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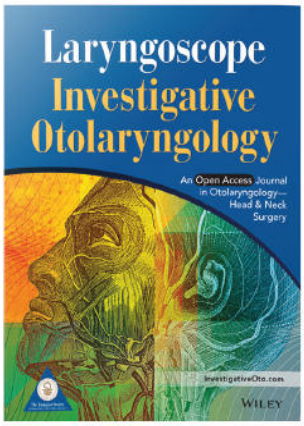

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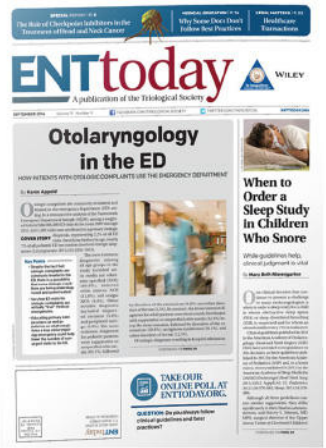

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Endoscopic Sinus Surgery for Type-2 CRS wNP: An Endotype-Based Retrospective Study

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Objectives: Nasal polyps are often characterized by type 2 inflammation and disease recurrence. We developed a new surgical technique, referred to as *reboot approach*, which aims to maximally remove all sinus mucosa and allow healthy re-epithelialization from the preserved nasal mucosa. We here review type 2 endotype chronic rhinosinusitis with nasal polyps (CRSwNP) patients who underwent classical mucosa-sparing endoscopic sinus surgery (ESS) or the reboot approach.

Methods: Retrospective case-control study of 50 consecutive CRSwNP patients who underwent endoscopic sinus surgery between 2015 and 2017, either as a classical non-reboot ESS (n = 20); a partial reboot approach removing the mucosa of the ethmoidal, sphenoidal, and maxillary sinuses (n = 18); or a complete reboot approach including Draf III and removal of all frontal sinus mucosa (n = 12). Polyp recurrence over the follow-up period of 2 years served as the primary outcome.

Results: All patients demonstrated a type 2 inflammation of the mucosal tissue harvested during surgery. In the classical approach group (n = 20), nine patients relapsed within 2 years (45%); in the partial reboot group, three out of 18 patients (17%) relapsed; and in the full reboot group one out of 12 patients (8%) relapsed. The relapse rates were significantly different between the non-reboot and the reboot groups ($P = 0.02$) but also between all treatment groups ($P = 0.038$).

Conclusion: Complete removal of diseased mucosa from the paranasal sinuses (reboot approach) significantly reduces the recurrence of nasal polyps for 30 months postoperatively compared to the current mucosa-sparing approach in type 2 inflammatory CRSwNP.

Key Words: CRSwNP, nasal polyps, chronic rhinosinusitis, endotypes, FESS, reboot approach.

Level of Evidence: 3b

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INTRODUCTION

Chronic rhinosinusitis (CRS) is a common health problem, with a prevalence reaching 10.9% in Europe and between 12% to 16% in the United States.[1–3] Chronic rhinosinusitis is currently divided into CRS without nasal polyps (CRSsNP) and CRS with nasal polyps (CRSwNP). Of these, CRSwNP continues to attract researchers' attention in the rhinology field because the percentage of patients with disease relapse still is considerably higher than in CRSsNP, with figures ranging from 38% to 60% at 12 months follow-up.[2,4] Reasons for treatment failure and disease recurrence have been studied, and factors such as bronchial asthma, eosinophilia, aspirin-exacerbated respiratory disease (AERD), and atopy were found to be the most important clinical risk factors.[4–7] Peripheral, mucus, and mucosal eosinophilia—and more precisely a type 2 T-cell inflammation—have recently been discovered to affect the severity of the disease and the recurrence of polyps.[6,8]

Although medical management with intranasal and oral glucocorticosteroids (GCS) has been shown to be effective, and further advances with humanized and fully human monoclonal antibodies (mAbs) such as anti-immunoglobulin-E (Ig-E), anti-interleukin (IL)-5, and anti-IL-4 receptor α are to be expected, the side effects of long-term use of GCS with its short-term benefits and the foreseen costs with mAbs are limiting the group of patients who possibly benefit from these medications.[9–12] The difficult-to-treat CRSwNP subjects are therefore often repeatedly exposed to surgical management of various kinds. Surgical approaches have varied over the years, ranging from the least extensive polyp extraction to the most extensive nasalization procedures.[13–15] Performing randomized controlled studies to compare different surgical techniques are demanding to perform, and reliable studies including sufficient patients are scarce. All types of sinus surgery are done in an attempt to control disease for the long term and to improve the patients' symptoms and overall quality of life. For CRSwNP, because of the high recurrence rates, more extended approaches have been proposed to widely access the sinuses in order to open them for local treatment, and reduce the inflammatory load.[16,17] However, removal or *stripping of the mucosa* was not recommended

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due to fear of scarring, inflammatory reactions of the denuded bone, and nonfunctional mucosa.[16,18]

In the process of understanding the disease at its molecular level, appreciating the type 2 inflammation and its associated deficiencies in defense against bacteria and viruses as well as epithelial repair, we here for the first time introduce the concept of *reboot surgery*, which is based on the removal of all inflamed sinus mucosa and allowing the regrowth of functional nasal mucosa for type 2 inflammatory CRSwNP.

