Surgical Endoscopy (2020) 34:1124–1131
https://doi.org/10.1007/s00464-019-06859-y

Anti-reflux mucosectomy using a cap-assisted endoscopic mucosal resection method for refractory gastroesophageal disease: a prospective feasibility study

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Received: 17 November 2018 / Accepted: 18 May 2019 / Published online: 28 May 2019

Abstract

Background and aims Endoscopic therapy of gastroesophageal reflux disease (GERD) overcomes the "treatment gap" for patients with refractory GERD, who are not willing to go into surgery. We propose an easy and efficient technique that is referred to as anti-reflux mucosectomy (ARMS) using cap-assisted endoscopic mucosal resection (EMR-C) which could be called ARMS-C. This study aimed to investigate the short-term outcomes of ARMS-C in GERD patients.

Methods From December 2016 to February 2018, we performed ARMS-C in 33 patients with pathologic reflux disease and esophageal hypersensitivity. ARMS-C involved endoscopic mucosal resection at the circumference of the esophagogastric junction (EGJ), resulting in narrowing of the hiatal opening after healing. The GERD symptoms, 24-h pH monitoring results, manometry, endoscopy, and EGJ distensibility were compared before and after the procedure.

Results Six months after ARMS-C, 63% of patients discontinued the use of pump inhibitors (PPIs), while 30% patients reduced their PPI dose. The GERD questionnaire scores significantly decreased after ARMS-C, from 11.0 to 6.0 ($P<0.001$). The median DeMeester score and acid exposure time based on pH monitoring also improved after ARMS-C. Furthermore, the median flap valve grade and EGJ distensibility decreased from 3.0 to 1.0 ($P<0.001$) and from 19.0 to 13.9 ($P<0.001$), respectively. Two patients were treated with balloon dilation due to stricture, but no other serious adverse events were encountered.

Conclusion ARMS-C may be an effective and safe treatment method for GERD in terms of short-term outcomes.

Keywords Gastroesophageal reflux disease · Anti-reflux mucosectomy · Short-term outcomes · Cap-assisted endoscopic mucosal resection

Gastroesophageal reflux disease (GERD) is one of the most common gastrointestinal diseases, and it is defined as a condition that develops when the reflux of stomach contents into the esophagus causes troublesome symptoms, esophageal injury, or adverse events. It results from disruption of the anti-reflux barrier, which is composed of the lower esophageal sphincter (LES) and the diaphragmatic crura [1].

Anti-acid medications, usually proton pump inhibitors (PPIs), form the first-line treatment for GERD. However, about 30–40% of GERD patients receiving PPI treatment continue to have symptoms and require additional medications [2]. Concerns have been increasingly raised regarding adverse events of long-term use of PPIs such as Clostridium difficile infection, bone fractures, hypomagnesemia [3, 4]. In addition, surgery such as fundoplication has complications, which include dysphagia, injury to the stomach,

These data were presented on June 4, 2018 at the Topic Forum session of Digestive Disease Week in Washington, USA.

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wound infections, and pneumonia, although less common [5]. Recently, incisionless endoscopic methods for GERD treatment have been introduced, including radiofrequency ablation and the use of endoscopic fundoplication devices [6]. Endoscopic methods can be considered as less invasive methods compared with surgery. However, these therapies have yet to be widely applied in clinical practice due to difficulties related to use or because they require expensive equipment that are unavailable in most countries.

On the other hand, endoscopic mucosectomy, a recently introduced method, is a simple and cost-effective technique which is first published by Inoue [7]. Therefore, in this study, we performed endoscopic mucosectomy using cap-assisted endoscopic mucosal resection (EMR-C) which is a modified version of anti-reflux mucosectomy (ARMS) [7]. We refer to this procedure as ARMS-C. The purpose of this study was to investigate the short-term outcomes of ARMS-C in GERD patients who continue to have symptoms despite taking anti-reflux medications.

Methods

Patient selection

This study was a prospective, single-center, and single-arm trial conducted at the CHA University Hospital in Korea with patients who underwent ARMS-C from December 2016 to February 2018. All patients provided informed consent prior to surgery, and all procedures were conducted in accordance with the ethical standards of the Hospital Ethics Committee and the Institutional Review Board of CHA University (Approval Number: CHAMC 2016-04-015). The patients were considered eligible for participation in the study if they had still complaints of symptoms such as heartburn or regurgitation despite PPI use. Patients with hiatal hernia > 3 cm or an esophageal motility disorder such as achalasia or incomplete LES relaxation in response to swallowing were excluded from the study.

