Prospective Controlled Study of Endoscopic Botulinum Toxin Injection for Retrograde Cricopharyngeus Dysfunction: The Inability to Belch Syndrome

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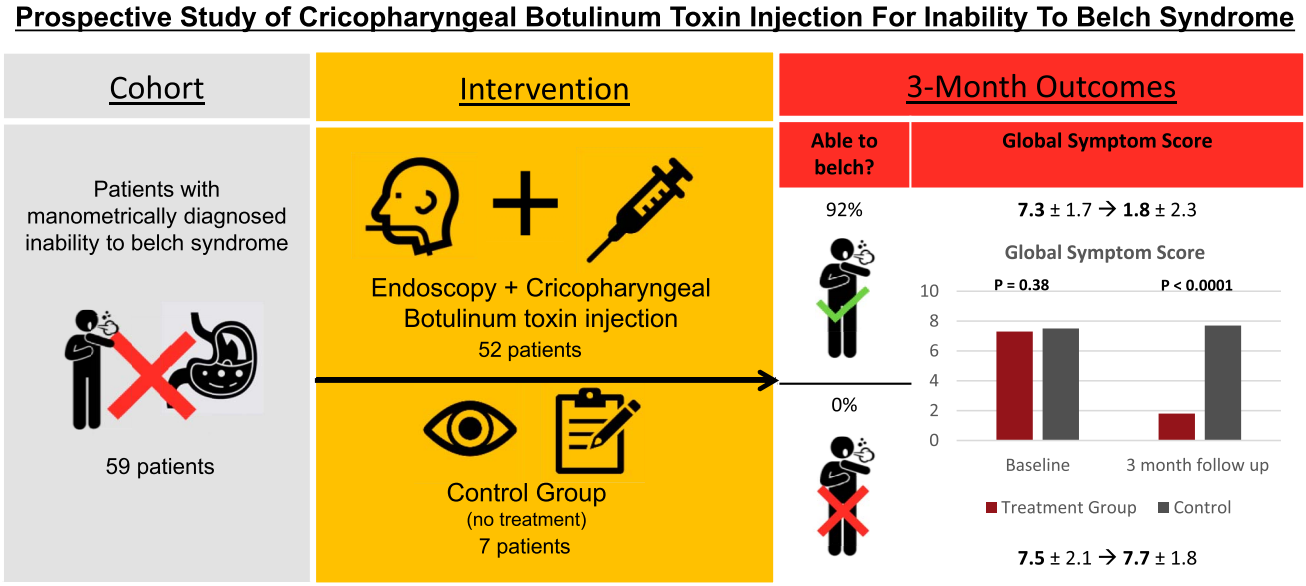
INTRODUCTION: **Complete inability to belch due to retrograde cricopharyngeus dysfunction (R-CPD) may lead to chronic gas-related gastrointestinal complaints. We aimed to validate high-resolution manometric (HRM) diagnostic criteria and prospectively evaluate the feasibility and efficacy of cricopharyngeal botulinum toxin injection (CBTI) by flexible endoscopy.**

METHODS: **Consecutive manometrically diagnosed patients with R-CPD were included. Asymptomatic volunteers were also included for diagnostic validation. Patients with R-CPD underwent CBTI (treatment group) or deferred/declined treatment (control group). Outcomes included ability to belch, clinical symptoms, and quality of life measured using self-report questionnaires.**



Flexible endoscopic cricopharyngeal Botulinum toxin injection is highly effective for symptomatic relief of the inability to belch syndrome, compared with no treatment.

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RESULTS: **Sixty-five subjects were included (52 treatment group, 7 controls, and 6 asymptomatic volunteers). All patients with R-CPD had inability to belch since childhood. During HRM with carbonated drink provocative testing, all R-CPD patients demonstrated characteristic esophageal pressurization patterns associated with failure of upper esophageal sphincter relaxation; these findings were never seen in asymptomatic volunteers. At 3 months, 92% patients who received CBTI were able to belch (compared with 0 controls; $P < 0.001$) and experienced improved clinical symptoms (global symptom score improved from 7.3 ± 1.7 to 1.8 ± 2.3, whereas in controls was static 7.5 ± 2.1 to 7.7 ± 1.8; $P < 0.0001$ for comparison). Quality of life significantly improved in the treatment group but not controls ($P = 0.0002$). At 3 months, 43/51 (84%) of the treatment group reported being satisfied or very satisfied with therapeutic outcome.**

DISCUSSION: **HRM with carbonated drink provocation demonstrates pathognomonic signs of R-CPD that were not seen in health. Flexible endoscopic CBTI is highly effective for symptomatic relief compared with no treatment.**

KEYWORDS: no burp syndrome; high-resolution esophageal manometry; cricopharyngeal Botox; upper esophageal sphincter dysfunction; belch reflex

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/D489

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INTRODUCTION

Dysfunction of the belch reflex was first demonstrated by Kahrilas et al (1) in 1987 by manometric and fluoroscopic means. This was described in a patient with complete inability to belch and associated incapacitating chest pain and other symptoms purported to be due to excessive retention of gas within the gastrointestinal tract. Nevertheless, this condition received little attention until a 2019 report by laryngologists, Bastian and Smithson, describing 51 cases diagnosed syndromically and treated with botulinum toxin injection to the cricopharyngeus (CBTI), with a high rate of symptomatic relief (2). Since then, a few other retrospective case series have been published in the ear, nose, and throat literature, all appearing to confirm high therapeutic efficacy from CBTI performed by laryngologists, either using rigid laryngoscopes or by percutaneous approach (3–5).

