# Radiofrequency Energy Delivery to the Lower Esophageal Sphincter Reduces Esophageal Acid Exposure and Improves GERD Symptoms: A Systematic Review and Meta-analysis

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**Purpose:** Studies of endoscopic application of radiofrequency energy to the lower esophageal sphincter for gastroesophageal reflux control have produced conflicting reports of its effectiveness. This study aimed to conduct a meta-analysis of randomized controlled trials and cohort studies to assess the impact of this treatment.

**Methods:** Twenty studies were included. Outcomes analyzed included gastroesophageal reflux disease (GERD) symptom assessment, quality of life, esophageal pH, and esophageal manometry.

**Results:** A total of 1441 patients from 18 studies were included. Radiofrequency treatment improved heartburn scores ($P = 0.001$), and produced improvements in quality of life as measured by GERD–health-related quality-of-life scale ($P = 0.001$) and quality of life in reflux and dyspepsia score ($P = 0.001$). Esophageal acid exposure decreased from a preprocedure Johnson-DeMeester score of 44.4 to 28.5 ($P = 0.007$).

**Conclusions:** Radiofrequency ablation of the lower esophageal sphincter produces significant improvement in reflux symptoms and may represent an alternative to medical treatment and surgical fundoplication in select patients.

**Key Words:** GERD, gastroesophageal reflux disease, radiofrequency

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Gastroesophageal reflux disease (GERD) causes significant morbidity in the western world, affecting up to 40% of Americans at least monthly.[1] This disease inflicts significant direct and indirect costs and loss of productivity. Proton pump inhibitors (PPI) provide effective symptom control for many GERD patients, but up to 20% may experience breakthrough heartburn and regurgitation.[2,3] Laparoscopic antireflux surgery provides excellent reflux control and high patient satisfaction rates.[4] However, the invasiveness, high costs, and risks associated with surgery are significant factors that deter some potential patients. These hurdles led physicians to pursue minimally invasive, effective, and durable treatment alternatives that directly address the pathophysiological mechanisms of GERD.[5,6]

Endolumenal approaches to GERD management were conceived as a bridge between medical management and surgical fundoplication. One such intervention, the Stretta procedure (Mederi Therapeutics Inc., Greenwich, CT), applies thermal radiofrequency energy to the lower esophageal sphincter (LES) to reduce GERD symptoms. It uses a flexible catheter with a balloon-basket assembly and nickel-titanium needle electrodes to deliver the radiofrequency energy into the esophageal wall and LES complex, while irrigating the overlying mucosa to prevent heat injury.[7] Since its introduction in 2000, multiple studies have demonstrated the safety and efficacy of the Stretta procedure for GERD therapy.[8–12] However, studies of its effectiveness and durability have produced mixed results.[13]

Definitive conclusions were not drawn because of the heterogeneity of measured variables in different studies of variable patient populations. This prompted us to perform a review and meta-analysis of all cohort series and randomized controlled trials (RCT) of the Stretta procedure published between 2000 and 2010. The aim of this study was to assess the impact of the Stretta procedure on GERD symptom control, patient quality of life (QOL), esophageal acid exposure, and pressures.

## MATERIALS AND METHODS

### Literature Search

A comprehensive and systematic search of the English literature, indexed in PubMed and Medline databases (1966 to 2010), was carried out electronically in November 2010 with the key terms "Stretta," "Radiofrequency ablation of esophagus," and "Radiofrequency GERD." The reference list of each article obtained was checked for further potential studies. The search included RCT, cohort series, and reviews of literature. The full texts and the abstracts were reviewed to evaluate their contents.

### Inclusion and Exclusion Criteria

Titles and abstracts of all identified articles were screened for the following inclusion criteria: study population—patients with GERD undergoing primary antireflux treatment; intervention—radiofrequency delivery to the gastroesophageal junction (GEJ); study design—RCT and cohort studies; availability of data on at least 2 of the following parameters: esophageal manometry, pH study, QOL indices, and medication usage.

