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Randomised clinical trial: oesophageal radiofrequency energy delivery versus sham for PPI-refractory heartburn

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Summary

Background: Oesophageal radiofrequency reduces use of proton pump inhibitors (PPIs) in patients with gastro-oesophageal reflux disease responding to PPIs.

Aim: To determine the efficacy of oesophageal radiofrequency in patients with PPI-refractory heartburn.

Methods: A randomised, double-blind, sham-controlled multicentre study was designed to assess the efficacy of oesophageal radiofrequency in PPI non-responding patients with heartburn. Patients had moderate-to-severe heartburn defined by at least 3 occurrences a week, and not improved by continuous PPI treatment. The primary endpoint was clinical success at week 24, defined by intake of less than 7 PPI doses over the 2 preceding weeks and adequate symptom control determined by the patient.

Results: Sixty two patients were randomised, 29 to the oesophageal radiofrequency group and 33 to the sham group. Intention-to-treat analysis showed that 1/29 (3.4%) and 5/33 (15.1%) achieved the primary endpoint in the oesophageal radiofrequency and sham groups, respectively (NS). There was no significant difference between oesophageal radiofrequency and sham regarding the number of days without heartburn, days with PPI consumption in the last 2 weeks, and patients not taking PPIs. No pH-impedance parameter was associated with clinical response. The occurrence of adverse events was similar in both groups.

Conclusion: This sham-controlled, randomised study did not demonstrate any efficacy of oesophageal radiofrequency for the treatment of PPI-refractory heartburn regarding symptom relief or consumption of PPIs. ClinicalTrials.gov NCT01682265.

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1 | INTRODUCTION

Typical gastro-oesophageal reflux disease (GORD) symptoms, ie heartburn and regurgitation, affect 25%-30% of adults in Western countries.[1] Acid suppression with proton pump inhibitors (PPIs) is the mainstay of therapy for GORD. However, approximately 30% of patients report partial or nonresponse to PPI therapy,[2,3] and PPI-refractory GORD has become one of the most common presentations of GORD in gastrointestinal clinical practice.[4]

The underlying mechanisms of reflux-related refractory heartburn may be a poorly controlled acid reflux ("true refractory GORD") or hypersensitivity to acidic or weakly acidic reflux episodes while a subgroup of patients have functional heartburn, ie heartburn refractory to PPIs not associated with any type of reflux on pH-impedance monitoring.[5,6]

The therapeutic management of PPI-refractory heartburn is challenging. In patients with reflux-related symptoms, several approaches have been proposed: laparoscopic fundoplication in well-selected patients,[7] anti-reflux medications such as baclofen (which use is limited by side-effects)[8] and pain modulators targeting visceral hypersensitivity.[9,10] Neuromodulators represent the only therapeutic option in patients with functional heartburn,[5] presuming that visceral hypersensitivity is a major determinant of symptom generation.

Radiofrequency energy delivery (Stretta® procedure) has been proposed two decades ago as an alternative to long-term medical or surgical treatment for GORD. The exact mechanism of action of oesophageal radiofrequency remains unclear. The procedure may induce inflammation and fibrosis at the level of the lower oesophageal sphincter (LOS) and subsequently increase LOS pressure,[11] decrease oesophago-gastric junction compliance[12] and occurrence of transient LOS relaxations.[13] The efficacy of oesophageal radiofrequency regarding improvement in both physiologic parameters (acid exposure time) and symptoms remains controversial. A meta-analysis of all randomised controlled trials and cohort studies concluded that oesophageal radiofrequency improved both subjective (symptoms and quality of life) and objective endpoints (acid exposure time),[14] while when only randomised controlled trials were considered, no significant changes could be demonstrated.[15] Most of these studies have included GORD patients dependent of a long-term PPI therapy, with the objective to decrease or stop medications. Few cohort studies have focused on patients with refractory GORD symptoms. Hillman et al have collected the results of six cohort studies in PPI nonresponsive patients and, although significant symptomatic improvement was observed (possibly related to a placebo effect), there was a wide range of PPI discontinuation rate and a marginal effect on oesophageal acid exposure.[16] The discrepancy between symptom improvement and marginal effect on acid exposure time[17] has raised the hypothesis that oesophageal radiofrequency may decrease oesophageal sensitivity.

Of note, all oesophageal radiofrequency studies performed included patients with documented GORD and complete or partial response to PPIs. Since most of the patients with refractory heartburn have functional oesophageal disorders (reflux hypersensitivity or functional heartburn) and considering a possible effect of oesophageal radiofrequency on oesophageal sensitivity, we designed a randomised sham-controlled study of oesophageal radiofrequency in unselected patients with refractory heartburn.