Endoscopic procedure

ARMS-C was performed using regular endoscopes (GIF-Q260; Olympus, Tokyo, Japan) equipped with a cap at the end. The patients were sedated using propofol (1.0 mg/kg) or midazolam (0.035 mg/kg), and kept under close monitoring of cardiorespiratory functions during the procedure. The EMR-C method, which is widely used for gastrointestinal mucosal lesion resection, induces mucosal contraction during the healing process after mucosal resection. Because of the need to narrow the lumen around the EGJ by inducing stenosis, approximately 60–80% of the EGJ circumference needs to be resected. Dots were made for marking around EGJ using an argon plasma coagulation (APC) unit at the 10'- and 6 o'-clock directions before the procedure. The procedure was performed on the lesser curvature side of the stomach, preserving the gastric sling fiber to fasten the EGJ. All endoscopic procedures were performed by a single experienced endoscopist (J.Y.C.) who has conducted more than 400 endoscopic resections annually for gastroesophageal neoplasia. The mucosa in the marked area was then excised by the EMR-C method, as described previously [8]. A medium-sized hard cap with an oblique cut (MAJ-296, Olympus, Japan) was used together with a thin diameter crescent snare (SD 221L/U-25, Olympus, Japan). A mixture of normal saline, epinephrine (1:10,000 dilution), and indigo carmine was injected into the submucosa along the markings using a 25-gage needle with a 4-mm tip. The snare was prelooped on the internal circumferential ridge of the cap by lightly pressing against and suctioning the mucosa. The captured mucosa was then resected with an electrosurgical current (forced coagulation mode, 30 W, effect 3, VIO300D ERBE, Tübingen, Germany). EMR-C was carried out in this manner until the marked mucosal area was completely resected. The procedure was repeated 4–10 times depending on the circumference of the EGJ and the degree of hiatal hernia. Bleeding, occurring during or after the procedure, was controlled using an APC (forced coagulation mode 40–60 W; VIO 300D ERBE).

Endoscopy

The patients underwent esophagogastroduodenoscopy before enrollment to rule out non-GERD diseases such as eosinophilic esophagitis, evaluate the gastroesophageal flap valve, and assess the presence of Barrett's esophagus or a hiatal hernia. Follow-up endoscopy was performed to evaluate delayed complications such as stricture, and changes of gastroesophageal flap valve grade [9]. For the comparison, flap valve grades 1, 2, 3, and 4 received scores of 1, 2, 3, and 4 points, respectively.

High-resolution manometry (HRM)

High-resolution manometry (HRM) was performed to exclude the esophageal motility disorder. Physiologic parameters of the esophagus, including LES pressure and integrated relaxation pressure (IRP), were measured using HRM (Insight G3 HRiM, Sandhill) for the differential diagnosis of esophageal motility disorders.

Twenty-four-hour pH monitoring

The 24-h pH monitoring was performed using a gastroesophageal pH meter (Sandhill Scientific Inc, Highlands Ranch, CO, USA). The probe was inserted transnasally into the

lower esophagus, and the sensor was located approximately 3–5 cm proximal to the EGJ. Measurement was performed continuously for 24 h. Abnormal acid exposure time (AET) was defined as percentage of total reflux time (esophageal pH < 4) above 4.2%.

EndoFLIP

EndoFLIP® (a balloon mounted on a thin catheter placed transorally at the time of sedated endoscopy) (Crospon Ltd., Galway, Ireland) was used to evaluate EGJ function. EndoFLIP examination was performed before and after ARMS-C by means of a single-use EndoFLIP catheter (EF-325N) by well-trained endoscopists at an outpatient clinic department. After proper balloon placement, the endoscope was removed, and the EndoFLIP balloon was inflated to 40 and 50 ml distension volumes. At each distension volume, a 30 measurement was made to determine cross-sectional area (CSA), intra-bag pressure, and EGJ distensibility index (DI). DI is defined as the minimum CSA (i.e., the narrowest portion of the EGJ) divided by intra-bag pressure. However, we only included DI in this study.