Yet, several unanswered questions remain regarding this condition, now most referred to as retrograde cricopharyngeus dysfunction (R-CPD; also retrograde upper esophageal sphincter dysfunction or the inability to belch syndrome). The clinical significance of an inability to belch has not yet been established. There is still no agreed upon diagnostic test or criteria, which is essential given that many of the classical symptoms (e.g., non-cardiac chest pain, bloating, distension, gurgling noises, and flatulence) are common and nonspecific. Prospective treatment data would be essential to establish the role of botulinum toxin in treating R-CPD more definitively. Furthermore, it would be interesting to know whether CBTI could be performed by flexible endoscopy.

Therefore, the aims of this study were as follows. First, we sought to quantify the symptom burden and detrimental effect on quality of life in patients with R-CPD. Second, we endeavored to validate a simple diagnostic protocol that could be performed in any center currently performing esophageal high-resolution manometry (HRM). Third, we aimed to provide prospective data on the technical feasibility, safety, and efficacy of CBTI by flexible endoscopy. We hypothesized that endoscopic CBTI would be more effective than no treatment in resolving the symptoms of R-CPD.

METHODS

Study design

A prospective cohort study was performed. Consecutive symptomatic patients from an esophageal referral center who had HRM findings consistent with R-CPD were included. All included patients were offered endoscopic CBTI. After explanation of expected benefits and risks, those who elected to proceed with CBTI formed the treatment group, whereas those who either declined or deferred therapy remained untreated and formed the control group. Aside from CBTI, treatment and control groups did not receive any other treatment changes during the study period. All patients were planned for 3 months of follow-up which was performed through telemedicine as many patients had traveled long distances to our center. Self-report questionnaires were completed through online link. Concurrently, we also included a cohort of normal belchers who were able to belch normally but had HRM performed for unrelated reasons, solely for the diagnostic validation portion of the study. Given the paucity of previous data, no sample size calculations were possible, and we arbitrarily aimed to include at least 50 patients with R-CPD undergoing treatment over a 12 month period. All subjects provided informed consent for their involvement in the study, and approval was obtained from the institutional Human Research Ethics Committee (2023/ETH01024).

Esophageal HRM protocol

We used a diagnostic protocol adapted and simplified from that described by Oude Nijhuis et al. (6) HRM was performed using a solid-state 36-channel system (Manoscan Eso Z, Medtronic). All testing was performed in the upright, seated position as per the Chicago Classification version 4.0 and our previously published standards (7). Initially, ten 5 mL saline swallows were administered. This was followed by a solid test meal consisting of 200 g of steamed white rice. Finally, all subjects underwent a carbonated drink provocative test, whereby the subject was instructed to drink a carbonated beverage through a straw at whatever pace they were able to, until characteristic manometric findings were

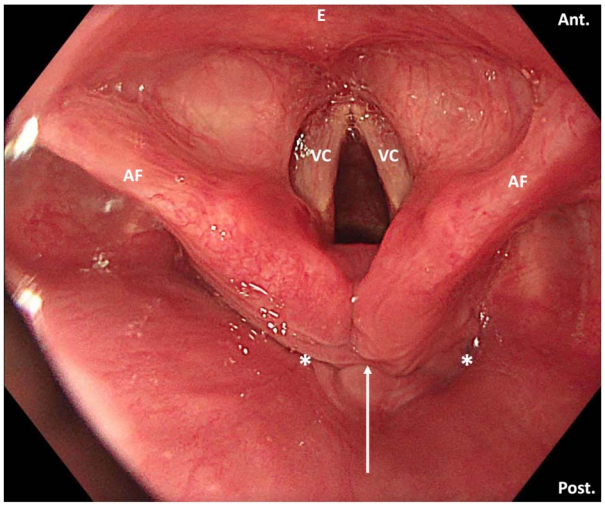

Figure 1. Endoscopic view of larynx and hypopharynx. Upon advancing the endoscope to the apex of the left pyriform fossa (*) a clockwise torque maneuver with further advancement will typically permit passage through the relatively tight and collapsed postcricoid region (direction indicated by white arrow) and subsequently into the cervical esophagus. The opposite equally applies when approaching through the right pyriform fossa. Using a distal attachment cap to aid visualization in the postcricoid region, injections were targeted to the posterior wall of this space, where the belly of the cricopharyngeus muscle lies. AF, aryepiglottic folds; E, epiglottis; VC, vocal cords.

seen or 375 mL ingested. To ensure standardization of carbonation, Coca Cola Zero Sugar cans were consistently used.

Questionnaires

Global R-CPD symptom score. We devised a 7-item self-report inventory aiming to capture the breadth and severity of symptoms experienced by patients with R-CPD in the preceding 7 days (see Supplementary Materials, http://links.lww.com/AJG/D489). The questionnaire includes items addressing common symptoms of the condition reported in the literature to date (inability to belch, bloating, noncardiac chest pain, and flatulence), impact on regular daily activities, and extent of mitigating dietary measures being undertaken. Scoring is scaled 0–10, with higher scores reflecting a greater symptom burden.