Studies were excluded from the analysis if they included children, or if the reported follow-up interval was $<3$ months. Also, preliminary studies containing patient populations that were subsequently reported in larger series with longer follow-up intervals were excluded.

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## Outcomes of Interest and Definitions

Subjective and objective outcomes of GERD treatment were identified from all studies. Subjective outcome assessments included heartburn and patient satisfaction scores calculated on a 5-point Likert scale,[14] disease-specific QOL scores [health-related quality-of-life score (HRQL)[15,16] and quality of life in reflux and dyspepsia score (QOLRAD)],[17,18] and global QOL assessment [short form 36 (SF-36) and short form 12 (SF-12)].[19–22] Objective treatment outcomes examined include Johnson-DeMeester score, esophageal acid exposure time, and mean LES pressure. Results available from at least 4 studies were pooled and included in the meta-analysis.

## Data Extraction

Data from each study, meeting the inclusion and exclusion criteria, were extracted and assessed using preformatted sheets. Data recorded included reference of study, study population characteristics, study design, inclusion and exclusion criteria, number of participating subjects, and results for each included endpoint. The studies were tabulated to assess the homogeneity of the sample population. Thereafter, critical appraisal of the extracted data was performed independently by all coauthors.

## Statistical Analysis

A meta-analysis of the pooled data was performed to evaluate the impact of the Stretta procedure on subjective and objective outcome measures. For each included study, pretreatment and posttreatment subjective and objective assessments were averaged across all patients enrolled in the study. When individual patient data were available, effectiveness was evaluated using a paired $t$ test to compare pretreatment and posttreatment variable scores. Conversely, when only average pretreatment and post-Stretta scores were available, outcomes were assessed using a weighted paired $t$ test. In this analysis, weights were set equal to the number of patients in each study so that each individual patient received equal weight for the inference. The weighted differences were examined to determine whether the weighted mean difference between pre-Stretta and post-Stretta QOL measurements were statistically different than zero. For those studies with more than 1 post-Stretta measurement, we included the longest available follow-up interval. Statistical analyses were performed using SAS (SAS Institute Inc., Cary, NC), which made the correct weight adjustments in calculating means and SE. A $P$ value of $<0.05$ was considered statistically significant.

# RESULTS

The results of the literature search, eligibility assessment, and classification of studies is outlined in Figure 1. The initial search yielded 68 potential articles containing information about the Stretta procedure. Of these, 42 did not meet the inclusion criteria and 4 were rejected based on the exclusion criteria. Of the 22 remaining studies, 2 were removed because of the presence of a more recent publication from the same authors or the same institution with a larger study population. Hence, a total of 20 studies published between 2001 and 2010 were included in the analysis. Two were randomized sham-controlled trials, whereas the remaining were cohort series.[2,8,10–13,23–36]

The study and patient characteristics are summarized in Table 1. Males comprised 52.9% of the study population. Patient sex was not documented in 2 studies. The mean age was 47.5 ± 7.2 years, and the average procedure time was 45.9 ± 5.4 minutes. The mean follow-up interval was 17.1 ± 15.5 months. Baseline and postprocedure subjective and objective outcomes are summarized in Table 2.