2 | PATIENTS AND METHODS

2.1 | Study design

We designed a multicentre double-blind sham-controlled trial performed in eight French centres to assess the efficacy of oesophageal radiofrequency in patients with PPI-refractory heartburn. All the patients who gave their written informed consent were included. During a 2-week run-in period after inclusion, a 24-hour pH-impedance monitoring on PPIs was performed, patients were requested to maintain their PPI intake at their usual dose and to fill in a diary card indicating intensity and frequency of heartburn and PPI intake every day. Before randomisation, the 2-week diary card was used to confirm inclusion criteria. Completed questionnaires consisting of the Gastrointestinal Symptoms Rating Scale (GSRS) and the Quality of Life in Reflux and Dyspepsia (QOLRAD) were collected at this visit. Patients were randomised to receive either oesophageal radiofrequency or a sham procedure by the Nantes Clinical Research Centre according to a centralised code (block of 4 per centre) provided by a dedicated software. In order to maintain double blind, the endoscopic procedure was performed by an independent physician not involved in the follow-up of patients. All patients were asked to take a double dose of PPIs after the procedure. Follow-up visits were planned at weeks 4, 8, 12, 18, 24 and 48 post-procedure to assess symptom relief, PPI use and side effects. At each visit, patients were systematically asked "Is your heartburn adequately controlled?". When the response was "yes", the patient was proposed to decrease PPIs from double to single dose, and from single dose to on-demand therapy. In patients with therapeutic success at week 24, an upper gastro-intestinal endoscopy was performed. At each visit, the intake of antacids as well as the presence of other digestive symptoms were assessed: regurgitation, epigastric pain, early satiety, dysphagia, bloating, vomiting and cough. At week 24, all patients with therapeutic failure were proposed an open oesophageal radiofrequency procedure with the same follow-up that for the initial blind phase, which could correspond either to the first procedure (patient in the sham arm) or the second one (patients in the oesophageal radiofrequency arm). An end of study visit was planned at week 48 to assess symptom relief, PPI intake and the systematic question, GSRS and QOLRAD scores, and an upper GI endoscopy. Patients and investigators were blinded to the treatment arm until the end of the study. All data were collected by the Nantes University Hospital clinical research centre. The study was approved by the "Comité de protection des personnes" Ouest V (Rennes, France) on December 11th, 2011 (ref 11/31-820) (ClinicalTrials.gov NCT01682265).

2.2 | Patients

Patients included were aged 18-78 years, with persistent moderate-to-severe heartburn at least three times per week despite a continuous PPI therapy, without oesophagitis > grade A according to the Los Angeles classification in the previous year. Patients were randomised after the run-in period if inclusion criteria were confirmed according to the symptom assessment on diary card, and if the per-procedure endoscopy ruled out the presence of >grade A oesophagitis, hiatal hernia >2 cm and Barrett's oesophagus >C0M1. Other exclusion criteria were presence of oesophageal stricture, gastric or oesophageal varices, achalasia, history of oesophageal or gastric surgery, presence of a cardiac pacemaker or any other implanted electro-medical device, impossibility to stop an anti-coagulant therapy or severe coagulopathy, cardiac, hepatic, renal insufficiency, obesity with body mass index >35, pregnancy, history of neoplasia, any contraindication to general anaesthesia or any life threatening disorders with a life expectancy of <1 year. According to the Rome IV classification[6] and Lyon consensus,[18] the phenotypes of the patients were defined as follows based on the results of 24-hour pH-impedance monitoring: persisting pathological GORD (acid exposure time >6% or more than 80 reflux episodes), reflux hypersensitivity (acid exposure time <6% and symptom index >50% or symptom association probability >95%) and functional heartburn (acid exposure time <6% and symptom index ≤50% and symptom association probability ≤95%).

2.3 | Interventions

The oesophageal radiofrequency procedure was performed according to a previously described technique in patients placed in left lateral position under general anaesthesia after endotracheal intubation. A diagnostic upper endoscopy was performed carefully to inspect the oesophagus and the cardia before the procedure. Briefly, the Stretta® system (Mederi Therapeutics inc.) consists in a RF generator (MDRF1) and a flexible catheter (ref 8800). The Stretta® catheter uses a balloon basket assembly to deploy four needle electrodes into the muscular layer of the oesophageal wall. Radiofrequency energy delivered by the needle electrodes causes a thermal reaction in the LOS. Deploying the needle electrodes at 5 mm levels above and below the squamo-columnar junction produced 56 thermal lesions. After completion of the procedure and catheter removal, the diagnostic endoscopy procedure was repeated to verify the absence of complications such as bleeding or perforation. For patients randomised to receive the sham procedure, the radiofrequency flexible catheter was also introduced, and the same protocol was used, the needle electrodes were deployed but without delivering radiofrequency energy. Patients were kept in the hospital overnight and were generally discharged the next day on PPI double dose until the next visit.