Functional digestive disorders quality of life. The Functional Digestive Disorders Quality of Life Questionnaire (FDDQL) is a demonstrably valid and reliable scale used to assess various aspects of life impacted in functional gastrointestinal disorders. It assesses daily activities, discomfort, sleep, diet, anxiety, coping with disease, perceived control over disease, and impact of stress using self-reported Likert scales. The cumulative score has a transformed range of 0–100, with higher scores representing better quality of life (8,9).

Overall satisfaction with therapy. Of those who underwent CBTI, overall satisfaction with the treatment regime was assessed at 3 months by the 5-point self-report Likert scale (1–5; very dissatisfied, dissatisfied, neither dissatisfied or satisfied, satisfied, and very satisfied respectively).

Flexible endoscopic CBTI

Upper gastrointestinal endoscopy was performed using a standard adult endoscope (Olympus GIF-HQ190) with a transparent distal cap attachment. In all cases, the procedure was performed under conscious sedation (propofol only) without endotracheal intubation but under the supervision of an anesthetist. Botulinum toxin type A (100 IU Botox; Allergan, North Sydney, Australia) was prepared in 2 mL of saline. Under direct endoscopic vision in the postcricoid region, several injections of 0.25–0.5 mL of the solution were targeted to the belly of the cricopharyngeus muscle (Figure 1). A total of 1.5–2.0 mL of solution was injected in all subjects (i.e., 75–100 IU of Botox).

Analysis and outcomes

Wilcoxon rank sum test or *t* test was used as appropriate to compare continuous variables. Fisher exact test was used to analyze categorical variables. Relationship between change in global

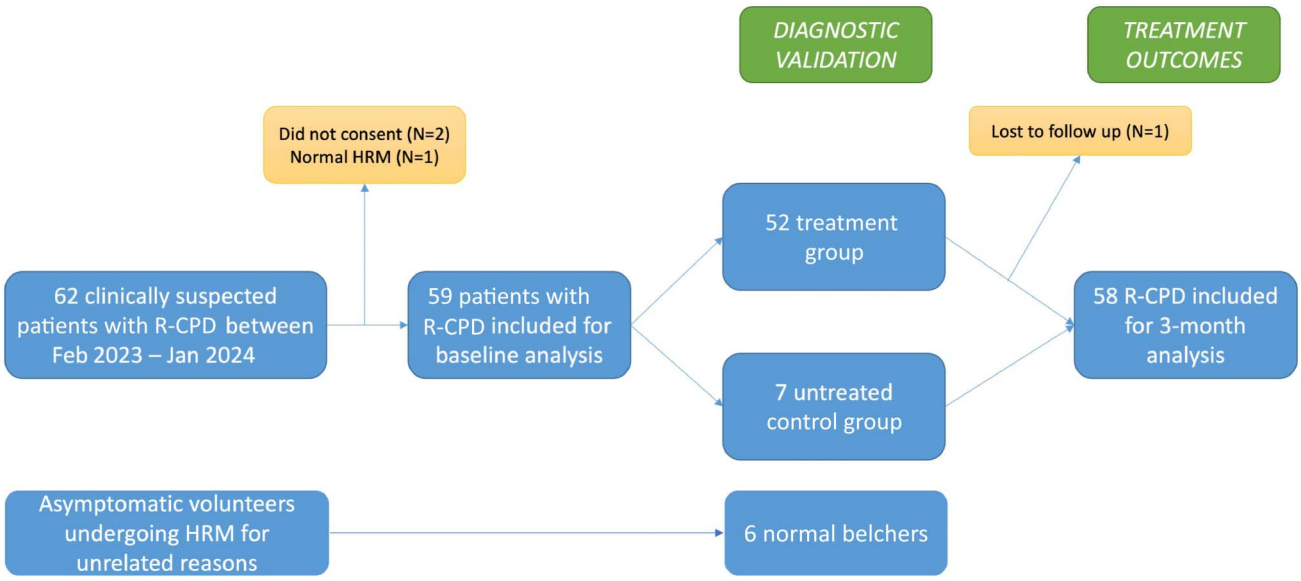

Figure 2. Study flow. HRM, high-resolution manometry; R-CPD, retrograde cricopharyngeus dysfunction.

Table 1. Symptom profile of patients with retrograde cricopharyngeus dysfunction (N = 59)

Symptom	Number affected (%)
Lifelong inability to belch	59 (100%)
Abdominal bloating	59 (100%)
Flatulence	58 (98%)
Gurgling sounds	57 (97%)
Noncardiac chest pain or discomfort	53 (90%)
Heartburn	18 (31%)
Regurgitation	14 (24%)
Dysphagia	6 (10%)

R-CPD symptom score and FDDQL was analyzed by Spearman correlation. Statistical analysis was performed using Graphpad Prism version 10. The primary outcome was the ability to belch at 3 month follow-up. Secondary outcomes included global symptom score, FDDQL, overall satisfaction with therapy, motor findings during HRM, technical success of injection, and adverse effects.

RESULTS

Baseline characteristics

Of the 62 subjects evaluated for R-CPD from February 2023 to January 2024, 59 were included based on HRM findings compatible with R-CPD (52 treatment group, 7 controls), whereas one had nondiagnostic HRM findings and 2 did not consent (Figure 2). Six normal belchers were also included. Therefore, in total 65 subjects were included in the study.