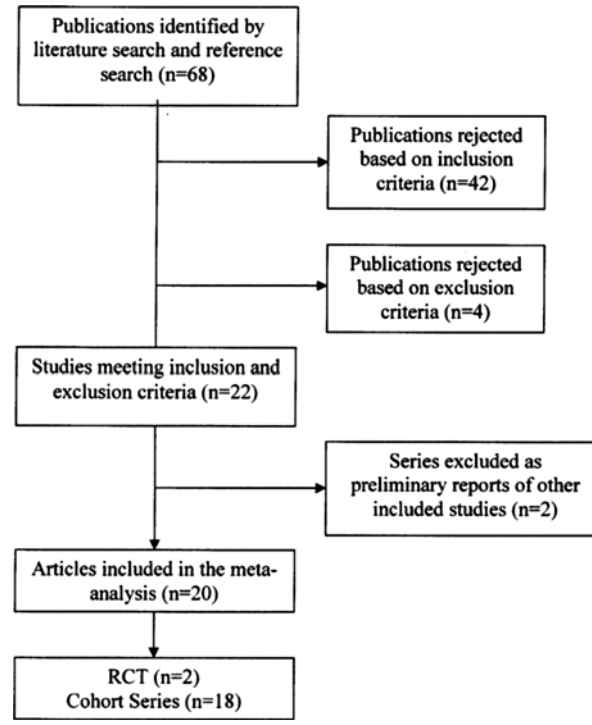


**FIGURE 1.** Flowchart showing the process of study selection for the meta-analysis. RCT indicates randomized controlled trial.

## GERD Symptoms and Patient Satisfaction

Five hundred twenty-five patients in 9 studies were evaluated with subjective heartburn scores. An overall decrease in heartburn was observed in the pooled population across all the relevant studies from a mean score of 3.55 ± 3.9 to 1.19 ± 3.4 over 24.1 months ($P = 0.0001$).

Five of the 20 articles, containing 366 patients, documented mean Likert satisfaction scores. These studies demonstrated an overall improvement in patient satisfaction with their medical condition from a mean of 1.43 ± 4.1 at baseline to 4.07 ± 3.1 after the Stretta procedure at a mean follow-up period of 21.9 months ($P = 0.0006$).

## Patient QOL

Patient QOL data are presented in Figure 2. Nine studies containing 433 patients evaluated the effect of treatment on patient QOL using the GERD-HRQL scale with an average follow-up interval of 19.8 months. These scores improved from 26.11 ± 27.2 at baseline to 9.25 ± 23.7 after treatment ($P = 0.0001$). QOLRAD scores were collected in 4 studies containing 250 patients and improved from 3.3 ± 5.9 to 4.97 ± 4.9 at a mean follow-up interval of 25.2 months ($P = 0.001$).

SF-36 was utilized to assess global QOL of the patient population in 6 studies. A total of 299 patients responded to the SF-36 physical form, during a mean follow-up period of 9.5 months, demonstrating an improvement from 36.45 ± 51.6 at baseline to 46.12 ± 61.9 postprocedure ($P = 0.0001$). Two hundred sixty-four patients in 5 of the 6

 

**TABLE 1.** Characteristics of Included Studies and Patients

| References | Study Type | Mean Follow-Up Interval (mo) | Patients Total (n) | Patients Male (n, %) | Patients Female (n, %) | Mean Age (y) | Mean Weight (kg) |
|---|---|---|---|---|---|---|---|
| Noar and Lotfi-Emran[2] | Cohort | 48 | 109 | 62 | 47 | 51 | 77 |
| Triadafilopoulos et al[8] | Cohort | 12 | 118 | 72 | 46 | 47 | 86.1 |
| Wolfsen and Richards[10] | Cohort | 8 | 558 | NR | NR | NR | NR |
| Reymunde and Santiago[11] | Cohort | 48 | 83 | 65 | 18 | NR | NR |
| Go et al[12] | Cohort | 10 | 50 | 22 | 28 | 47 | NR |
| Dundon et al[13] | Cohort | 53 | 32 | 14 | 18 | 46 | NR |
| Corley et al[23] | RCT | 6 | 64 | 33 | 31 | 45 | NR |
| Aziz et al[24] | RCT | 12 | 36 | 24 | 12 | 36.9 | 86 |
| Tam et al[25] | Cohort | 12 | 20 | 10 | 10 | 51.2 | NR |
| Houston et al[26] | Cohort | 6 | 41 | 16 | 25 | 46 | NR |
| Lutfi et al[27] | Cohort | 26.2 | 61 | 24 | 37 | 52.1 | NR |
| Arts et al[28] | Cohort | 6 | 13 | 4 | 9 | 51 | 76.5 |
| Cipolletta et al[29] | Cohort | 12 | 32 | 20 | 12 | 46 | NR |
| Torquati et al[30] | Cohort | 27.1 | 36 | — | — | 46.8 | NR |
| DiBaise et al[31] | Cohort | 6 | 18 | 11 | 7 | 38 | NR |
| Meier et al[32] | Cohort | 12 | 60 | 31 | 29 | 47 | 77 |
| Higuchi et al[33] | Cohort | 6 | 9 | 6 | 3 | 62.4 | NR |
| Mattar et al[34] | Cohort | 20 | 7 | 0 | 7 | 49 | NR |
| Richards et al[35] | Cohort | 7.3 | 65 | 27 | 38 | 46 | NR |
| Mansell[36] | Cohort | 4 | 29 | 7 | 22 | 63.1 | NR |
| Total | — | 17.1 ± 15.5 | 1441 | 448 | 399 | 47.5 | 80.5 |

