



Clinical experience with the Stretta[®] procedure

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Gastroesophageal reflux disease (GERD) is a chronic disorder that affects as many as 14 million Americans daily [1]. GERD typically manifests as heartburn, regurgitation or dysphagia, and may lead to esophagitis, Barrett's metaplasia, and esophageal adenocarcinoma [2]. The disease impacts on quality of life often more than heart failure and angina pectoris [1,3]. Patients report lost wages, poor job performance, reliance on medication, chronic pain, anxiety, and fear of cancer or heart disease. [3] In most cases, GERD requires long-term anti-secretory drug therapy or anti-reflux surgery. More recently, radiofrequency energy therapy of the gastroesophageal junction (Stretta[®] procedure) has been added as an option for the treatment of this chronic condition. Despite skepticism [4], the procedure is widely performed in the United States and its use is spreading around the world.

The Stretta[®] system (Curon Control Module, Curon Medical, Inc., Sunnyvale, California) consists of a radiofrequency generator and a single-use RF energy catheter. The RF generator delivers pure sine-wave energy through a temperature feedback control system. The RF energy delivery catheter is comprised of a soft, 6mm shaft with a guide-wire tip, a balloon-basket assembly which inflates to a maximum 3cm diameter, four electrode delivery sheaths positioned radially around the balloon, as well as suction and irrigation (Fig. 1). The generator delivers RF in an automated fashion under temperature control using thermocouple monitoring, while the power output is regulated by computer algorithm. Target tissue as well as mucosal temperature are achieved and maintained through a special suction and irrigation system. There is a curved nickel-titanium

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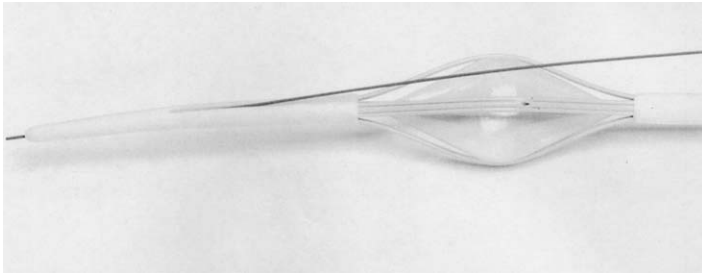


Fig. 1. The Stretta[®] disposable catheter tip carrying the balloon/basket combination prior to introduction over a guide wire.

needle electrode (25 gauge, 5.5 mm length) within each delivery sheath, each with a thermocouple at the tip and base of the needle. When the catheter is positioned and the needles deployed into the circular muscle of the distal LES or cardia, RF energy is delivered to each electrode to achieve a temperature of 85°C in the muscle, while irrigation maintains mucosal temperature < 50°C. The result is a thermal lesion in the muscle with intact overlying mucosa (Fig. 2).

Mechanisms of action of Stretta[®] in humans

Radiofrequency treatment of the gastroesophageal junction has several beneficial effects. First, some evidence suggests that the lower esophageal sphincter pressure (LESP) increases after Stretta[®], providing a barrier to reflux. Tam [5], in a human trial with 20 patients showed a 60% increase in basal LES pressure 6 months after Stretta[®]. They studied patients with GERD before and 6 months

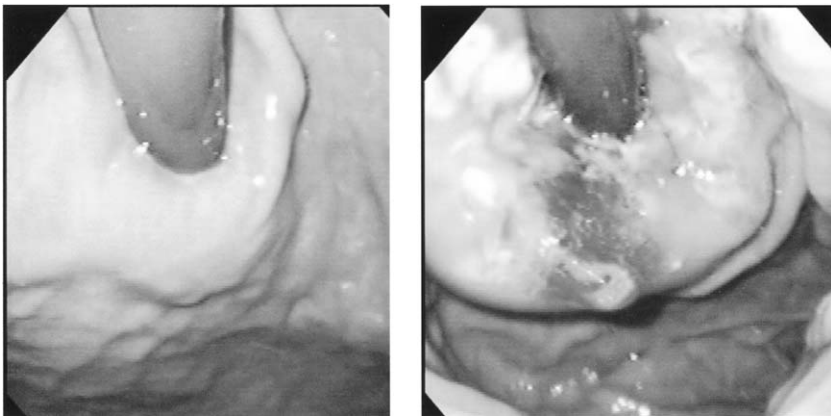


Fig. 2. Endoscopic appearance of the gastroesophageal junction (GEJ) before and immediately after Stretta[®]. (Left) Retroflexed view of GEJ. (Right) Mucosal burn marks straddling the GEJ. These marks disappear within 10 days after Stretta[®]. (See also Color Plate 6.)

after Stretta[®] and noted that the resting LESP remained significantly higher for at least 2 hours postprandially after the procedure as compared to before. The effect of Stretta[®] in patients with delayed gastric emptying and GERD symptoms was evaluated by Noar [6]. Baseline half-time gastric emptying was 106 to 250 minutes in 6 patients. Normalization of gastric emptying was noted in five patients 8 months after Stretta[®], while the remaining patient had improvement but was not normalized. It is hypothesized that augmenting the anti-reflux barrier improves gastric motility efficiency in these patients who demonstrate baseline impairment [7].