2.4 | Efficacy endpoints, outcome measures and safety assessments

The primary endpoint was clinical success at week 24 defined as an adequate symptom relief together with a PPI intake of less than 7 doses over the 2 preceding weeks. In the other case, the patient was defined as therapeutic failure. The secondary endpoints were clinical success at week 48, number of days without heartburn and digestive symptoms over the two preceding weeks at weeks 24 and 48, PPI consumption and number of patients not taking PPIs during the last 2 weeks at weeks 24 and 48, GSRS and QOLRAD scores at weeks 24 and 48, 24-hour pH-impedance parameters associated with clinical success at week 24 and side effects of the procedure assessed at each follow-up visit.

The GSRS includes 15 items: reflux, abdominal pain, indigestion, diarrhoea and constipation. The GSRS has a 7-graded Likert type scale where 1 represents absence of bothersome symptoms and 7 very bothersome symptoms. The QOLRAD, a disease-specific quality-of-life questionnaire, covers five dimensions: emotional distress, sleep disturbance, problems with eating and drinking (food and drink problems), limitations in physical and social functioning and lack of vitality. Responses were rated on a 7-grade Likert scale. The lower the score, the more severe the impact was on daily functioning during the past week. Both questionnaires have been demonstrated appropriate for use in clinical trials of therapeutic interventions for patients with heartburn.[19]

2.5 | Statistical analysis

Sample size was estimated assuming that 20% and 55% of patients in the sham and oesophageal radiofrequency groups, respectively (35% treatment difference), would achieve the primary end point criteria with a significance level of 5% ($\alpha = 0.05$). With these assumptions, a sample size of 27 patients in each treatment group would provide 80% power to detect statistically significant treatment differences. We planned to randomise 60 patients to compensate protocol deviations and patients lost to follow-up. Missing data were handled using the "worst-case" analysis methodology for the primary endpoint (therapeutic failure) and key secondary endpoints. The main analysis was an intention-to-treat analysis, which included all patients who underwent randomisation. The per-protocol analysis included all patients in the intention-to-treat population who completed the follow-up without any major protocol deviation. All analyses were stratified by analysis centre, and comparisons between groups were performed using linear or logistic regressions, accordingly. All dimensions for QOLRAD and GSRS questionnaires were calculated by mean value for the items in each dimension. Missing data were imputed if less than 50% of the item scores within a dimension. Time effect was tested in interaction with every dimension for two questionnaires. Threshold of 0.05 was considered statistically significant. All analyses were performed using R version 3.4.0. All

authors had access to the study data, reviewed and approved the final manuscript.

3 | RESULTS

3.1 | Patients

Among the 70 patients initially included from March 2012 to November 2017, a total of 62 patients were randomised (49 women, mean age 51.2 years (range 18-78), 29 in the oesophageal radiofrequency group and 33 in the sham group) and were included in the intention-to-treat analysis (Figure 1). The characteristics of the patients in each group are indicated in Table 1. All patients were taking daily PPIs, either a single (n = 15) or a double dose (n = 47). According to 24-hour pH-impedance monitoring on PPIs, 29 patients had functional heartburn, 17 reflux hypersensitivity, 10 persisting GORD and 6 were not classified (normal reflux parameters but no symptoms reported during the recording). Five patients were lost to follow-up and one withdrew his consent to participate, therefore the per-protocol population consisted of 26 patients in the oesophageal radiofrequency group and 30 in the sham group. Follow-up ended on November 2018. All patients assigned to the oesophageal radiofrequency group had the complete procedure.

3.2 | Primary endpoints

In the intention-to-treat population, 1/29 (3.4%) and 5/33 (15.2%) patients achieved clinical success in the oesophageal radiofrequency and sham groups, respectively (OR = 0.20, CI 95% [0.02-1.88], P = 0.158). In the per-protocol population, 1/26 (3.8%) and 5/30 (16.7%) patients achieved clinical success in the oesophageal radiofrequency and sham groups respectively (OR = 0.20, CI 95% [0.02-1.84], P = 0.155) (Figure 2).

3.3 | Secondary endpoints

After the week 24 evaluation, 7 additional patients were lost to follow-up. At week 24, oesophageal radiofrequency was proposed to the patients who failed to achieve therapeutic success, ie a second procedure in the oesophageal radiofrequency group (n = 24) and a first procedure in the sham group (n = 19). There was no significant difference in success rates in patients who received a second procedure (7/24, 29.2%) compared to patients in whom only one procedure was performed (3/19, 15.8%, OR 2.40, CI95% [0.48-11.91], P = 0.285). As a whole, among the 49 patients who completed the week 48 visit, 16 (32.7%) were considered to have a therapeutic success, without significant difference between patients who received one (9/25, 36.0%) and two (7/24, 29.2%) procedures (OR 0.73, CI95% [0.22-2.43], P = 0.611). Among the five patients who received no procedure, three were lost to follow-up at 48 weeks, one had a therapeutic success and one had a therapeutic failure. No patient had oesophagitis at follow-up endoscopy.

