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CLINICAL ENDOSCOPY

Endoscopic radiofrequency Stretta therapy reduces proton pump inhibitor dependency and the need for anti-reflux surgery for refractory gastroesophageal reflux disease

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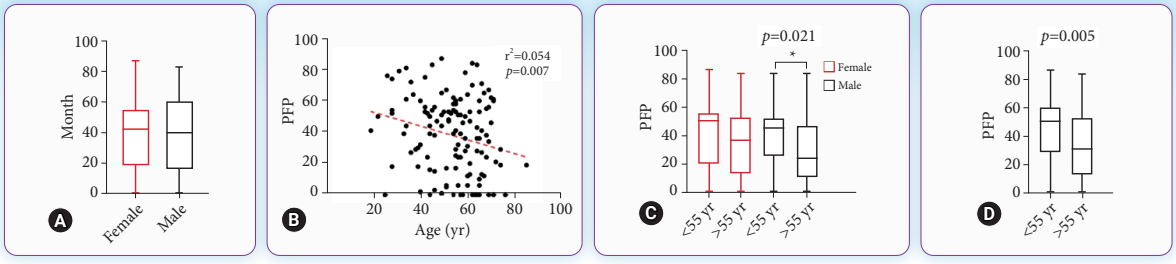

- **There was a significant negative correlation between proton pump inhibitor-free period (PFP) and age (p=0.007), with no differences between sexes (p=0.96).**
- **Younger males had a significantly longer PFP than older males (p=0.021).**
- **Patients younger than 55 years of age had a longer PFP than their older counterparts (p=0.005).**

Stretta can be a safe and feasible option for treating refractory GERD, especially in younger patients and can increase the lead-time to surgery in patients with refractory GERD.

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Background/Aims: Radiofrequency treatment of the gastroesophageal junction using the Stretta procedure for treating gastroesophageal reflux disease (GERD) is observed to improve the symptoms and proton pump inhibitor (PPI) dependence and reduce the need for anti-reflux operations. As one of the largest studies in Europe, we evaluated the clinical outcomes of Stretta in patients with medically refractory GERD.
Methods: A tertiary UK center evaluated all patients with refractory GERD who underwent Stretta between 2014 and 2022. Patients and primary care professionals were contacted to obtain information regarding the initiation of PPI and reintervention after Stretta.
Results: Of the 195 patients (median age, 55 years; 116 women [59.5%]) who underwent Stretta, PPI-free period (PFP) data were available for 144 (73.8%) patients. Overall, 66 patients (45.8%) did not receive PPI after a median follow-up of 55 months. Six patients (3.1%) underwent further interventions. The median PFP after Stretta was 41 months. There was a significant negative correlation between PFP and age (p=0.007), with no differences between sexes (p=0.96). Patients younger than 55 years of age had a longer PFP than their older counterparts (p=0.005). Younger males had a significantly longer PFP than older males (p=0.021). However, this was not observed in the female cohort (p=0.09) or between the younger men and women (p=0.66).
Conclusions: Our findings suggest that Stretta is a safe and feasible option for treating refractory GERD, especially in younger patients. It prevents further anti-reflux interventions in most patients and increases the lead-time to surgery in patients with refractory GERD.

Keywords: Fundoplicatio; Gastrooesophageal reflux; Proton pump inhibitors; Radiofrequency therapy

INTRODUCTION

Gastroesophageal reflux disease (GERD) is one of the most common digestive disorders resulting in the reflux of gastric contents into the esophagus through an incompetent lower esophageal sphincter (LES).[1-3] GERD causes considerable symptoms in some patients and requires medical or surgical management.[1] GERD has been reported worldwide, with a wide range of prevalence based on geographical and sociocultural factors.[2] In the United States (US), there are approximately 6 million hospital visits per year for symptoms of GERD[3] and in financial terms, more than $10 billion per year is spent on proton pump inhibitors (PPI) alone.[4] GERD manifests predominantly in men aged 40 to 60 years and has increased in the recent years because of lifestyle factors and obesity.[5,6] The insidious nature of the disease, with frequent symptoms of heartburn and reflux, results in a delayed presentation, significant financial burden, and affects the quality of life (QOL).[1] The spectrum of primary treatment for GERD ranges from lifestyle modifications (elevating the head end of the bed, abstaining from smoking and alcohol, and dietary changes) to medications (PPI, H2-receptor antagonists), where PPI remains the mainstay therapy.[1,7] Despite this, more than 30% of patients with GERD are refractory to PPIs.[8] For such patients, a more invasive endoscopic or surgical treatment approach is warranted, with the recent years observing an increase in the use of minimally invasive techniques in the treatment of refractory GERD, including endoscopic transoral incisionless fundoplication, magnetic sphincter augmentation (LINX; Torax Medical), or radiofrequency (RF) therapy (Stretta).[9-11]