A second, potentially synergistic mechanism of action of Stretta[®], is the disruption of the triggering mechanism for transient LES relaxations (tLESRs). DiBaise et al [8], reported a 44% reduction in stimulated tLESRs in humans after RF delivery, whereas Tam et al [5] found a 50% reduction in stimulated reflux events and a 25% reduction in tLESRs. Transient LESRs are considered a neurologic event, reduced by vagal blockade [8] and the GABA_B-receptor agonist baclofen [9], therefore radiofrequency energy may disrupt these aberrant intramural vagal afferent nerve pathways within the gastric cardia.

Patient selection

Candidates for Stretta[®] should have chronic heartburn or regurgitation, regularly requiring and responding at least in part to anti-secretory drug therapy for GERD. Patients with failed, non-displaced fundoplication or other gastric surgery could also be considered on an individual basis. Although more efficacy data are needed in this regard, patients with extraesophageal manifestations of GERD (ENT, pulmonary) should also be considered. All patients should have adequate esophageal peristaltic function and LES relaxation in response to swallows during a motility study and pathologic esophageal acid exposure on 24-hour ambulatory pH testing [10]. Candidates should be counseled regarding the treatment options for GERD, including anti-reflux surgery. Non-eligible patients are those who are pregnant, poor surgical candidates (ASA IV), those with a > 2 cm sliding hiatal hernia, active grade III or IV esophagitis, long segment Barrett's metaplasia, high-grade dysplasia or cancer, shortened esophagus, or collagen vascular disease. Gastric emptying delay is not an exclusion criterion for Stretta[®].

Safety and tolerability in humans

In an open label US trial of 118 patients [10,11], the procedure complication rate was 8.6%. All complications were acute and self-limited, and included fever without leukocytosis for 24 hours, transient chest pain or dysphagia, sedation-induced transient hypotension, allergy to topical anesthesia, and superficial mucosal injury during catheter insertion. There were no perforations, infections, or deaths, and there were no late complications such as stricture formation,

Table 1
Complications of Stretta[®]

Complication	n	%
Mucosal ulcer	2	0.11%
Bleeding	1	0.05%
Esophageal mucosal injury	1	0.05%
Esophageal perforation	4	0.22%
Pneumonia, death	2	0.1%
Pleural effusion	1	0.05%
Atrial fibrillation	1	0.05%
Microperforation, air leak below diaphragm (negative barium swallow)	3	0.16%
Dispersive electrode skin injury	1	0.05%

development of dysphagia, gastrointestinal bleeding or achalasia. Safety and tolerability in other human trials has been similar. If Stretta[®] leads to incomplete symptom control, subsequent fundoplication is feasible without additional difficulty. Two studies that assessed vagal function and gastric emptying [12,13] before and after Stretta[®] showed preservation of normal function at the 6-month follow-up.

Postmarketing experience with Stretta[®] has confirmed the overall safety of the procedure. Table 1 shows the various complications that have been reported so far; Fig. 3 graphs the number of adverse events reported to the FDA through the medical device reporting (MDR) system since the introduction of the procedure in the US market. Despite the increasing and widespread use of the procedure in

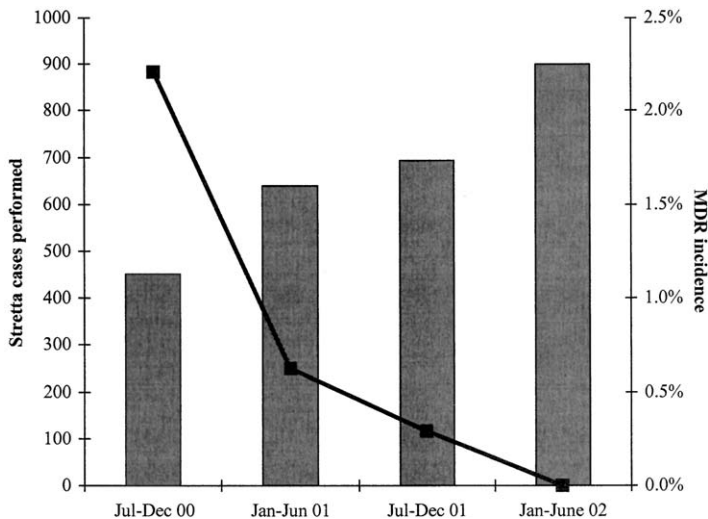


Fig. 3. Rate of adverse events (MDRS) reported to the FDA per number of Stretta[®] cases performed since its introduction to the US market.