As indicated in Table 2, there was no significant difference between oesophageal radiofrequency and sham groups at weeks 24 and 48 regarding days without heartburn, days without any other digestive symptoms, PPIs and antacids intake, and the number of patients not taking PPIs. No pH-impedance parameter was identified as a predictive factor of therapeutic success.

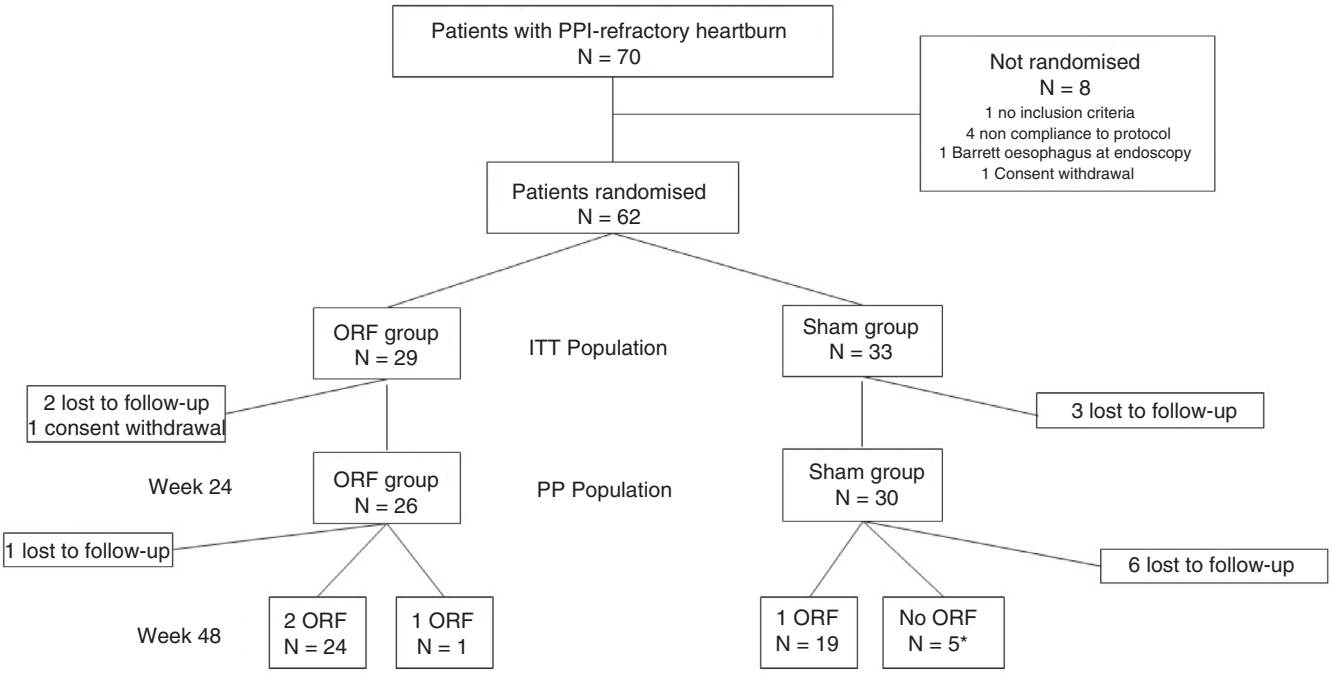

FIGURE 1 Flow diagram for the study. *including three patients lost to follow-up. ORF, oesophageal radiofrequency; ITT, intention to treat; PP, per-protocol

TABLE 1 Demographic and clinical characteristics of the patients at baseline

	SHAM (N = 33)	ORF (N = 29)
Age	54.2 (±14.4)	48.5 (±14.2)
Females – no (%)	25 (75.8%)	24 (82.8%)
Body mass index (kg/m^2)	25.3 (±4.6)	24.8 (±5.7)
Oesophagitis– no (%)	1 (3.2%)	1 (3.7%)
Days without heartburn	0.9 (±2.3)	0.8 (±2.1)
Days without digestive symptoms	0.4 (±1.2)	0.6 (±2.7)
PPI dose single/double	8/25	7/22
24-hour pH-impedance results		
Total number of reflux events	44.9 (±45.1)	44.5 (±33.1)
Acid reflux events	21.9 (±40.2)	15.3 (±20.7)
Weakly acidic reflux events	25.0 (±22.4)	24.3 (±23.0)
Acid exposure time (%)	5.1 (±18.5)	4.1 (±12.6)
Pathological reflux– no (%)	5 (15.2%)	5 (17.9%)
Reflux hypersensitivity– no (%)	11 (33.3%)	6 (21.4%)
Functional heartburn– no (%)	13 (39.4%)	16 (57.1%)
No symptom reported	4 (12.1%)	1 (3.4%)

Note: Plus–minus values are means ± SD.
Abbreviation: ORF, oesophageal radiofrequency.