Endoscopic RF therapy of the gastroesophageal junction (GEJ) for the treatment of GERD is a proven and cost-effective treatment modality.[12,13] Since its introduction and approval in 2000, over 25,000 cases have been reported in the US.[14] Stretta is the only RF device licenced by the National Institute for Health and Care Excellence for use in the UK for refractory GERD.[15] It uses a balloon-tipped four-needle catheter to deliver RF to the LES while irrigating the mucosa to prevent heat injury.[1] The safety, short- and long-term efficacy, reduction in PPI dependency, improvement in the QOL, and patient satisfaction with Stretta have been evaluated multiple times with mixed results.[12,16-19] A recent Seoul consensus on the diagnosis and management of GERD suggested that GERD has multiple reflux phenotypes with individual pathophysiologies.[20] They recommended personalized diagnostic and therapeutic approaches to minimize unnecessary treatments and efficient use of medical resources.[20] This may explain the heterogeneous results obtained from investigations involving Stretta.

This prospective observational study was conducted to evaluate our practice, validate the long-term clinical outcomes and reinterventions, and investigate the relationship between Stretta and patient characteristics that may help provide personalized treatment for patients with refractory GERD.

METHODS

The prospective data of all patients who underwent Stretta from October 2014 were included in the analysis. This study

was registered with the South Tees NHS Foundation Trust. The data were anonymized and standard data safeguards were followed. Demographic data, further Stretta procedures, and details regarding fundoplication were gathered from clinical letters from the hospital electronic database. The patients were assessed via telephone to confirm whether they were on regular PPI medication and to ascertain when they started taking PPIs after completing Stretta. When the team failed to make contact twice during working hours (9 am–5 pm) and once during non-working hours (5 pm–7 pm), the general practice and electronic database linked to the hospital were checked to identify the PPI prescription date. The primary outcome was the PPI-free period (PFP), defined as the time between Stretta and the recommendation of prescribed and daily consumption of PPI medication. Patients using PPI on an 'as and when' required basis were considered to be off PPI and included in the PFP calculation. The secondary outcome was to appraise the frequency and types of reintervention after Stretta therapy. The median age (55 years) was used to dichotomize patients into younger and older cohorts.

Statistical analyses and graphical presentation were performed using Minitab 19.1 (Minitab LLC) and GraphPad Prism 8.0.2 (GraphPad Software Inc.). The Shapiro-Wilk test was used to determine the normality of the data distribution. The Pearson's correlation coefficient was used to determine the magnitude and significance of the linear variable relationships. Data are presented as median (interquartile range) for non-parametric data. Two sets of non-parametric data were compared using the Mann-Whitney *U*-test. The statistical significance was set at $p<0.05$.

All adult patients with refractory GERD were considered for Stretta therapy. Patients were deemed refractory if they had persistent symptoms affecting their QOL despite a minimum of two courses of PPIs for a minimum duration of 8 weeks and did not want to continue medical management for GERD. Patients with GERD symptoms with pathological acid reflux (acid exposure time >6) on 24-hour pH studies with esophagitis (Lyon Consensus 2018) and non-erosive reflux disease were included in the study. Biopsies were performed on selected patients to rule out eosinophilic esophagitis. The diagnosis and sizing of the hiatus hernia was determined using endoscopy, manometry, and barium contrast studies. The exclusion criteria included the presence of a concomitant hiatus hernia (>2 cm) or severe esophagitis and stricture formation (Los Angeles classification). The preoperative workup included gastroscopy, barium studies, and pH and manometry studies.