GERD-Q questionnaire

Patients recorded a self-administered six-item diagnostic questionnaire GERD-Q before and after ARMS-C. The frequencies of six symptoms including heartburn, regurgitation, sleep disturbances due to reflux symptoms, the use of over-the-counter medications, epigastric pain, and nausea are evaluated with a 4-grade Likert scale (0–3). A cutoff level of 8 has the highest specificity and sensitivity for the diagnosis of gastroesophageal reflux disease (GERD) [10], and therefore, symptomatic gastroesophageal reflux was defined as a GERD-Q score ≥ 8.

Study outcome

The primary outcome was improvement of GERD-Q scores 6 months after ARMS-C and discontinuation rate of PPI.

The secondary outcomes were objective comparisons of GERD parameters, [11, 12] such as DeMeester scores and AET on 24-h pH monitoring, esophageal flap valve grade on endoscopy, and gastroesophageal distensibility on EndoFLIP. Moreover, we performed HRM to evaluate whether there was an esophageal motility change. Subsequently, we classified the patients into three groups based on their symptom scores and post-ARMS-C PPI dose requirements. In terms of group allocation, the complete response (CR) group was defined as patients with post-ARMS-C GERD-Q scores of < 8 and discontinued PPI medication. Patients with post-ARMS-C GERD-Q scores of < 8 and a reduced PPI dose were allocated to the partial response (PR) group. Patients with improved GERD-Q scores but still requiring the same dose of PPI were placed in the no-response (NR) group. In addition, we investigated the correlations between the procedure-induced EGJ distensibility change and other outcomes (e.g., flap valve grade, GERD-Q score, DeMeester score, acid exposure time, LES pressure, and IRP).

Statistical analysis

The patients' variables, such as age, procedure duration, percentage of time at pH < 4, and GERD-Q score, DeMeester score, flap valve grade, EGJ DI, acid exposure time, LES pressure, and IRP, were summarized by means (standard deviation) or median (range). Wilcoxon signed-rank test was used for GERD-Q score, DeMeester score, flap valve grade, EGJ distensibility index, and AET, which were not normally distributed. Independent *t* test was used to evaluate LES pressure or IRP.

Spearman's rho test was used for analyzing the relationship between EGJ distensibility and other procedure-related outcomes (including flap valve grade, DeMeester pH score, AET, LES pressure, and IRP). After group allocation according to the PPI response, the influential variables were evaluated by Mann–Whitney *U* test. All data were analyzed using SPSS 20.0 (SPSS Inc, Chicago, Ill, USA). A *P* value < 0.05 was considered statistically significant.

Management and follow-up after ARMS-C

Patient management after ARMS-C was similar to the recovery process after EMR-C for esophageal or stomach tumor resection. The patients were allowed oral intake of food the day after the procedure. They were administered PPIs that were continued for 8 weeks after ARMS-C and then stopped if possible. All patients underwent endoscopy 2 weeks later, and then follow-up exams after 6 months with endoscopy, 24-h pH monitoring, HRM, and EndoFLIP post- ARMS-C assessment.

Results

We enrolled 50 patients who complained of symptom despite of PPI use. However, we excluded 17 patients who did not perform one of the 6-month follow-up exams. Therefore, finally, 33 patients were enrolled. Table 1 shows the baseline demographics of these patients. Among the 22 male and 11 female patients enrolled, the mean age was 51.3 years, and the median duration of GERD symptoms was 5.3 years (range 1–30 years). With regard to diagnosis, 8 patients had Barrett's esophagus, 12 had a hiatal hernia that was < 2 cm the length of the esophagus, 24 had pathologic reflux disease, and 9 had esophageal hypersensitivity.