Patients with R-CPD had a median age of 30 years (interquartile range [IQR] 24.5–39.5), and 42 (71%) were female. All but 1 patient were self-referred after reading about R-CPD online and believing their symptoms to be compatible. The cohort included patients from all continental states and territories of Australia and Tasmania. Symptomatically, all 59 patients described a lifelong inability to belch. Incidence of other common symptoms is provided in Table 1. A slight majority, 30 (51%) had been empirically treated with proton pump inhibitors previously, although this was universally ineffective in absolving their complaints.

Normal belchers comprised 6 adults (median age 38.5 years, 50% female) who all confirmed they belched regularly without difficulty. Reasons for undergoing esophageal studies were suspected gastroesophageal reflux disease (N = 4), suspected laryngopharyngeal reflux (N = 1), or for screening purposes (N = 1). However, only 1 normal belcher (17%) had pathological reflux confirmed on subsequent ambulatory reflux study.

At baseline, the mean global symptom score in patients with R-CPD was 7.3 ± 1.7 (of a maximum score of 10). The mean FDDQL was 38.7 ± 17.6 (of a maximum of 100). For both scores, there was no significant difference between the treatment group and controls ($P = 0.38$ and 0.32 respectively; Figure 3).

Diagnostic validation: esophageal HRM

Carbonated drink provocative test. All subjects underwent the carbonated drink provocative test during HRM. In all R-CPD cases, the patient's typical symptoms could be reproduced. In association with symptoms, in all cases a characteristic manometric pattern was present. We observed repeated gastroesophageal gas reflux events always related to a transient lower esophageal sphincter relaxation and associated with mild esophageal pressurization (typically no greater than 15 mm Hg), failure of expected upper esophageal sphincter relaxation, and gas clearance by secondary peristalsis. This characteristically would repeat in an oscillating pattern, often in conjunction with audible gurgling noises (Figure 4). The duration of this oscillating pattern was highly variable from as few as 2 occurrences to more than 30, often continuing without cessation until removal of the catheter. In cases where termination of the sequence was observed, this would occur following a secondary peristaltic

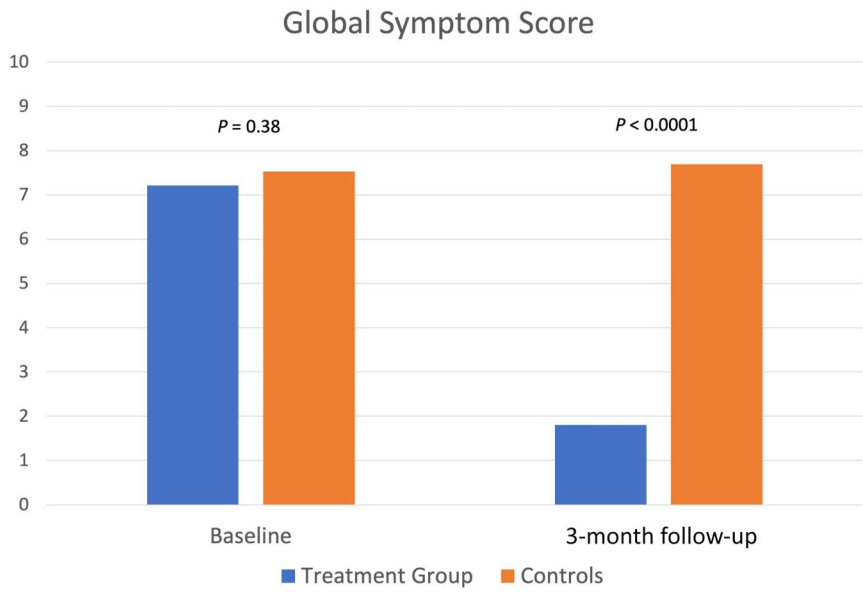

Figure 3. Global retrograde cricopharyngeus dysfunction symptom score (0–10, higher scores represent increased symptom burden). Significant improvement in symptoms was observed in treated patients but not controls.