Stretta procedure

The distance from the incisor to the esophagogastric junction was measured during an initial endoscopic assessment to confirm the suitability of the procedure. Subsequently, the guidewire was placed beyond the pylorus. A Stretta catheter was passed over the guide wire, and 56 thermal treatments were delivered at six levels around the LES.[21] An endoscopy check was performed upon completion to assess the mucosal integrity. Overall, 84.1% (n=164) of patients underwent the procedure under sedation, while the remaining patients were under general anaesthetic as day cases. All patients went through a process of informed consent and counselling pre- and post-procedure. A leaflet advised them to be on a liquid-or a soft-diet for two weeks and to stop PPI after 5 weeks. All patients were encouraged to follow standard anti-reflux dietary and lifestyle advice.

Ethical statements

The study was performed in accordance with the guidelines of the Declaration of Helsinki for Biomedical Research from 1964 and the standards of the institutional review board, and was registered with the James Cook University Hospital research and audit department (No: JCUH/2013/6641).

RESULTS

A total of 195 patients underwent Stretta at our hospital between October 2014 and June 2022. No procedure-related complications occurred. Of these, 144 (73.8%) patients were contacted, and PFP and reintervention details were confirmed. Notably, three patients (1.5%) had repeat Stretta, and three patients underwent fundoplication. One patient died of an unrelated condition. The demographic characteristics are outlined in Table 1. The overall (n=144) median PFP was 41 months (3.5 years). Notably, 66 (45.8%) patients had not been on PPI since Stretta therapy and had a median PFP of 53 months (4.5 years). There were no significant differences in the PFP between sexes (median 40 months for men vs. 42 months for women, p=0.96). However, there was a significant negative correlation between age and PFP (r=−0.233, p=0.007). PFP was significantly different between the younger and older cohorts, with the younger cohort having a median PFP of 50 months and the older cohort having a median PFP of 31 months (p=0.005) (Fig. 1). Furthermore, there was a significant difference in the PFP

between men younger than the median age and men older than the median age (p=0.021). There were no statistical differences between the older (median 36 months) and younger women (median 50 months) (p=0.09), or between younger men (median, 49.5 months) and younger women (median 50 months) (p=0.66). There was no difference between patients with PFP and small hiatus hernia in this cohort.

DISCUSSION

Stretta is a minimally invasive, day-case endoscopic procedure that has been proven to eliminate or significantly reduce the use of medical treatment for GERD. Multiple endoscopic therapeutic options are available to treat GERD, such as TIF, overstitch, and RF treatment of the GEJ using Stretta. Of these, Stretta is the only procedure that does not result in structural changes within the lumen and does not affect future surgery.[22] Although there are several theories, it remains unclear how Stretta produces an effect.[14] A sub-ablative application of thermal RF energy denatures muscle fibers, which subsequently regenerate through the remodelling process, inducing muscular hypertrophy and strengthening the LES.[22] Other studies have suggested an effect on the neuromuscular function of the LES. In a preclinical trial, a group investigating the impact of Stretta on LES pressure after the injection of botulinum toxin to LES identified a significant increase in the LES pressure in the Stretta group compared with the placebo. The authors concluded that Stretta reversed the loss of LES pressure induced by botulinum toxin injection.[23] Another animal study on dogs concluded that Stretta delivery to the gastric cardia reduced the gastroesophageal reflux.[24] In a double-blind, randomized crossover human trial, a total of 22 patients were divided into Stretta and placebo treatment groups. The authors suggested that Stretta reduced the GEJ compliance and contributed to symptomatic benefit by reducing the volume of reflux.[18]

Stretta is arguably the safest, least invasive, and most tolerated procedure among currently available therapeutic procedures for GERD.[14] The common complications include transient epigastric and chest pain, dyspepsia, dysphagia, odynophagia, gastroparesis, bleeding, and oesophagitis.[25-27] The benefits of Stretta have been demonstrated in multiple randomized controlled trials showing an improvement in the heartburn scores and QOL for up to 12 months.[18,28-31] Longer follow-up studies have shown a sustained reduction in PPI use, improved patient satisfaction,

Table 1. Patient demographics and post-Stretta outcomes

Demographic	Value
Age (yr, max–min)	55 (19–85)
Sex (male:female)	79:116
Follow-up	55 (42–67)
Overall PFP	41 (17–56)
PFP (male)	40 (15.5–60.75)
PFP (female)	42 (18–55)
PFP (age <55 yr)	50 (28.5–61.25)
PFP (age >55 yr)	31 (12.5–53)
No. not on any PPI (n=144)	66 (45.8)
Further procedures (Stretta/surgery) (n=195)	6 (3.2)

Values are presented as median (interquartile range) or number (%) unless otherwise indicated.
PFP, proton pump inhibitor-free period; PPI, proton pump inhibitor.