major medical centers as well as community practice settings, the number of complications has remained low overall. Principles of care and guidelines to prevent Stretta[®] complications are as follows:

- Proper patient selection
- Technical considerations
 - Proper sedation
 - Mucosal protection (cooling)
 - Balloon pressure (~ 2.5 psi)
 - Catheter positioning (< 1 cm above z-line)
 - Endoscopy confirmation after 1st treatment set
 - Use of guidewire catheter
- Patient management guidelines
 - Stretta patient discharge card
 - Physician guidelines and patients' instructions

Clinical efficacy

In an open label US trial of 118 patients, [10,11] there was a significant improvement in heartburn scores from a median of 4 (baseline) to 1 (12 months, $P \leq 0.0001$). Median GERD scores improved from 27 to 9 ($P \leq 0.0001$). Median patient satisfaction scores improved from 1 to 4 ($P \leq 0.0001$). Improvements for all parameters persisted when intent-to-treat analysis was applied ($P \leq 0.0001$). Patients had superior satisfaction and GERD scores at 12 months compared to those at baseline while on their anti-secretory drugs. There were also significant improvements at 12 month in mental and physical quality of life, as assessed by the SF-36 questionnaire.

In this trial, median distal esophageal acid exposure time improved from 11.7% to 4.8% ($P \leq 0.0001$) and median DeMeester score improved from 44.4 to 20.9 ($P \leq 0.0001$). Proximal esophageal acid exposure improved from 2.5% to 0.5% ($P \leq 0.0001$). At baseline, 90% of these reported patients used, on average, twice-daily PPI therapy. At 6 months, 70% of patients used no medications. In this group at 12 months, 77% of patients used no medications.

In a single-center Australian study, Tam et al [5], reported on 20 patients with chronic GERD who underwent Stretta[®]. In these patients, esophageal acid exposure was reduced from 10.8% to 6.6% ($P < 0.05$) and basal LES pressure was increased by 60%. At 6 months, 75% of patients were able to discontinue all anti-secretory medications. There was also significant improvement in esophagitis grade, GERD scores (19 to 6, $P < 0.01$) and quality of life scores, similar to that seen in the open label US trial [5].

A series of single-center studies have shown similar results. Reymunde et al [14], in 82 consecutively treated patients, reported an overall 70% improvement in GERD quality of life scores. Ninety-seven percent of patients were able to discontinue baseline PPI use. Mansell [15], treated 22 women and 7 men (age

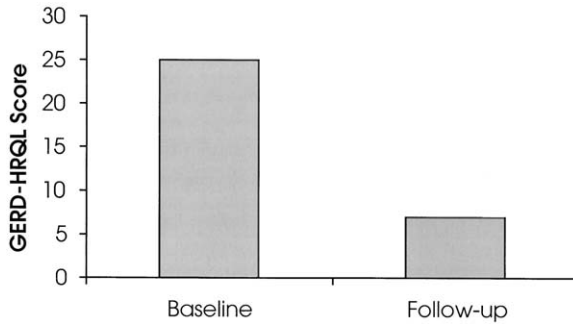


Fig. 4. Gastroesophageal reflux disease health-related quality of life scores before and after Stretta[®] in reported clinical trials [10–14].

63.1 ± 14 years, mean ± SD) with and without hiatal hernia. At follow-up (136 ± 78 days), there were significant improvements in the median heartburn score (4 to 1, $P < 0.001$), GERD score (32 to 9, $P < 0.001$), satisfaction (1 to 5, $P < 0.001$), mental SF-36 (52.5 to 59.4, $P = 0.001$), physical SF-36 (31.3 to 39.2, $P < 0.001$). Subgroup analysis demonstrated that presence of a hiatal hernia had no impact on the observed improvements in GERD, heartburn, quality of life (QOL), or medication use ($P > 0.05$). Medication use improved from baseline (79% 2 × PPI, 17% 1xPPI, and 4% H₂RA) to post-treatment (17% 2 × PPI, 7% 1 × PPI, 7% H₂RA, and 69% no drug or prn medication only). There were no adverse effects requiring therapeutic or diagnostic intervention. One patient had fundoplication for incomplete symptom control.

DiBaise et al [8], reported on 10 patients with chronic GERD treated with Stretta[®]. A dramatic reduction in symptom scores (113.4 versus 82.4, $P = 0.023$) and antacid use (14.5/wk versus 2.3/wk, $P = 0.008$) was noted. Ninety percent of patients discontinued all anti-secretory medications.