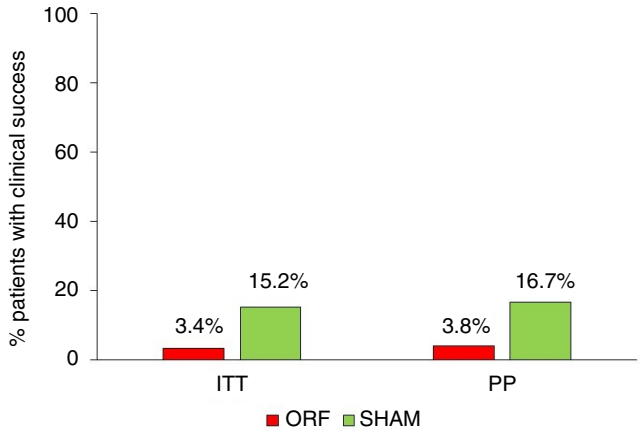

FIGURE 2 Percentages of patients who achieved clinical success at week 24 after sham and oesophageal radiofrequency procedure (no significant difference). Clinical success was defined as an adequate symptom relief together with a PPI intake of less than seven doses over the 2 preceding weeks. ORF, oesophageal radiofrequency; ITT, intention to treat; PP, per-protocol

The effects of assigned treatment and time on GSRS and QOLRAD scores are indicated in Table 3. Most of the scores improved with time at weeks 24 and 48, but no significant effect could be attributed to treatment arm. There was a significant increase in the "indigestion subscore" of the GSRS in patients of the oesophageal radiofrequency group.

3.4 | Safety

There were no procedure-related perforations, bleeding episodes or deaths. During the study, 23 serious adverse events occurred in 11 patients (6 in the oesophageal radiofrequency group, 1 before randomisation), but only 2 were related to the procedure: 2 patients reported severe chest pain after the procedure, 2 in the oesophageal radiofrequency group and 1 in the sham group that resulted in a 24-hour and 48-hour prolonged hospitalisation respectively. No perforation was observed, and symptoms resolved with analgesics. A total of 167 adverse events occurred during the study (Table 4), 79 in the oesophageal radiofrequency group and 88 in the sham group. Only 43 (25.7%) were considered by the investigators as related to the procedure, 28 in the oesophageal radiofrequency group and 15 in the sham group. Most adverse events were of mild (45.5%) or moderate (49.1%) intensity. There were 9 severe adverse events, 7 in the oesophageal radiofrequency group: epigastric pain (n = 3), delayed gastric emptying, vomiting, headache, and one leiomyoma. At the end of follow-up, 21.6% of side effects were ongoing (9.0% and 12.6% in oesophageal radiofrequency and sham groups, respectively), most of them being related to reflux symptoms and long-lasting chronic diseases.

4 | DISCUSSION

We report the results of the first randomised, sham-controlled, oesophageal radiofrequency in patients with PPI-refractory heartburn. There was no significant difference in clinical outcome PPI consumption and quality of life scores between patients who received oesophageal radiofrequency and those who had the sham procedure.

The population of patients who participated in the study was representative of the expected population with PPI-refractory heartburn. Indeed, most patients had functional oesophageal disorders, ie functional heartburn (46.8%) and reflux hypersensitivity (27.4%), while a minority of patients had poorly controlled GORD (16.1%). This is consistent with the results of pH-impedance studies on PPIs.[20,21] In a cohort of 177 patients with confirmed refractory heartburn enrolled in a randomised controlled trial recently published, a very similar repartition of phenotypes was observed, namely, 56% with functional heartburn, 21% with reflux hypersensitivity and 23% with true refractory acid reflux.[7]

Only a minority of patients achieved the primary endpoint, 3.4% and 15.2% in oesophageal radiofrequency and sham groups respectively. These very low rates may be related to the definition of therapeutic success, combining both adequate symptom relief and significant decrease in PPI intake. This stringent definition was used on purpose, considering the cost of the procedure and its potential side effects. However, no significant difference was observed regarding the number of days without heartburn and PPI intake analysed separately. Of note, the rate of patients with clinical success increased at week 48, after one (15.8%) and two (29.2%) procedures. However, it is difficult to draw any conclusion since it was an unblinded part of the study, and consequently, a placebo effect cannot be ruled out. To

