen in these patients, the very high-DCI swallows might not result in the proper clearance of the esophagus or that the high-amplitude contraction itself results in a sensation of incomplete passage. Indeed, the relationship between bolus passage and contractility is poor\(^{18}\). Another possibility is that the high contractility is secondary and necessary to overcome an outflow obstruction. Previously it has already been suggested that hypercontractility could be caused by EGJ obstruction\(^{10}\). In the opossum, experimental EGJ obstruction resulted in smooth muscle hypertrophy and excitability\(^{19}\). Similarly, in a study in which in humans the laparoscopic gastric band was overfilled by 20%, representing a model of EGJ obstruction, an increased proportion of hypertensive and repetitive contractions was found\(^{20}\). Furthermore, another study suggested that patients with EGJ outflow obstruction might exhibit a spastic motor pattern with multi-peaked high-amplitude contractions, and a prolonged contraction duration\(^{21}\). The resulting theory is that the lack of LES relaxation causes an obstruction to the flow through the EGJ, increasing the intrabolus pressure and resulting in hypercontractility. In our study we found that the DCI correlated with the IRP of the hypercontractile swallows and with the IBP, supporting the idea that an outflow obstruction or a lack of LES relaxation results in hypercontractility. Therefore, in this subset of patients
it could be beneficial to start with the treatment of the underlying EGJ outflow obstruction rather than attempting to treat the hypercontractility with e.g. calcium channel antagonists or nitrates. Prior to the treatment of the EGJ outflow obstruction a barium swallow can be considered.

IRP is a metric for the relaxation of the LES, and therefore one can expect that a high IRP would result in complaints of dysphagia as the LES does not relax as much, possibly resulting in an outflow obstruction. Interestingly, dysphagia was not associated with the IRP but it was significantly associated with the IBP. Our study suggests that IBP, which is also a manometric measure of outflow obstruction, could be a better marker to explain the presence of dysphagia in jackhammer patients. An impaired relaxation of the LES does not necessarily mean that there is an outflow obstruction. It is understandable that an outflow obstruction which results in an increased IBP is more likely to give a sensation of dysphagia than an outflow obstruction which does not result in an increased IBP. Additionally, all patients with a DCI of the LES zone exceeding 2000 mmHg·s·cm had dysphagia and a trend was found towards an association between the DCI of the LES zone and the presence of dysphagia. This supports the decision made in the CC v3.0 to incorporate the LES zone into the DCI measurement in instances in which the LES seems to be involved. Not only is this important as LES involvement results in more frequent dysphagia complaints, but 14.7% of the patients would not have met the criteria for the CC v3.0 if the LES was not included in the measurement of the DCI. Including a provocation with a meal stimulus during the manometry could be interesting in this patient population in the future.

In CC v3.0, the requirement for jackhammer esophagus was modified from ≥10% of swallows with a DCI > 8000 mmHg·s·cm to ≥20% of swallows with a DCI > 8000 mmHg·s·cm. The reason for this change in definition was that control subjects occasionally met the previous criterion and therefore this was deemed of uncertain relevance. In our study we found that the patients who met the previous criteria but not the new criteria did not differ in clinical characteristics to those who did meet the CC v3.0. We found that the DCI was significantly lower in the patients who did not fulfill the CC v3.0 criteria, which can be expected as only one swallow had a DCI > 8000 mmHg·s·cm. The other HRM parameters did not change significantly, yet a trend was found towards a lower IRP and IBP in the patients not meeting the criteria. As mentioned earlier, a higher IBP was associated with the symptom dysphagia. Therefore, the diagnosis of jackhammer esophagus is more likely to be significant in the patients who fulfill the CC v3.0 criteria. However, the finding of one swallow with a DCI > 8000 mmHg·s·cm remains rare in healthy controls. Since these groups are very similar in both clinical characteristics and in HRM metrics, caution is warranted in labeling patients with one swallow with a DCI > 8000 mmHg·s·cm as normal. A possible link between this finding and symptoms such as chest pain and dysphagia should be considered, definitely in the presence of a high IBP. Future studies should
investigate whether these hypercontractile contractions persist despite symptoms being relieved.

As mentioned previously, in a subset of these patients there is a concomitant diagnosis of EGJ outflow obstruction\textsuperscript{11}. Since these patients also exhibit some nearly normal peristaltic contractions, they are not labelled as type III achalasia. However, a possible therapeutic approach could be to reduce the underlying EGJ obstruction. In addition to EGJ outflow obstruction, which was present in 20.6\% of our patients, previous studies have also found an association with GERD\textsuperscript{11}. In our cohort, a concomitant diagnosis of GERD and hypersensitive esophagus were found in 5.9\% and 11.8\% of the patients, respectively. A previous study found that anti-reflux therapy resulted in the resolution of symptoms in approximately half of the patients in whom a concomitant diagnosis of GERD was made\textsuperscript{10}. It is important to note that the clinical relevance of this is uncertain as it is unclear whether the treatment of reflux results in the alleviation of the hypercontractile swallows, and whether symptoms would have subsided without treatment. Other treatment options for jackhammer esophagus include calcium channel antagonists\textsuperscript{22}, nitrates\textsuperscript{22}, botulinum toxin injection\textsuperscript{23}, pneumatic esophageal dilatation\textsuperscript{24} and peroral endoscopic myotomy (POEM)\textsuperscript{25}.

The relevance of multipeaked contractions has previously been studied in jackhammer patients\textsuperscript{10}. In a study by Sampath et al.\textsuperscript{26} the importance of these multipeaked contractions was questioned as the authors believed multipeaked contractions could be the result of respiration as the distal esophagus and diaphragm are attached at the EGJ and therefore move in unison during respiration. This movement relative to the sensor recording the contraction could give the appearance of a multipeaked pattern. As in the study by Roman \textit{et al.}\textsuperscript{10}, 88.2\% of our patients with jackhammer esophagus had multipeaked contractions, of which half were synchronized with respiration. We also found that most of the HRM characteristics were not dependent on the presence of respiratory synchronization or multipeak contractility. The only significant difference we found was that multipeaked synchronous contractions tended to have a higher DCI and a higher maximum DCI\textsubscript{+LES} in comparison to the multipeaked asynchronous contractions. Due to the lack of substantial differences between the subgroups, this distinction seems to be of limited relevance.

We acknowledge that no standardized and/or validated questionnaires were used to analyze the presence of symptoms. Instead the presence of symptoms was based on reviewing the referral letter and clinician notes, which is a limitation of the study. However, in both centers involved in this study, an esophageal HRM is not performed without a good referral letter and most patients were referred from within the two centers. As a result, we are confident that the data on presence or absence of chest pain and dysphagia is reliable, despite the non-use of symptom questionnaires.

In conclusion, we described a large cohort of patients with jackhammer esophagus. These patients usually present with dysphagia or chest pain. While chest pain was
not associated with any manometric findings, dysphagia is associated with strong contractions of the LES, signs of a possible outflow obstruction, and a very high DCI. EGJ outflow obstruction could be a possible mechanism resulting in secondary jackhammer esophagus in a subset of the patients. The presence of a multipeaked contraction seems to be of limited relevance, and caution is warranted in labeling patients with one swallow with a DCI > 8000 mmHg·s·cm as normal. Future studies should investigate whether hypercontractile contractions persist despite the alleviation of symptoms, and what the best treatment options are.
REFERENCES


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