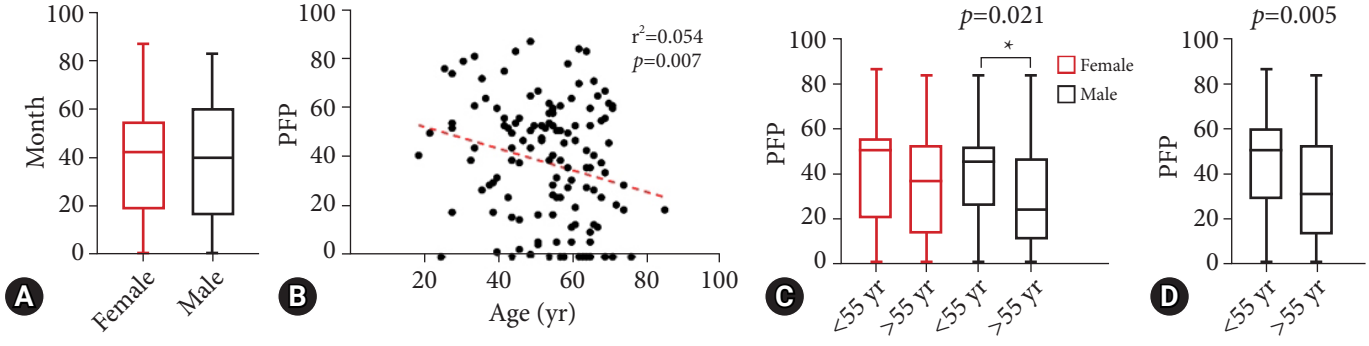

Fig. 1. Post-Stretta outcomes. (A) Box and whisker plot showing PFP between the sexes. (B) Scatterplot with a negative correlation between PFP and age. (C) Box and whisker plot showing PFP between younger (<55 years) and older (>55 years) patients from both sexes. (D) Box and whisker plot showing significantly higher PFP in the younger cohort of patients. PFP, proton pump inhibitor-free period. *p<0.05.

and heartburn scores.[19,32,33]

In this observational study, we investigated 195 patients with refractory GERD who underwent Stretta in a UK tertiary center, making it one of the most significant European studies to date. We present PFP after a median follow-up of 55 months (4.6 years), along with the reinterventions needed in this cohort. Our data suggest a clear correlation between younger age and longevity of PFP, particularly in younger male patients. The progressive loss of LES tone with reduced structural anti-reflux mechanisms is one of the key pathophysiological findings in GERD.[34] An early diagnosis in younger patients may account for the significant benefits observed in this group. Another potential explanation is related to aging. A systematic review investigating the effect of aging on GERD did not find any increase in the prevalence of GERD symptoms with age. However, the study showed that in patients with GERD, aging was associated with more severe symptoms.[35] This could partly explain our finding of significantly reduced PFP in patients over 55 years of age (p=0.005). The denaturation of muscle fibers followed by remodelling is one of the postulated mechanisms of action of Stretta, and aging plays a significant role in the remodelling process. All phases of the healing process are delayed with aging, with a quantitative and qualitative reduction in remodelling being observed.[36] Associated medical comorbidities likely to be seen in the older population may further delay this process and worsen GERD symptomatology. There is also a strong association between GERD symptoms, psychological issues, and the associated functional dyspeptic symptoms, mainly mood and anxiety disorders, which are predominant in the female population. This may partly explain why no difference in PFP was observed between younger and older women in our study. From a long-term sequelae perspective, a reduced exposure of the lower esophagus to gastric acid has the potential to decrease the incidence of Barrett's esophagus, a precursor of esophageal adenocarcinoma.

This study had several limitations. The recall bias may have affected data collection. Patients using over-the-counter Gaviscon or PPI on an 'as and when required' basis were included in the PFP group. However, before Stretta, they were on multiple PPIs, with or without H2 antagonists, and continued to experience refractory symptoms. This finding justifies their inclusion in the PFP group. Although a cost-effectiveness analysis was not performed, significant financial benefits can be attributed to a reduction in regular PPI use. A theoretical decrease in the number of surgical interventions required in patients with refractory GERD has potential financial implications. It is also important to note that most of these fit patients were considered for surgery before the introduction of Stretta.