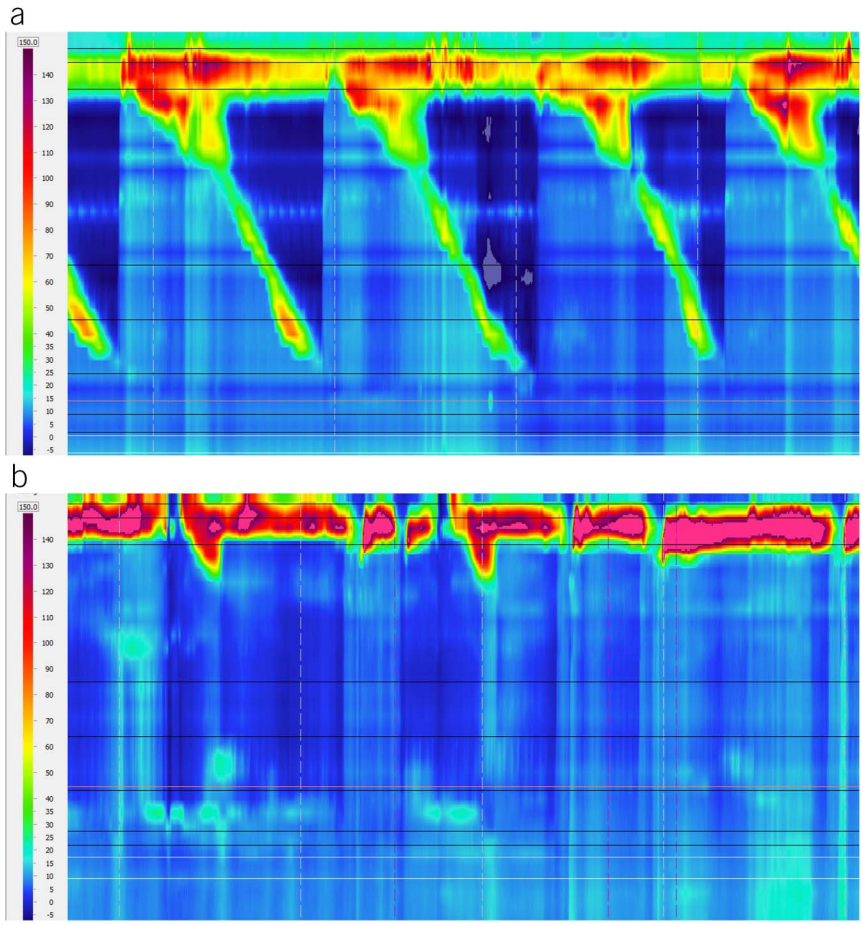

Figure 4. Response to the carbonated drink provocative test during esophageal high-resolution manometry. Several findings were observed in patients with retrograde cricopharyngeus dysfunction (**a**) and never seen in normal belchers (**b**): (i) gastroesophageal gas reflux causing a common cavity phenomenon with esophageal pressurization up to the level of gastric pressure and not >15 mm Hg, (ii) failure of upper esophageal sphincter relaxation despite esophageal pressurization, (iii) secondary peristalsis transiently normalizing esophageal body pressure by clearing esophageal gas back in to the stomach, (iv) immediate repressurization of the esophagus, (v) repetition of the sequence in an oscillating manner, often associated with audible gurgling noises. By contrast, in normal belchers the provocative test led to minor degrees of esophageal pressurization (<10 mm Hg), frequent upper esophageal sphincter relaxation associated with opening (i.e., belching), and no secondary peristalsis events.

event without any subsequent transient lower esophageal sphincter relaxation. Notably, even in cases where hypomotility was found on testing with single water swallows and the solid test meal, some degree of (secondary) peristaltic contraction was always observed with the carbonated drink provocative test. In such cases, the vigor of the secondary peristaltic contractions was invariably weak or ineffective by Chicago Classification criteria, often with distal contractile integral below 100; but these contractions were nevertheless able to effectively clear the esophagus of the refluxed gas (see Supplementary Figure, http://links.lww.com/AJG/D489). Some of the variability in findings between patients with R-CPD may be accounted for by differences in the rate and volume of carbonated drink ingested. By contrast, the carbonated drink provocative test in normal belchers resulted in no sustained esophageal pressurization due to demonstrable upper esophageal sphincter relaxation. There was no overlap in the findings of provocative testing between R-CPD and normal belchers.

Other manometric findings. In patients with R-CPD, the median integrated relaxation pressure during water swallows was 5.5 mm Hg (interquartile range 3.4–8.1), and 3 patients had a raised integrated relaxation pressure. There was a high incidence of hypomotility. Thirty-one (52.5%) had aperistalsis during water swallows, another 18 (30.5%) were classified as ineffective esophageal motility, and only 10 patients (16.9%) had normal esophageal motility during water swallows by Chicago Classification 4.0 criteria. No patients exhibited spastic motor disorders.

Provocative testing with a solid test meal was performed in 55/59 patients with R-CPD (93.2%). With the added challenge of the solid meal, a higher number of patients (N = 36) had adequate contractility (65.4%). However, 18 (34.5%) still had persistently ineffective esophageal motility, and 1 (1.8%) had aperistalsis on the solid test meal. One (1.8%) fulfilled criteria for hypercontractile esophagus, but no patients had disorders of esophagogastric junction relaxation.

Endoscopic findings and technical success

Of the 52 patients who underwent endoscopy (treatment group), significant findings were uncommon. Reflux esophagitis was present in 16 patients (31%): Los Angeles Grade A in 13, Grade B in 2, and Grade C in 1. A small hiatus hernia was found in 3 patients (6%). No patients had any endoscopically visible mucosal lesion or structural