NR indicates not reported.

studies responded to the SF-36 Mental form demonstrating improvement from 46.79 ± 20.5 to 55.16 ± 17.6 at 10-month follow-up ($P = 0.0015$).

## Esophageal Acid Exposure and LES Pressure

Preprocedure and postprocedure esophageal pH studies were documented in 11 of the 20 studies. The Johnson-DeMeester score improved from 44.37 ± 93 pre-Stretta to 28.53 ± 33.4 post-Stretta over an average period of 13.1 months in 267 patients across 7 studies ($P = 0.0074$).

EAET was reported in 11 studies comprising of 364 patients over a mean follow-up period of 11.9 months. Esophageal acid exposure decreased from a mean of 10.29% ± 17.8% to 6.51% ± 12.5% ($P = 0.0003$).

LES pressure was reported in 7 studies including 263 patients. The average pressure increased from 16.54 ± 34.7 mm Hg pre-Stretta to 20.24 ± 29.1 mm Hg post-Stretta with a mean follow-up period of 8.7 months ($P = 0.03$).

## DISCUSSION

The central aim of this meta-analysis was to examine the impact of the Stretta procedure on GERD symptom control, patient QOL, esophageal acid exposure, and LES pressure. The included studies were published between 2000 and 2010 and contained 1441 patients with a mean follow-up interval of 15 months. Radiofrequency energy delivery to the LES produced significant improvements in GERD symptoms and both disease-specific and global QOL. Esophageal acid exposure was improved, but not normalized after treatment; and the Stretta procedure did not significantly increase LES pressure.

GERD is a common disease that causes significant symptoms and negatively impacts patient QOL. PPI therapy is highly successful in relieving heartburn symptoms in 80% to 90% of patients; however, many patients suffer from relapse of symptoms or persistent volume reflux and require life-long medical therapy.[37] Primary antireflux surgery controls GERD symptoms in 90% of patients, but is associated with troubling side effects and the morbidity and

**TABLE 2.** Comparison of Baseline and Posttreatment Subjective and Objective Outcome Measures

| Outcome Variables | Studies (n) | Patients (n) | Mean Follow-Up (mo) | Pre-Stretta | Post-Stretta | *P* |
|---|---|---|---|---|---|---|
| GERD-HRQL score | 9 | 433 | 19.8 | 26.11 | 9.25 | 0.0001 |
| QOLRAD score | 4 | 250 | 25.2 | 3.30 | 4.97 | 0.0010 |
| SF-36 physical | 6 | 299 | 9.5 | 36.45 | 46.12 | 0.0001 |
| SF-36 mental | 5 | 264 | 10.0 | 46.79 | 55.16 | 0.0015 |
| Heartburn score | 9 | 525 | 24.1 | 3.55 | 1.19 | 0.0001 |
| Satisfaction score | 5 | 366 | 21.9 | 1.43 | 4.07 | 0.0006 |
| Esophageal acid exposure (% pH < 4) | 11 | 364 | 11.9 | 10.29 | 6.51 | 0.0003 |
| Johnson-DeMeester score | 7 | 267 | 13.1 | 44.37 | 28.53 | 0.0074 |
| LES pressure (mm Hg) | 7 | 263 | 8.7 | 16.54 | 20.24 | 0.0302 |

GERD indicates gastroesophageal reflux disease; LES, lower esophageal sphincter; QOLRAD, quality of life in reflux and dyspepsia score; SF-36, short form 36.