Moreover, a few patients on aspirin for cardio-protection or stroke prevention were advised to continue low-dose PPI as a gastroprotective agent. However, patients who would have strengthened the analysis were not included in the PFP calculation. Ideally, pre- and post-procedure pH and manometry studies would have helped quantify the benefit of Stretta in our cohort of patients. Due to the logistic constraints, post-procedure pH and manometry studies were carried out only to reinvestigate patients who failed the initial Stretta treatment. Moreover, previous studies have quantified the benefit of Stretta using pre- and post-procedure pH and manometry studies, as mentioned in the introduction.

Conflicts of Interest

The authors have no potential conflicts of interest.

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None.

Author Contributions

Conceptualization: AJ, YV; Data curation: AJ, AK, EH, HF, SK, SM; Formal Analysis: AJ, GK; Investigation: AJ, AK, EH, HF, HH, ST; Methodology: AJ, ST, YV; Project administration: YV; Resources: SM, HH, ST; Software: AJ, GK; Supervision: YV; Validation: YV; Visualization: AJ; Writing–original draft: AJ, AK; Writing–review & editing: all authors.

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REFERENCES

1. Liang WT, Wang ZG, Wang F, et al. Long-term outcomes of patients

with refractory gastroesophageal reflux disease following a minimally invasive endoscopic procedure: a prospective observational study. BMC Gastroenterol 2014;14:178.
2. El-Serag HB, Sweet S, Winchester CC, et al. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut 2014;63:871–880.
3. Peery AF, Crockett SD, Murphy CC, et al. Burden and cost of gastrointestinal, liver, and pancreatic diseases in the United States: update 2018. Gastroenterology 2019;156:254–272.
4. Shaheen NJ, Hansen RA, Morgan DR, et al. The burden of gastrointestinal and liver diseases, 2006. Am J Gastroenterol 2006;101:2128–2138.
5. Patti MG. An evidence-based approach to the treatment of gastroesophageal reflux disease. JAMA Surg 2016;151:73–78.
6. Ma L, Li T, Liu G, et al. Stretta radiofrequency treatment vs Toupet fundoplication for gastroesophageal reflux disease: a comparative study. BMC Gastroenterol 2020;20:162.
7. Hershcovici T, Fass R. Pharmacological management of GERD: where does it stand now? Trends Pharmacol Sci 2011;32:258–264.
8. Naik RD, Meyers MH, Vaezi MF. Treatment of refractory gastroesophageal reflux disease. Gastroenterol Hepatol (N Y) 2020;16:196–205.
9. Fass R, Cahn F, Scotti DJ, et al. Systematic review and meta-analysis of controlled and prospective cohort efficacy studies of endoscopic radiofrequency for treatment of gastroesophageal reflux disease. Surg Endosc 2017;31:4865–4882.
10. Rodríguez de Santiago E, Sanchez-Vegazo CT, Peñas B, et al. Antireflux mucosectomy (ARMS) and antireflux mucosal ablation (ARMA) for gastroesophageal reflux disease: a systematic review and meta-analysis. Endosc Int Open 2021;9:E1740–E1751.
11. Rettura F, Bronzini F, Campigotto M, et al. Refractory gastroesophageal reflux disease: a management update. Front Med (Lausanne) 2021;8:765061.
12. He S, Xu F, Xiong X, et al. Stretta procedure versus proton pump inhibitors for the treatment of nonerosive reflux disease: a 6-month follow-up. Medicine (Baltimore) 2020;99:e18610.
13. Funk LM, Zhang JY, Drosdeck JM, et al. Long-term cost-effectiveness of medical, endoscopic and surgical management of gastroesophageal reflux disease. Surgery 2015;157:126–136.
14. Lee DP, Chang KJ. Endoscopic management of GERD. Dig Dis Sci 2022;67:1455–1468.
15. Nevins EJ, Dixon JE, Viswanath YK. The outcome of endoscopic radiofrequency anti-reflux therapy (STRETTA) for gastroesophageal reflux disease in patients with previous gastric surgery: a prospective cohort study. Clin Endosc 2021;54:542–547.
16. Utley DS. The Stretta procedure: device, technique, and pre-clinical study data. Gastrointest Endosc Clin N Am 2003;13:135–145.
17. Noar MD, Lotfi-Emran S. Sustained improvement in symptoms of GERD and antisecretory drug use: 4-year follow-up of the Stretta procedure. Gastrointest Endosc 2007;65:367–72.
18. Arts J, Bisschops R, Blondeau K, et al. A double-blind sham-controlled study of the effect of radiofrequency energy on symptoms and distensibility of the gastro-esophageal junction in GERD. Am J Gastroenterol 2012;107:222–230.
19. Viswanath Y, Maguire N, Obuobi RB, et al. Endoscopic day case antireflux radiofrequency (Stretta) therapy improves quality of life and reduce proton pump inhibitor (PPI) dependency in patients with gastro-oesophageal reflux disease: a prospective study from a UK tertiary centre. Frontline Gastroenterol 2019;10:113–119.
20. Jung HK, Tae CH, Song KH, et al. 2020 Seoul Consensus on the diagnosis and management of gastroesophageal reflux disease. J Neurogastroenterol Motil 2021;27:453–481.
21. Triadafilopoulos G. Stretta: a valuable endoscopic treatment modality for gastroesophageal reflux disease. World J Gastroenterol 2014;20:7730–7738.
22. Jung HY. In which situation is endoscopic radiofrequency anti-reflux therapy (Stretta) effective for controlling gastroesophageal reflux symptoms? Clin Endosc 2021;54:451–452.
23. Utley DS, Kim M, Vierra MA, et al. Augmentation of lower esophageal sphincter pressure and gastric yield pressure after radiofrequency energy delivery to the gastroesophageal junction: a porcine model. Gastrointest Endosc 2000;52:81–86.
24. Kim MS, Holloway RH, Dent J, et al. Radiofrequency energy delivery to the gastric cardia inhibits triggering of transient lower esophageal sphincter relaxation and gastroesophageal reflux in dogs. Gastrointest Endosc 2003;57:17–22.
25. Chen D, Barber C, McLoughlin P, et al. Systematic review of endoscopic treatments for gastro-oesophageal reflux disease. Br J Surg 2009;96:128–136.
26. Liu HF, Zhang JG, Li J, et al. Improvement of clinical parameters in patients with gastroesophageal reflux disease after radiofrequency energy delivery. World J Gastroenterol 2011;17:4429–4433.
27. Perry KA, Banerjee A, Melvin WS. Radiofrequency energy delivery to the lower esophageal sphincter reduces esophageal acid exposure and improves GERD symptoms: a systematic review and meta-analysis. Surg Laparosc Endosc Percutan Tech 2012;22:283–288.
28. Triadafilopoulos G, DiBaise JK, Nostrant TT, et al. The Stretta procedure for the treatment of GERD: 6 and 12 month follow-up of the U.S. open label trial. Gastrointest Endosc 2002;55:149–156.
29. Corley DA, Katz P, Wo JM, et al. Improvement of gastroesophageal