TABLE 2 Secondary endpoints at week 24 (n = 56) and week 48 (n = 49)

	SHAM	ORF	Coefficient	95% CI	*P*
Days without heartburn week 24	3.8 (±5.4)	2.8 (±5.2)	−0.91	[−3.7 to 1.9]	0.529
Days without heartburn week 48	6.1 (±5.9)	5.8 (±5.9)	−0.32	[−3.6 to 3.0]	0.849
Days without symptoms week 24	2.6 (±4.8)	0.6 (±2.8)	−1.98	[−4.1 to 0.1]	0.075
Days without symptoms week 48	3.3 (±5.0)	2.0 (±3.6)	−1.36	[−3.9 to 1.2]	0.300
PPIs intakes week 24	10.8 (±5.8)	11.1 (±5.5)	0.28	[−2.7 to 3.2]	0.853
PPIs intakes week 48	8.1 (±6.3)	7.7 (±6.2)	−0.40	[−3.9 to 3.1]	0.822
No PPI intakes week 24	3/30 (10.0%)	3/26 (11.5%)	0.85	[0.2-4.6]	0.852
No PPI intakes week 48	5/24 (20.8%)	7/25 (28.0%)	0.68	[0.2-2.5]	0.561
Antacids intakes week 24	13/30 (43.3%)	8/25 (32.0%)	0.52	[0.1-1.8]	0.298
Antacids intakes week 48	9/24 (37.5%)	11/25 (44%)	1.31	[0.4-4.5]	0.670

Note: Results are expressed in numbers (percentage) and mean ± SD.

Abbreviation: ORF, oesophageal radiofrequency.

TABLE 3 Gastrointestinal Symptoms Rating Scale (GSRS) and the Quality of Life in Reflux and Dyspepsia (QOLRAD) scores at baseline, week 24 and week 48

	Baseline	Week 24	Week 48	Coefficient	95% CI	*P*
GSRS						
Diarrhoea						
Sham	1.0 (1.0-3.0)	2.0 (1.0-2.0)	2.0 (1.0-2.0)			
ORF	2.0 (1.0-3.3)	2.0 (1.0-3.3)	1.3 (1.0-2.0)	0.31	[−0.23 to 0.84]	0.267
Indigestion						
Sham	3.6 (2.5-4.2)	3.2 (2.0-3.7)	3.6 (2.4-4.0)			
ORF	4.2 (3.6-5.0)	3.6 (3.0-4.5)	3.6 (2.8-4.3)	0.62	[0.07-1.18]	0.031
Constipation						
Sham	2.3 (1.3-3.0)	2.8 (1.7-3.7)	2.8 (1.3-3.0)			
ORF	2.3 (1.7-3.0)	2.8 (1.7-3.3)	2.8 (2.0-4.7)	0.24	[−0.43 to 0.92]	0.479
Abdominal pain						
Sham	3.3 (2.3-4.3)	3.0 (2.0-3.3)	3.2 (2.0-3.4)			
ORF	3.3 (4.2-4.3)	3.2 (2.3-4.0)	3.2 (2.0-3.3)	0.30	[−0.13 to 0.73]	0.170
Reflux						
Sham	3.5 (3.0-4.0)	3.3 (2.5-4.0)	3.3 (2.5-3.5)			
ORF	3.3 (3.0-4.0)	3.3 (3.0-4.0)	3.3 (2.5-4.0)	0.20	[−0.43 to 0.70]	0.433
QOLRAD						
Emotional distress						
Sham	3.7 (2.3-4.7)	4.0 (3.0-6.2)	3.9 (3.8-6.4)			
ORF	3.2 (1.8-3.9)	3.9 (2.5-3.9)	3.9 (2.3-5.8)	−0.57	[−1.31 to 0.17]	0.135
Sleep disturbances						
Sham	3.2 (2.4-4.0)	4.0 (3.6-6.0)	4.1 (4.0-6.3)			
ORF	3.6 (2.0-4.2)	4.0 (3.0-4.2)	4.0 (2.8-6.0)	−0.38	[−1.05 to 0.30]	0.272
Food\drink problems						
Sham	3.7 (2.7-4.2)	3.8 (3.0-5.2)	3.8 (3.7-5.8)			
ORF	3.2 (2.1-3.8)	3.8 (2.7-3.8)	3.8 (2.7-4.8)	−0.46	[−1.02 to 0.10]	0.110
Physical/social functioning						
Sham	4.6 (3.4-5.6)	5.2 (4.4-6.4)	4.8 (4.6-6.7)			
ORF	4.2 (2.8-5.4)	4.6 (3.4-4.6)	4.6 (3.6 −6.0)	−0.56	[−1.22 to 0.11]	0.101
Vitality						
Sham	3.3 (2.0-4.7)	4.0 (3.0-5.3)	3.9 (3.8-6.0)			
ORF	3.0 (2.0-3.9)	3.9 (3.0-4.3)	3.9 (3.3-5.7)	−0.30	[−0.97 to 0.36]	0.373

Note: Results are expressed as median (IQR).