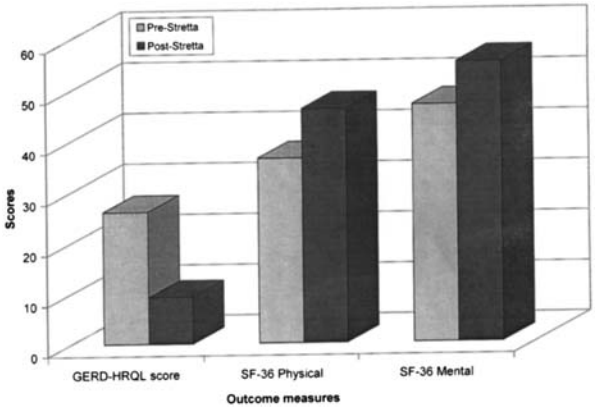


**FIGURE 2.** Clustered bar diagram of baseline and postprocedure disease-specific and global quality-of-life measures. GERD indicates gastroesophageal reflux disease; HRQL, health-related quality-of-life; SF-36, short form 36.

mortality associated with any major intraabdominal surgery.[38] Efficacious endoluminal GERD treatments with good side-effect profiles and low complication rates have long been sought as a bridge between long-term medical therapy and laparoscopic Nissen fundoplication.

The Stretta procedure is an outpatient endoscopic procedure approved by the FDA for the treatment of symptomatic GERD. After the measurement of the distance to the Z-line by upper endoscopy, the Stretta device is used to deliver radiofrequency energy through 4 electrodes to the LES complex at 5 mm intervals between 1 cm proximal and 1 cm distal to the Z-line. Continuous irrigation of the esophageal mucosa and surface temperature monitoring is utilized to prevent thermal mucosal injury.[9,12,26]

In this analysis, the Stretta procedure produced significant improvements in heartburn symptoms, patient satisfaction, and patient QOL.[2,8–12,25,28,31] Mean heartburn score decreased in each individual study and showed a significant change from 3.55 to 1.19 in the pooled analysis. Studies have consistently shown improvements in disease-specific and global patient QOL metrics. GERD-HRQL scores decreased from 26.11 to 9.25 after Stretta therapy, and studies showed consistent improvement in SF-36 physical component scores. Finally, overall patient satisfaction with their medical condition increased from 1.43 to 4.10 on a 5-point Likert scale after treatment. These consistent improvements in validated, patient-centered metrics demonstrate that the Stretta procedure improves patients' GERD symptoms and QOL, and results in a high level of patient satisfaction, at least at short to intermediate follow-up intervals.

Although there is a dearth of long-term follow-up data on the procedure in the literature, 2 studies, with a mean follow-up of 48 months, reported a significant decrease in the mean heartburn score at the time of the final follow-up compared with the pre-Stretta values. Noar and Lotfi-Emran further demonstrated an improvement in the overall GERD-HRQL score from 27.8 to 7.1 and the satisfaction score from 1.4 to 3.8. Notably, 75% and 86% of patients were medication free at 48 months with the rest experiencing a significant decrease in the use of PPI or other antisecretory medications.[2,11] However, Dundon et al,[13] presented a more unfavorable picture in an unselected patient population. With a mean long-term follow-up of 53 months, they reported a statistically insignificant overall decrease in heartburn score from 2.43 pre-Stretta to a score of 1.77 post-Stretta. The rate of failure of the procedure was almost 59% with the patients requiring antireflux surgery about 6 months after the Stretta procedure. They further recommended that minimal response at 6 months should be considered failure of the procedure and other avenues should be considered for the surgical management of GERD. Only 2 of 13 responders (15%) were found to be off PPI at the time of long-term follow-up. However, the group that ultimately underwent surgery also experienced significant improvement in their baseline heartburn symptoms and overall GERD condition post-Stretta compared with pre-Stretta.