Table 1 Clinical and endoscopic characteristics of patients

Variables	Patients with GERD ($n=33$)
Age, mean ± SD, years	51.3 ± 16.3
Female, *n* (%)	11 (33.3)
BMI, mean ± SD (kg/m^2)	23.5 ± 4.1
Duration of symptom, median, years (range)	5.3 (1–30)
Barrett's esophagus, *n* (%)	8 (24.2)
Hiatal hernia, *n* (%)	12 (36.4)
Diagnosis, *n* (%)	
Pathologic reflux disease	24 (72.7)
Esophageal hypersensitivity	9 (27.3)
FVG, median (range)	3 (1–4)
DeMeester, median (range)	19 (5–46.1)
DI, median (range)	33 (0.8–53)
GERD-Q, median (range)	11 (5–18)
AET, mean ± SD (%)	3.1 ± 3.1
LES pressure, mean ± SD	16.3 ± 8.9
IRP, mean ± SD	7.3 ± 4.8
Procedure time, minutes median (range)	31.2 (15–68)
Extent, median (range, %)	70 (50–80)

GERD gastroesophageal reflux disease, *BMI* body mass index, *FVG* flap valve grade, *DI* distensibility index, *GERD-Q* GERD questionnaire, *AET* acid exposure time, *LES* lower esophageal sphincter, *IRP* integrated relaxation pressure

Details of ARMS-C and the endoscopic findings at the 6-month follow-up are shown in Fig. 1. The median procedure time was 31.2 min (range 15–68 min). At the 2-week follow-up, no patient had bleeding on endoscopy, and two patients were treated with balloon dilation due to stricture. Furthermore, during the 6-month follow-up, two patients underwent repeat ARMS-C due to persistence of symptoms. Repeat mucosectomy was conducted by avoiding scar formation site. There were no complications associated with repeat procedure, and these symptoms of patients were relieved after repeat ARMS-C. No other major adverse events occurred.

As shown in Table 2, at the 6-month follow-up, the median post- ARMS-C GERD-Q symptom score was 6, compared to 11, prior to the treatment ($P<0.001$). Similarly, the mean DeMeester score for 24-h pH monitoring decreased from 11.6 pre-ARMS-C to 4.0 ($P<0.001$).). DeMeester scores of pre-ARES and at 6 months are both in the normal range. Because nine esophageal hypersensitivity patients whose reflux within the physiological range (as determined by pH monitoring) were included. The endoscopic findings also demonstrated that the median EGJ flap valve grade was significantly improved from 3 to 1 ($P<0.001$) after ARMS-C. Moreover, the EGJ distensibility, as measured by EndoFLIP, was also reduced from 19 to 13.9 ($P<0.001$) at 6 months. Among the manometric findings, LES pressure and IRP increased after ARMS-C within normal range.

Of the 33 patients, 21 (63.6%) and 10 (30.3%) were allocated to the CR and PR groups, respectively. The remaining two patients were placed in the NR group. Because the NR group has only two patients, we analyzed the clinical outcomes by dividing CR group and NR or PR groups. Between these groups, the mean age, sex, body mass index (BMI), duration of symptoms, portions of the Barrett's esophagus and hiatal hernia, and pathologic esophagitis and esophageal hypersensitivity rates were determined. Among the parameters of GERD exams, DeMeester score and AET were significantly higher in patients for whom ARMS-C had low therapeutic efficacy (i.e., the NR or PR group) (Table 3).

We also evaluated correlations between the EGJ distensibility changes and other related outcomes including flap valve grade, DeMeester pH score, etc. EGJ distensibility was only correlated with AET ($r=0.34$; $P=0.04$) (Fig. 2). Also, EGJ distensibility correlated with flap valve grade ($r=0.30$; $P=0.08$) with borderline significance, probably because of the small number of patients (not shown in graph). However, no correlations were found between EGJ distensibility and the DeMeester score, LES pressure, IRP, and GERD-Q score changes.

Discussion

With the recent development of endoscopic techniques and tools, patients with refractory GERD have been able to choose various treatment methods besides surgery, and the development of new therapeutic methods is expected to continue in the future [13]. One such method is Stretta, a minimally invasive and simple procedure with few adverse events. However, this procedure is expensive, and long-term effectiveness is unclear [14, 15]. Some endoscopic suturing methods have also been identified as promising options for endoscopic fundoplication, although it has been reported that their beneficial effects are less persistent compared to those of surgery, and they require expensive equipment [7]. Mucosal resection is another alternative to surgery, and has the advantage of requiring only an endoscopic approach without the need of general anesthesia. In addition, no endoprostheses are left in situ. Therefore, it can be a convenient and effective treatment option for patients with GERD, who are not responding to medication or willing to undergo surgery. Due to the small number of patients and short-term outcomes, we need an enlargement in the number of studies for reliability. However, it is worth noting that, in our series, the majority of the patients (29/33) showed a significant reduction in GERD-Q scores.