Abbreviation: ORF, oesophageal radiofrequency

TABLE 4 Adverse events

	Sham (N = 33)	ORF (N = 29)
Digestive symptoms		
Mild	20	15
Moderate	9	18
Severe	1	3
Infections		
Mild	10	4
Moderate	7	4
Severe	1	0
General disorders		
Mild	3	1
Moderate	4	4
Severe	0	0
Neurologic symptoms		
Mild	3	5
Moderate	3	5
Severe	3	1
Miscellaneous		
Mild	7	8
Moderate	19	8
Severe	0	3
Total		
Mild	43	33
Moderate	43	39
Severe	2	7
	N = 88	N = 79

Abbreviation: ORF, oesophageal radiofrequency.

date, both randomised and cohort studies have reported much better results of oesophageal radiofrequency regarding clinical outcome and PPI consumption, but all these studies have included patients with proven GORD who have been partially or completely responsive to antisecretory therapy.[14,15] The population of patients included in the present study is very different, with a majority of functional oesophageal disorders. Although controversial,[15] the effects of oesophageal radiofrequency on LOS pressure and oesophago-gastric junction compliance had little chance to benefit to these patients without clear failure of anti-reflux barrier. Indeed, in patients with functional oesophageal disorders, the prevailing view considers oesophageal hypersensitivity as a major underlying mechanism of symptom generation,[6,22] although the trigger stimuli are unclear in functional heartburn. Previous reports have suggested an effect of oesophageal radiofrequency on oesophageal afferences and sensitivity. Indeed, oesophageal radiofrequency has been demonstrated to improve symptoms without significant effect on acid exposure time,[17,23] to decrease oesophageal sensitivity to acid perfusion,[24] and the occurrence of transient LOS relaxations elicited by stimulation of gastric vagal afferents.[13] These data led us to consider that oesophageal radiofrequency may have room in the management of patients in whom oesophageal hypersensitivity is present, but this was not confirmed by the results of the present study.

Oesophageal radiofrequency may be considered as a relatively invasive procedure for a benign disorder. Therefore, we aimed at showing a clear difference between the effective and sham procedures and used stringent criteria to define therapeutic success. Nevertheless, our study further confirms that oesophageal radiofrequency is a safe procedure. The initial safety concerns for oesophageal perforation have not been confirmed and the most reported side effect is self-limited chest pain,[25,26] similar to our study. Of note, in the present study, a minority of patients had low-grade oesophagitis at inclusion, and all patients had normal appearance of oesophageal mucosa at the 1-year post-procedure endoscopy.

The present study has some limitations. First, the 70 included patients were recruited over a 5-year period, thus reflecting difficulties in the recruitment process. By contrast to other countries (especially USA), oesophageal radiofrequency is not available in France and can only be performed in the context of clinical trials. Many patients (as well as referring physicians) expressed concerns about the safety of the procedure and were reluctant to participate in the study. Second, the number of patients was too small to demonstrate any difference between patients with true refractory GORD, reflux hypersensitivity and functional heartburn. In the absence of available data in such a population of patients with PPI-refractory heartburn, the sample size was estimated to provide a 35% difference between the two groups, similar to a previous sham-controlled study in GORD patients [23]; our hypothesis can therefore be considered as reasonable. Consequently, a type 2 error cannot be ruled out, but the number of patients who eventually achieved the primary endpoint was so small that only the inclusion of a huge number of patients could have demonstrated a difference between groups. Third, we did not perform pH-impedance monitoring off therapy to assess whether the patients had baseline GORD or not, although we can assume that most of them had functional oesophageal disorders since they did not respond to PPIs. We designed a pragmatic study similar to the controlled trial from Spechler et al (surgical vs medical treatment of refractory heartburn) who included their patients on the basis of pH-impedance monitoring on PPI therapy.[7] Fourth, we did not perform follow-up pH-impedance monitoring to demonstrate the effects of oesophageal radiofrequency on physiologic parameters. However, since most patients had normal baseline pH-impedance monitoring, as expected, the information provided by a follow-up recording would have been relatively limited.

In conclusion, this sham-controlled randomised study did not demonstrate any efficacy of oesophageal radiofrequency for the treatment of PPI-refractory heartburn regarding symptom relief and PPIs consumption. This technique cannot be recommended for the treatment of refractory heartburn.