Houson et al [16] reported on 41 patients undergoing the Stretta procedure between August 2000 and August 2001. At 7 months, there was a significant

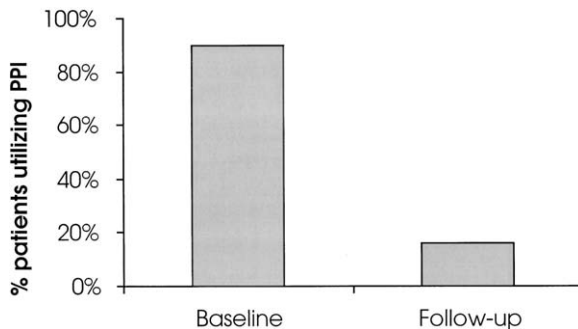


Fig. 5. Percent of patients using proton pump inhibitors before and 6 to 12 months after Stretta[®] in reported clinical trials [10–14].

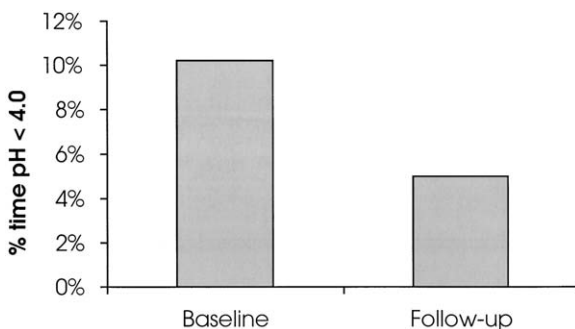


Fig. 6. Percent distal esophageal acid exposure over 24 hours, before and 6 months after Stretta[®] in reported clinical trials [10–14].

decrease in esophageal acid exposure time ($8.4 \pm 0.9\%$ to $4.4 \pm 1.3\%$, $P < 0.03$). The quality of life scores were significantly improved at 6 months: quality of life scores increased from 3.7 ± 0.2 to 5.1 ± 0.2 ($P < 0.001$), SF12 mental score increased from 44.3 ± 2.0 to 51.8 ± 1.7 ($P < 0.001$), and SF12 physical score increased from 26.2 ± 2.4 to 33.1 ± 3.8 ($P < 0.001$). Twenty of 31 patients (65%) available for 6 months follow-up were completely off proton pump inhibitors, while an additional 30% of patients had reduced the dose or frequency of their PPI. Results from these studies are summarized in Figs. 4–6.

Data from two unpublished studies, a randomized, double-blind sham-controlled trial, and a national post-marketing registry study of 590 patients, have been presented at DDW (Digestive Disease Week) 2002, further supporting the safety and effectiveness seen in previous studies [17,18].

Summary

The benchmarks in GERD therapy comprise the commonly prescribed anti-secretory drugs (H₂RAs and PPIs) and anti-reflux surgery [19]. Although drugs are typically safe, cost and patient compliance are challenges to long-term management [20]. Furthermore, while heartburn may be controlled with aggressive medical therapy, other symptoms such as regurgitation may persist, reducing patient satisfaction and adversely affecting quality of life. Surgical anti-reflux procedures, most commonly laparoscopic Nissen fundoplication, improve GERD symptoms and normalize esophageal acid exposure in most patients [21]. Patient perception of the potential risk of abdominal surgery and general anesthesia may limit willingness to undergo surgery resulting in only a small portion of GERD sufferers that actually undergo anti-reflux surgery each year.

Overall, the Stretta[®] procedure is well tolerated, with an acceptably low incidence of complications and obviates the need for anti-secretory drug therapy for most patients at the 6- and 12-month follow-up. GERD symptom scores,

heartburn, satisfaction, and SF-36 scores significantly improve over the baseline and this effect lasts at least 12 months. The symptomatic improvement after Stretta[®] at 12 months in one trial (GERD score, 27 to 9) is similar to that reported by Velanovich after fundoplication (GERD score, 27 to 3). [11] Furthermore, the significant reduction in median esophageal acid exposure time (distal 10.6% to 6.2%, proximal 1.9% to 0.9%), provides objective evidence of an anti-reflux effect. Although the reported studies have been non-randomized, the objective improvement observed in esophageal acid exposure and the persistence of GERD symptom score improvement with repeated measure analysis over a course of 12 months make a significant placebo effect unlikely. Stretta[®] is a promising new technology for the treatment of GERD that should be considered for patients who wish to discontinue a lifelong anti-secretory medication regimen or who have incomplete GERD symptom control on drugs, but are not yet accepting anti-reflux surgery.

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