Our study has several important points. First, we reported this emerging technique with extensive monitoring by

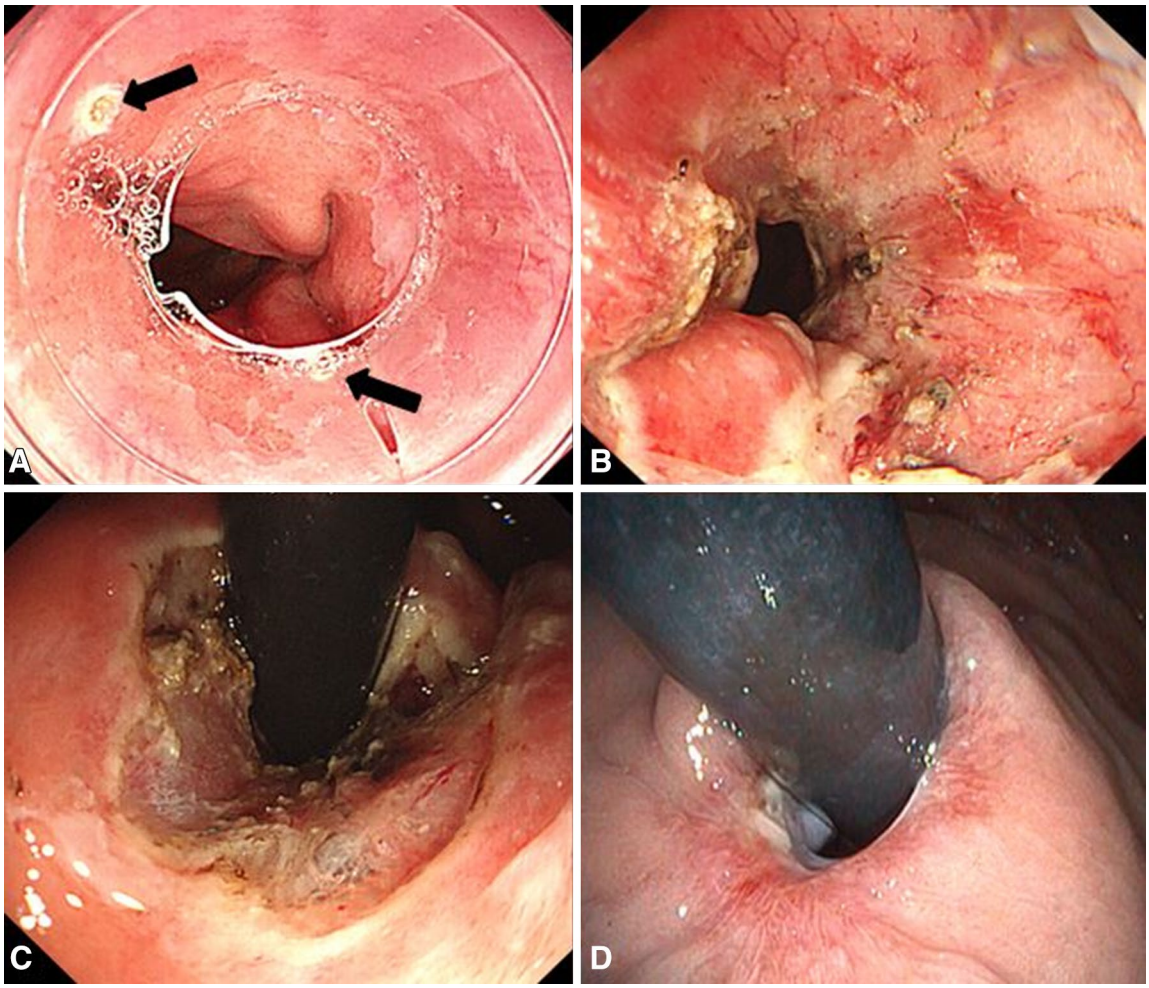

Fig. 1 Anti-reflux mucosectomy using cap. **a** The lesion to be resected in the esophagogastric junction (EGJ) is marked using argon plasma coagulation at the 10 o'clock and 6 o'clock directions before ARMS-C (arrow). **b** Using the EMR-C method, the mucosa was resected at approximately 270° (endoscopic forward view). **c** Immediately after ARMS-C (endoscopic retroflexed view). **d** 6 months after ARMS-C (endoscopic retroflexed view)