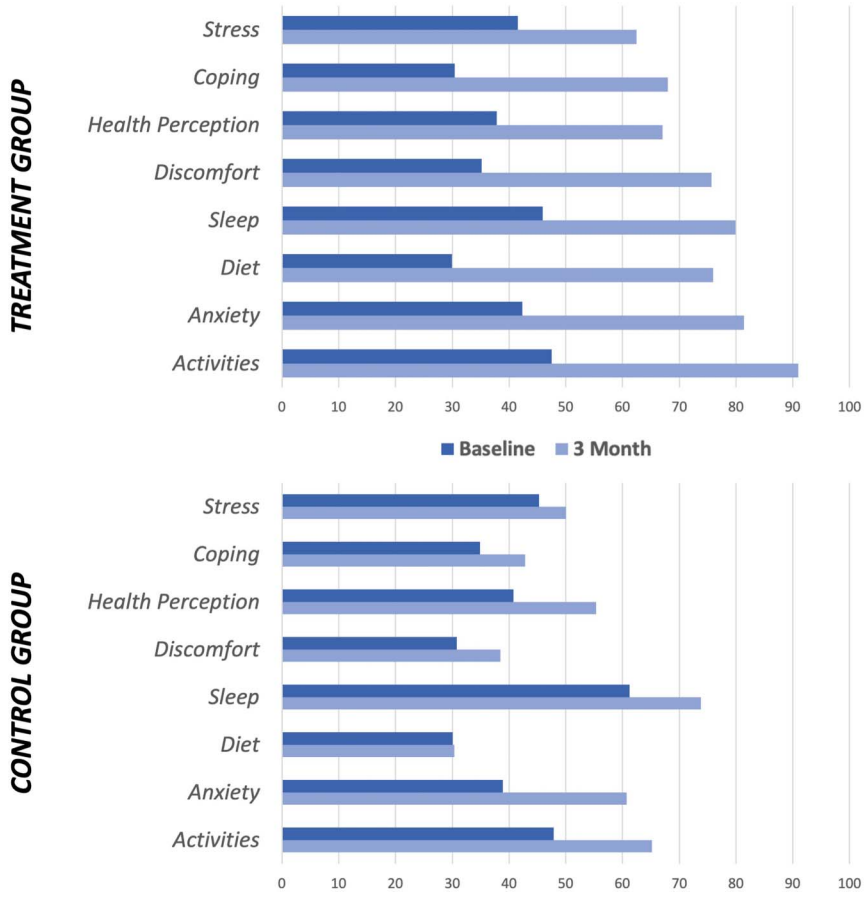

Figure 5. Quality of life assessed by the Functional Digestive Disorders Quality of Life Questionnaire. Higher scores (0–100) reflect a better quality of life. At 3 months, significant improvement in quality of life was observed in treated patients ($P < 0.0001$) but not controls ($P = 0.20$).

abnormality in the pharynx or cervical esophagus. Four patients (8%) had fasting gastric residue, although in all cases this was attributable to use of drugs affecting gastric motility.

CBTI was technically successful by flexible endoscopy in all 52 cases. The dose of botulinum toxin administered was 75 IU in 39 subjects (75%), 87.5 IU in 12 (23%), and 100 IU in 1 (2%). The latter higher injection amounts occurred where, due to some difficulty in maintaining endoscopic visualization, there was concern about adequacy of 1 or more of the initial injections.

Primary outcome: ability to belch

Three-month follow-up data were available in 58/59 patients with R-CPD. The primary outcome was significant at 3 month follow-up. At 3 months, 47/51 (92.1%) treated patients were able to belch compared with 0 controls ($P < 0.001$ for comparison). Of the 4 treated subjects not belching at 3 months, only 1 had no belching whatsoever after CBTI; the other 3 had some degree of belching after CBTI that was not sustained. The treated patient lost to follow-up was belching appropriately at initial 1 month follow-up. On the contrary, 3/47 of those belching at 3 months felt they were belching insufficiently and not receiving adequate relief of symptoms.

Effect of therapy on symptoms and quality of life

There was a significant reduction (improvement) in the global symptom score at 3 months in the treatment group (7.3 ± 1.7 to 1.8 ± 2.3; $P < 0.0001$). By contrast, there was no change in the global symptom score in controls (7.5 ± 2.1 to 7.7 ± 1.8; $P = 0.55$). The difference in the 3 month symptom score between the treatment group and controls was statistically significant ($P < 0.0001$; Figure 3).

In conjunction, there was a significant increase (improvement) in the FDDQL score at 3 months compared with that at baseline in the treatment group (38.1 ± 17.8 to 76.9 ± 15.0; $P < 0.0001$), whereas, in the control group, the FDDQL did not significantly change at 3 months (40.66 ± 17.25 to 52.4 ± 15.6; $P = 0.20$). The 3 month treatment group and control group FDDQL scores were significantly different ($P = 0.0002$; see Figure 5).

There was a significant, moderate inverse relationship between the change in global R-CPD symptom score after therapy and the change in FDDQL after therapy (Spearman's $R = -0.39$, $P = 0.004$).

Adverse events

Dysphagia occurred in all patients, necessitating dietary modification and/or compensatory swallowing strategies. In 47/52 subjects, dysphagia was only for solid foods, but in 5 subjects liquid dysphagia was also present. Nevertheless, all patients were able to resume a normal solid diet at latest 4 weeks after injection. Other adverse effects included regurgitation in 10 subjects (19.2%), heartburn 8 (15.4%), dyspnea 5 (9.6%), dysphonia 3 (5.8%), and syncope 1 (1.9%). Three subjects (5.8%) required prescription of proton pump inhibitors for reflux symptoms. Of the cohort, 1 patient required rehospitalization for 48 hours, due to persistent regurgitation 2 days after CBTI. This was one of the

cases where fasting gastric residue was found in setting of concomitant opiate therapy. After intravenous fluid therapy and antiemesis, she was discharged. No other medications were prescribed for adverse effects. Severity of adverse events appeared unrelated to the dose of botulinum toxin administered.

Satisfaction with therapy

Notwithstanding the adverse event profile, the median Likert score for overall satisfaction with therapy at 3 months was very high, at 5 (very satisfied; IQR 4–5). In total, 43/51 (84.3%) reported being satisfied or very satisfied with therapeutic outcome.