The Stretta procedure has demonstrated the ability to reduce, but not consistently normalize esophageal acid exposure. Johnson-DeMeester score and EAET have been reported to improve significantly in most studies with a few exceptions. DiBaise et al[31] reported a 72% improvement in the distal esophageal acid exposure with normalization of the EAET in 4 of 18 patients at 6 months after the Stretta procedure. However, these results failed to reach statistical significance. Corley and colleagues reported absence of significant decrease in the distal esophageal acid exposure in their study population at 6 months as well. However, upon stratifying the patients on the basis of responders and nonresponders, they observed significant improvement in the acid exposure of the former group after the procedure.[23] These results demonstrate the effectiveness of the Stretta procedure in reducing distal acid exposure, at least in those who respond to treatment.

The mechanism of action of radiofrequency delivery to the GEJ for the management of GERD is not fully understood. One possible theory is a reduction in the frequency of the transient LES relaxations (TLESR), which is incriminated as the primary cause of GERD. Ablation of the vagal afferent pathways by radiofrequency energy may result in the decrease in TLESR after the Stretta procedure.[39] Another school of thought believes that heat-induced alteration of the GEJ musculature, resulting in decrease in tissue compliance and increase in tensile strength, is responsible for the therapeutic action of the Stretta device.[35,40] The third theory proposes progressive tissue remodeling of the GEJ, secondary to thermal energy, as the cause of reduced frequency of TLESR when the stomach is distended by air or ingested food.[31] Changes in the manometric characteristics of the LES after the Stretta procedure have been inconsistent, and no significant change in LES pressure from baseline was demonstrated in the pooled analysis. As such, the examination of manometric changes performed to date provides little help in elucidating the mechanism of action for this procedure. Differential manometric changes in the LES between responders and nonresponders have not been sufficiently studied and may provide a target for further investigation.

The most common complications encountered after the Stretta procedure are gastroparesis and ulcerative esophagitis.[8,23,24,26,29,35] These are known to be transient and reversible. There were reports of esophageal perforations associated with this procedure at its inception which was attributed to the inexperience of the surgeons; however, no such grave complications have been reported since. A recent RCT published the use of double radiofrequency treatment in patients who did not experience an improvement in their GERD-HRQL by 75% at 4 months

 

after initial Stretta.[24] This subgroup of the patients achieved increased improvement in esophageal function and reduction in GERD medications compared with the regular single Stretta group. But the double therapy was associated with increased incidence of complications, especially gastroparesis in 2 of 12 patients, thereby questioning the implementation of this aggressive treatment.

The consistent improvement in patient's symptoms after the Stretta procedure suggests that this technique can provide significant benefit for select patients. However, the definition of the appropriate patient populations for Stretta therapy remains controversial. The paradigm for the surgical treatment of GERD, advocated by Richards et al,[35] recommended the Stretta procedure for patients having hiatal hernias $\leq 2$ cm, LES pressure $> 8$ mm Hg and absence of Barrett esophagus. The majority of the studies since this publication have more or less abided by these guidelines. LF was reserved for larger hiatal hernias and inadequate LES barriers where the anatomic and mechanical barrier to reflux could be reconstructed. They observed slightly improved outcomes in the management of the extraesophageal manifestations of GERD with LF as well. These data suggest that patients with typical GERD symptoms with minimal anatomic disruption at the LES are likely to benefit from Stretta treatment.

Our meta-analysis is limited by differences in methodology and definition of criteria for some variables between studies, and absence of blindness in most of the included studies. The heterogeneity of the study population across these reports may also influence the interpretation of the pooled results.

In conclusion, radiofrequency ablation of the LES produces significant improvement in GERD symptoms, patient satisfaction, and QOL at short and intermediate term follow-up. These findings suggest that the Stretta represents a viable treatment option for select patients with symptomatic GERD. Larger and longer-term studies are required to establish the durability of the treatment effect, and to identify the patient populations that gain the greatest benefit from this treatment.

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