repeated endoscopy, EndoFLIP, 24-h esophageal pH monitoring, and manometry. Based on our findings, we demonstrated that objective variables improved without compromising LES function. Based on the manometry finding, after ARMS-C, LES pressure and IRP were greater than those prior to ARMS-C within the normal limit. The goal of an anti-reflux procedure is to restore an anatomically and functionally competent gastroesophageal barrier. Keller et al. [16] demonstrated that anti-reflux surgery could correct diaphragmatic crural defects, reestablish an intra-abdominal esophageal segment, and enhance the pressure of the gastroesophageal high-pressure zone. In addition, Weijenborg et al. [17] found that anti-reflux surgery could also ameliorate the strength of esophageal peristalsis due to increased outflow resistance at the level of the gastroesophageal junction as shown by manometry. In addition, AET and DeMeester scores at 24-h esophageal pH monitoring decreased after ARMS-C. The ARMS-C procedure has shown improved functional parameter of GERD.

Second, this technique is easy to adopt because it is performed anteriorly and does not require work in the retroflexed position. EMR-C is a simpler and easier refinement of EMR methods and used primarily in upper GI tract neoplasia. This technique is a minimally invasive, organ-sparing endoscopic method. EMR-C can be considered as a better technique than band ligation-associated EMR [18] because endoscopist does not need to repeat the insertion of endoscopy and removal of equipment. It consists of simple steps as the injection, inserting the snare through the hole, and then resecting the lesion.

Third, we first evaluated the flap valve and the EGJ distensibility pre- and postprocedures. EGJ distensibility using impedance planimetry was also assessed in the present study because this may be useful for predicting the degree of

Table 2 Short-term therapeutic outcomes based on ARMS-C

	Pre-ARES	6 months Post-ARES	*P* value
Subjective outcome			
GERD-Q score, median (range)	11 (5–18)	6 (3–16)	< 0.001[a]
Objective outcome			
DeMeester score, median (range)	11.6 (0.8–46.1)	4.0 (0.8–40.0)	< 0.001[a]
FVG, median (range)	3 (1–4)	1 (1–3)	< 0.001[a]
DI, median (range)	19 (5–53)	13.9 (2–29)	< 0.001[a]
AET (range)	2.7 (0.0–12.3)	0.9 (0.0–10.0)	0.031[a]
Manometric finding			
LES pressure, mean (SD)	16.3 ± 8.9	20.7 ± 11.5	0.005[b]
IRP, mean (SD)	7.3 ± 4.8	9.4 ± 5.9	0.052[b]
Complications, *n* (%)			
Bleeding		0 (0)	
Stricture		2 (6.0)	
Repeated ARES		2 (6.0)	

GERD Q GERD questionnaire, *FVG* flap valve grade, *DI* distensibility index, *AET* acid exposure time, *LES* lower esophageal sphincter, *IRP* integrated relaxation pressure, *ARMS-C* anti-reflux mucosectomy using cap

[a]Wilcoxon signed rank test

[b]Independent *t* test

Table 3 Comparison of patient and procedure characteristics between the two groups

	CR (*n* = 21)	PR or NR (*n* = 12)	*P* value[a]
Age, years, mean	49.8	54.0	0.126
Female, *n* (%)	6 (28.6)	5 (41.7)	0.390
BMI, kg/m^2 mean	23.0	24.3	0.494
Duration of symptom, years, median	3.7	6.1	0.315
Barrett's esophagus	5 (23.8)	3 (25)	0.431
Hiatal hernia, *n* (%)	10 (47.6)	2 (16.7)	0.204
Diagnosis, *n* (%)			0.390
Pathologic reflux disease	15 (62.5)	9 (37.5)	
Esophageal hypersensitivity (%)	6 (66.6)	3 (33.3)	
FVG, median	3.0	3.0	0.272
DeMeester score	3.6	15.0	0.010
DI	20.0	16.7	0.294
GERD-Q	10.0	12.0	0.436
AET	1.4	4.1	0.039
LES pressure	19.5	16.0	0.640
IRP	7.0	5.0	0.105
Extent, mean (%)	65.7	69.5	0.964