DISCUSSION

We have presented several novel findings with regard to the relatively under-recognized condition, R-CPD. First, R-CPD appears to as a rule present with run of the mill complaints encountered in any gastroenterology practice, including bloating, flatulence, and noncardiac chest pain. Second, the condition is associated with marked impairment in quality of life. Third, R-CPD is associated with highly specific manometric findings that were never observed in asymptomatic volunteers. Fourth, the condition does not appear to remit spontaneously. Fifth, CBTI is technically feasible by flexible endoscopy; and we present the first prospective controlled data confirming remarkably high efficacy not just in inducing belching but in relieving associated symptoms and improving quality of life. As such, we believe it is essential that all gastroenterologists now familiarize themselves with this condition.

The existing literature for CBTI in R-CPD consists of retrospective series where injection was performed by ear, nose, and throat surgeons, mostly using rigid laryngoscopes. The present data are the first to demonstrate that R-CPD can also be treated by flexible endoscopy, with technical success in all cases. Furthermore, our therapeutic success rate of 92.1% appears to be comparable in efficacy to the direct laryngoscopic approach (reported efficacy rates 88.2%–95%) (2–6,10). However, a flexible endoscopic approach has advantages, including favorable safety profile compared with rigid scopes and avoidance of general anesthesia. Fewer studies have evaluated the percutaneous, in-office (transcervical) approach, although the effectiveness appears to be significantly lower (11). Therefore, we propose the flexible endoscopic approach to be a first-line option for CBTI in R-CPD.

In our experience R-CPD causes significant, chronic morbidity with marked impact on daily activities. At baseline, patients with R-CPD had a mean FDDQL score of 38.7, of a maximum of 100 where lower scores indicate a worse quality of life. This compares unfavorably with reported FDDQL scores in irritable bowel syndrome (ranging from 50 to 62) (12,13), functional dyspepsia (59) (14), and normal individuals (84–90) (13,14). Furthermore, we found a correlation between degree of symptomatic improvement after therapy and degree of improvement in quality of life. This provides further confirmation that it is indeed the symptoms induced by the inability to belch which are having a detrimental impact on the patient's wellbeing. Our study provides other, indirect evidence for the impact on patient's quality of life by this condition. Notwithstanding the significant (albeit temporary) adverse effect profile, most patients (84%) reported being very satisfied or satisfied with the therapeutic journey overall. Furthermore, we are no longer surprised to have patients traveling to our center for this condition from long distances—interstate and overseas; it is reasonable to assume that patients would not be willing to do so were the impact on life not significant.

The work of Kahrilas (1), Oude Nijhuis et al. (6) in first identifying manometric abnormalities in a total of 9 patients with R-CPD should be acknowledged. The present data add to this in 2 important ways. First, we confirm that in a much larger cohort of R-CPD cases, the characteristic manometric findings appear to be uniformly present. Furthermore, we report the manometric response to the carbonated drink provocation test in health, which until now was not described. Our findings demonstrating distinction in manometric findings between health and disease confirm its utility as a diagnostic tool. Being safe, easy to perform, and relatively accessible, we recommend all patients with clinically suspected R-CPD have the diagnosis confirmed with HRM before consideration of therapy. While Oude Nijhuis et al also performed ambulatory reflux monitoring in these patients, our data appear to imply that HRM alone is diagnostic, and such a strategy reduces the diagnostic burden on these patients who have often already undergone extensive and unfruitful testing.

During baseline HRM, we also unexpectedly found a very high incidence of esophageal hypomotility. This is particularly noteworthy given that dysphagia was not a feature of the cohort at presentation. Furthermore, reflux esophagitis was observed in 31%; given the known association between reflux and hypomotility, these findings may be related. Although purely speculative, it may be that the chronic and marked esophageal distension (anecdotally reported by laryngologists during rigid scopy without insufflation (15)) has some impact on esophageal motor function leading to these findings. Further research is certainly warranted to explore such possibilities.

Adverse events were common, and patients should be warned about these before contemplating therapy. The adverse effect profile is no different to that described in all other reports of CBTI using either laryngoscopic or percutaneous approach, and side effects therefore appear predominantly related to the intended chemodenervation of the cricopharyngeus muscle. As such, all adverse effects were self-limited and resolved with loss of effect of botulinum toxin. Dysphagia was universal and significant dietary modification and compensatory swallowing strategies were sometimes necessary for up to 1 month after injection. Dyspnea and dysphonia in a small proportion of cases were most likely related to diffusion of toxin to the posterior cricoarytenoid muscles (lying adjacent to the cricopharyngeus), leading to a degree of vocal cord paresis. In fact, a theoretical risk of CBTI is asphyxiation from complete bilateral vocal cord paresis due to inadvertent injection of the posterior cricoarytenoids. Meticulous attention to endoscope positioning is essential in the tight postcricoid space to ensure selective injection of the cricopharyngeus only. We further mitigated this risk by minimizing the volume of fluid injected.