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REFERENCES

1. El-Serag HB, Sweet S, Winchester CC, Dent J. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut*. 2014;63:871-880.
2. El-Serag H, Becher A, Jones R. Systematic review: persistent reflux symptoms on proton pump inhibitor therapy in primary care and community studies. *Aliment Pharmacol Ther*. 2010;32:720-737.
3. Sifrim D, Zerbib F. Diagnosis and management of patients with reflux symptoms refractory to proton pump inhibitors. *Gut*. 2012;61:1340-1354.
4. Scarpellini E, Ang D, Pauwels A, De Santis A, Vanuytsel T, Tack J. Management of refractory typical GERD symptoms. *Nat Rev Gastroenterol Hepatol*. 2016;13:281-294.
5. Fass R, Zerbib F, Gyawali CP. AGA clinical practice update on functional heartburn: expert review. *Gastroenterology*. 2020;158:2286-2293.
6. Aziz Q, Fass R, Gyawali CP, Miwa H, Pandolfino JE, Zerbib F. Functional esophageal disorders. *Gastroenterology*. 2016;150:1368-1379.
7. Spechler SJ, Hunter JG, Jones KM, et al. Randomized trial of medical versus surgical treatment for refractory heartburn. *N Engl J Med*. 2019;381:1513-1523.
8. Li S, Shi S, Chen F, Lin J. The effects of baclofen for the treatment of gastroesophageal reflux disease: a meta-analysis of randomized controlled trials. *Gastroenterol Res Pract*. 2014;2014:307805.
9. Viazis N, Keyoglou A, Kanellopoulos AK, et al. Selective serotonin reuptake inhibitors for the treatment of hypersensitive esophagus: a randomized, double-blind, placebo-controlled study. *Am J Gastroenterol*. 2012;107:1662-1667.
10. Weijenborg PW, de Schepper HS, Smout AJ, Bredenoord AJ. Effects of antidepressants in patients with functional esophageal disorders or gastroesophageal reflux disease: a systematic review. *Clin Gastroenterol Hepatol*. 2015;13:251-259.
11. Franciosa M, Triadafilopoulos G, Mashimo H. Stretta radiofrequency treatment for GERD: a safe and effective modality. *Gastroenterol Res Pract*. 2013;2013:783815.
12. 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.
13. Tam WC, Schoeman MN, Zhang Q, et al. Delivery of radiofrequency energy to the lower oesophageal sphincter and gastric cardia inhibits transient lower oesophageal sphincter relaxations and gastro-oesophageal reflux in patients with reflux disease. *Gut*. 2003;52:479-485.

14. Fass R, Cahn F, Scotti DJ, Gregory DA. 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.
15. Lipka S, Kumar A, Richter JE. No evidence for efficacy of radiofrequency ablation for treatment of gastroesophageal reflux disease: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2015;13:1058-1067.e1051.
16. Hillman L, Yadlapati R, Whitsett M, Thuluvath AJ, Berendsen MA, Pandolfino JE. Review of antireflux procedures for proton pump inhibitor nonresponsive gastroesophageal reflux disease. *Dis Esophagus*. 2017;30:1-14.
17. 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.
18. Gyawali CP, Kahrilas PJ, Savarino E, et al. Modern diagnosis of GERD: the Lyon Consensus. *Gut*. 2018;67:1351-1362.
19. Talley NJ, Fullerton S, Junghard O, Wiklund I. Quality of life in patients with endoscopy-negative heartburn: reliability and sensitivity of disease-specific instruments. *Am J Gastroenterol*. 2001;96:1998-2004.
20. Mainie I, Tutuian R, Shay S, et al. Acid and non-acid reflux in patients with persistent symptoms despite acid suppressive therapy: a multicentre study using combined ambulatory impedance-pH monitoring. *Gut*. 2006;55:1398-1402.
21. Zerbib F, Roman S, Ropert A, et al. Esophageal pH-impedance monitoring and symptom analysis in GERD: a study in patients off and on therapy. *Am J Gastroenterol*. 2006;101:1956-1963.
22. Fass R, Tougas G. Functional heartburn: the stimulus, the pain, and the brain. *Gut*. 2002;51:885-892.
23. 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.
24. Arts J, Sifrim D, Rutgeerts P, Lerut A, Janssens J, Tack J. Influence of radiofrequency energy delivery at the gastroesophageal junction (the Stretta procedure) on symptoms, acid exposure, and esophageal sensitivity to acid perfusion in gastroesophagal reflux disease. *Dig Dis Sci*. 2007;52:2170-2177.
25. Noar M, Squires P, Noar E, Lee M. Long-term maintenance effect of radiofrequency energy delivery for refractory GERD: a decade later. *Surg Endosc*. 2014;28:2323-2333.
26. Auyang ED, Carter P, Rauth T, Fanelli RD. SAGES clinical spotlight review: endoluminal treatments for gastroesophageal reflux disease (GERD). *Surg Endosc*. 2013;27:2658-2672.

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