BMI body mass index, *FVG* flap valve grade, *DI* distensibility index, *GERD-Q* GERD questionnaire, *AET* acid exposure time, *LES* lower esophageal sphincter, *IRP* integrated relaxation, *CR* complete response group, *PR* partial response group, *NR* no response group

[a]Mann–Whitney test

destructive LES changes in patients with refractory GERD [19]. Some correlations were observed for EGJ distensibility and flap valve grade, which may be influenced by anatomic changes. Furthermore, as the EGJ distensibility decreased after ARMS-C, AET showed related improvements. This result showed that the possibility of DI measurement by EndoFLIP could predict also functional improvement, not only anatomical improvement.

Fourth, there were some benefits that were different from other procedures. The presence of Barrett's

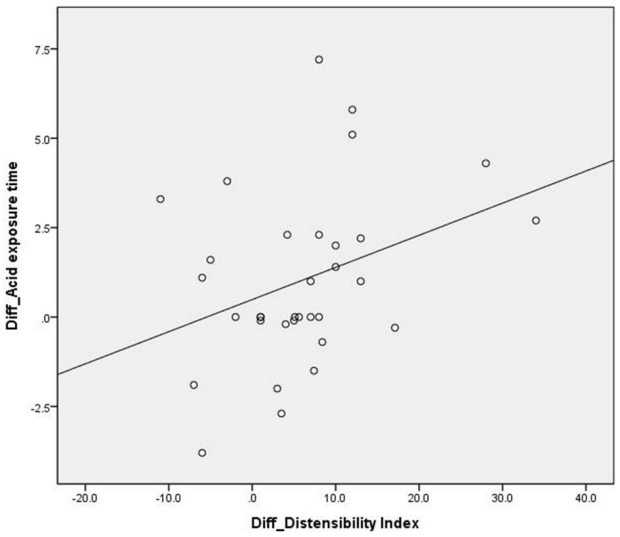

Fig. 2 Correlation between the differences in acid exposure time and EGJ distensibility after ARMS-C; $r = 0.34$, $P = 0.04$

esophagus does not preclude the performance of ARMS-C. One of the advantage of this procedure is complete excision of barrett's mucosa and its ability to analyze the pathologic result whether there is a dysplasia or not. Further, it is expected that research on refractory GERD mechanism by evaluating the tissue can be improved. In addition, patients with minimal hiatal hernia or esophagitis could be included for ARMS-C unlike Stretta. In our study, six of nine patients previously diagnosed with esophageal hypersensitivity discontinued PPIs after ARMS-C. ARMS-C may be effective for esophageal hypersensitivity regarding its pain control.

The limitation of this study is that there was no group of PPI patients for comparison. Unlike in the case of ARMS-C, it is difficult to perform intense follow-up examinations for those who take only PPIs. If we compared the ARMS-C group with patients who took medications, the efficacy of ARMS-C would be understood better.

Another limitation is that the study needs to be confirmed by a larger number of samples with long-term follow-up.

In conclusion, ARMS-C is simple and easy technique to treat GERD. With recent studies having proven associations of PPIs with multiple adverse events and fundoplication being an invasive procedure, there ought to be an alternative, particularly in patients with refractory symptoms. Our results showed that ARMS-C resulted in a significant decrease in the GERD symptoms' objective variables at the 6-month follow-up. However, to demonstrate its efficacy and find the appropriate indication for this procedure, long-term data are needed, and comparisons to other treatments are required.

Acknowledgements We thank the Center for Clinical Development (CHA Health Systems) for providing the statistical help.

Author contributions WJK, JYC designed the report; HSK, JC, HKK recruited patients; WHK, SPH organized the report; JHK, AÖY reviewed the case and gave critical revision; and IY, WJK wrote the paper.

Compliance with ethical standards

Disclosures Authors In kyung Yoo, Weon Jin Ko, Hak Su Kim, Hee Kyung Kim, Jung Hyun Kim, Won Hee Kim, Sung Pyo Hong, Abdullah Özgür Yeniova, Joo Young Cho have no conflicts of interest or financial ties to disclose.

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