reflux symptoms after radiofrequency energy: a randomized, sham-controlled trial. Gastroenterology 2003;125:668–676.
30. Coron E, Sebille V, Cadiot G, et al. Clinical trial: radiofrequency energy delivery in proton pump inhibitor-dependent gastro-oesophageal reflux disease patients. Aliment Pharmacol Ther 2008;28:1147–1158.
31. Aziz AM, El-Khayat HR, Sadek A, et al. A prospective randomized trial of sham, single-dose Stretta, and double-dose stretta for the treatment of gastroesophageal reflux disease. Surg Endosc 2010; 24:818–825.
32. Dughera L, Rotondano G, De Cento M, et al. Durability of stretta radiofrequency treatment for GERD: results of an 8-year follow-up. Gastroenterol Res Pract 2014;2014:531907.
33. Noar M, Squires P, Noar E, et al. Long-term maintenance effect of radiofrequency energy delivery for refractory GERD: a decade later. Surg Endosc 2014;28:2323–2333.
34. De Giorgi F, Palmiero M, Esposito I, et al. Pathophysiology of gastro-oesophageal reflux disease. Acta Otorhinolaryngol Ital 2006; 26:241–246.
35. Becher A, Dent J. Systematic review: ageing and gastro-oesophageal reflux disease symptoms, oesophageal function and reflux oesophagitis. Aliment Pharmacol Ther 2011;33:442–454.
36. Gerstein AD, Phillips TJ, Rogers GS, et al. Wound healing and aging. Dermatol Clin 1993;11:749–757.