Strengths of this study compared with existing literature include its novelty, prospective design, and systematic inclusion of a uniform cohort of patients all with a confirmed manometric diagnosis. Loss to follow-up was minimal. The main limitation in the interpretation of the findings is that this was not a randomized clinical trial. As such, the control group was unavoidably small, and one might attribute some of the treatment response to placebo effect. However, the magnitude of difference in response we found between treated patients and controls was huge, and to our knowledge placebo response rates in gastrointestinal motor disorders have never come close to reaching 90%. We also cannot make any inference about long-term effectiveness based on these data. Other reports have suggested that the symptomatic benefit persists long after the effect of botulinum toxin subsides, although this too needs to be evaluated in a prospective manner.

In conclusion, our findings demonstrate that R-CPD is a potential cause of chronic gas-related gastrointestinal symptoms, can be diagnosed by esophageal physiology testing, and is amenable to endoscopic therapy. As such, we encourage gastroenterologists to take ownership of this condition and add it to their list of differential diagnoses for such symptoms. Our history-taking when encountering a patient with bloating or chest discomfort now includes the simple question, "Do you burp, ever?" Based on these data, we suggest that all gastroenterologists do the same, so as not to miss cases of this highly morbid but treatable condition.

CONFLICTS OF INTEREST

Guarantor of the article: Santosh Sanagapalli, MBBS, PhD, FRACP.
Specific author contributions: S.S.: study conception and design, recruitment, performed study interventions, data analysis, manuscript writing. M.E.: data collection, recruitment, critical review of manuscript. M.B.S.K.: study conception, critical review of manuscript. F.T.: data collection, data analysis, critical review of manuscript.

Study Highlights

WHAT IS KNOWN

- ✓ Inability to belch due to retrograde cricopharyngeus dysfunction may lead to chronic gas-related gut symptoms.
- ✓ Being underrecognized, retrograde cricopharyngeus dysfunction is often misdiagnosed as irritable bowel syndrome or reflux, given similar symptom profiles.
- ✓ Cricopharyngeal botulinum toxin injection via rigid laryngoscopy appears to be effective in treating the condition, but no prospective data exists.

WHAT IS NEW HERE

- ✓ Retrograde cricopharyngeus dysfunction causes significant morbidity and impairment of quality of life.
- ✓ Description and validation of a new diagnostic protocol for the condition, the Carbonated Drink Provocation Test, performed during high-resolution esophageal manometry.
- ✓ Cricopharyngeal botulinum toxin injection is technically feasible via flexible endoscopy, and highly effective in alleviating patient's symptoms.

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Potential competing interests: None to report.

REFERENCES

1. Kahrilas PJ, Dodds WJ, Hogan WJ. Dysfunction of the belch reflex. A cause of incapacitating chest pain. Gastroenterology 1987;93(4):818–22.
2. Bastian RW, Smithson ML. Inability to belch and associated symptoms due to retrograde cricopharyngeus dysfunction: Diagnosis and treatment. OTO Open 2019;3(1):2473974x19834553.
3. Karagama Y. Abelchia: Inability to belch/burp-a new disorder? Retrograde cricopharyngeal dysfunction (RCPD). Eur Arch Otorhinolaryngol 2021;278(12):5087–91.
4. Siddiqui SH, Sagalow ES, Fiorella MA, et al. Retrograde cricopharyngeus dysfunction: The Jefferson experience. Laryngoscope 2023;133(5):1081–5.
5. Hoesli RC, Wingo ML, Bastian RW. The long-term efficacy of botulinum toxin injection to treat retrograde cricopharyngeus dysfunction. OTO Open 2020;4(2):2473974x20938342.
6. Oude Nijhuis RAB, Snelleman JA, Oors JM, et al. The inability to belch syndrome: A study using concurrent high-resolution manometry and impedance monitoring. Neurogastroenterol Motil 2022;34(5):e14250.
7. Sanagapalli S, McGuire J, Leong RW, et al. The clinical relevance of manometric esophagogastric junction outflow obstruction can be determined using rapid drink challenge and solid swallows. Am J Gastroenterol 2021;116(2):280–8.
8. Chassany O, Marquis P, Scherrer B, et al. Validation of a specific quality of life questionnaire for functional digestive disorders. Gut 1999;44(4):527–33.
9. Sundas A, Sampath H, Lamtha SC, et al. Psychosocial quality-of-life correlates in functional gastrointestinal disorders. Revista de Gastroenterología de México (English Edition) 2024;89(1):11–8.
10. Miller ME, Lina I, Akst LM. Retrograde cricopharyngeal dysfunction: A review. J Clin Med 2024;13(2):413.
11. Doruk C, Pitman MJ. Lateral transcervical in-office botulinum toxin injection for retrograde cricopharyngeal dysfunction. Laryngoscope 2024;134(1):283–6.
12. Schneider A, Rosenberger S, Bobardt J, et al. Self-help guidebook improved quality of life for patients with irritable bowel syndrome. PLoS One 2017;12(7):e0181764.
13. Azpiroz F, Guyonnet D, Donazzolo Y, et al. Digestive symptoms in healthy people and subjects with irritable bowel syndrome: Validation of symptom frequency questionnaire. J Clin Gastroenterol 2015;49(7):e64–70.
14. Feng-Bin L, Yong-Xing J, Yu-Hang W, et al. Translation and psychometric evaluation of the Chinese version of functional digestive disorders quality of life questionnaire. Dig Dis Sci 2014;59(2):390–420.
15. Bastian RW. R-CPD esophageal findings, 2024. https://laryngopedia.com/r-cpd-esophageal-findings/. Accessed Sept 24, 2024.