MATERIALS AND METHODS

Study Design

We conducted a retrospective case-control study of CRSwNP patients who underwent sinus surgery for nasal polyps between January 2015 and August 2016 at the Department of Otorhinolaryngology, UZ Gent Hospital. Patients who underwent a standard functional endoscopic sinus surgery (FESS) with the minimally invasive mucosa sparing technique were considered as control and grouped as the non-reboot group, whereas patients who underwent the reboot technique were considered as cases and were subdivided into two different groups: a *partial reboot* group, which involves the clearance of all sinonasal polyps and mucosa down to the periosteum (see the discussion section); and a *full reboot* group, which also includes a Draf III procedure. Polyp recurrence was considered when at least small polyps of score 1 (using the Davos polyp scoring system) at one side were noted by the surgeon upon nasal endoscopy postoperatively. A questionnaire containing Visual Analogue Scale (VAS) and Sinonasal Outcome Test-22 (SNOT-22) scores was also sent to all study subjects by mail at the beginning of January 2018—and another at the beginning of March 2018. All patients were exposed to the same postoperative care and follow-up, consisting of nasal douching, doxycycline 100 mg per day for 6 weeks, and topical GCS drops (fluticasone propionate) once daily for long-term. The use of postoperative long-term (6–8 weeks) doxycycline has shown to improve mucosal healing in different studies.[19,20]

The study was approved by the ethics committee of UZ Gent Hospital, Ghent, Belgium (approval number: 2016/0939), and informed consents were obtained from all subjects.

TABLE I.
Patients Characteristics.

Parameter	Full Reboot	Partial Reboot	Non-Reboot	*P* Value
N	12	18	20	
Gender F/M	3/9	3/15	10/10	0.07*
Age, (mean ± SD), years	39.5 ± 11.9	52.3 ±14.0	48.7 ±13.1	0.05†
Previous surgeries (patients, surgeries/patient)	9, 3.3	14, 2.07	10, 1.7	0.09*
Davos polyp score (mean± SD)	3.7 ± 2.1	4.9 ± 1.5	4.5 ± 1.9	0.4†
Asthma	7	10	15	0.11*
AERD	1	2	1	0.67*
Allergy	4	7	10	0.58*

*Chi^2-test.
†Kruskall-Wallis test.
AERD = aspirin exacerbated respiratory disease; F = female; M = male; SD = standard deviation.

Data Analysis

Data were reviewed from the hospital integrated electronic patient record system, and all patients' clinical visits, laboratory analysis, operative notes, and histopathological results were obtained.

Of the 50 questionnaires sent to patients at the end of the observation time, we received 25 (n = 9 for the non-reboot, n = 9 for the partial reboot, and n = 7 for the full reboot) back. Furthermore, we received 32 complete sets of pre- and postoperative VAS scores (n = 16 for the non-reboot, n = 10 for the partial reboot, and n = 6 for the full reboot).

In one patient 28 months after reboot surgery, biopsies were taken and stained with PAS.

Inflammatory Biomarkers

Tissue and blood samples from all patients had been collected during surgery and had been stored in −80 and − 20°C freezers, respectively, at the Upper Airway Research Laboratory in Gent.

To determine a type 2 immune reaction, tissue samples were analyzed for total immunoglobin E (IgE), staphylococcal enterotoxin-IgE (SE-IgE), eosinophilic cationic protein (ECP), and IL-5, whereas serum samples were analyzed for total IgE, SE-IgE, and periostin.

As previously described,[21] each 0.1 g of tissue was diluted in 1 mL of 0.9% NaCl solution containing a protease inhibitor cocktail (Complete; Roche Diagnostics, Mannheim, Germany), homogenized at 50 Hz for 2 minutes, and centrifuged at 1500 g for 10 minutes at 4°C. Concentrations of ECP, total IgE, and IgE specific to a mixture of *S. aureus* enterotoxins (staphylococcal enterotoxins A and C and toxic shock syndrome toxin 1) were assayed by using the UniCAP system (Thermo Fisher Diagnostics NV, Groot-Bijgaarden, Belgium). Concentrations of IL-5 were assayed with the Bio-Plex 200 system (Biorad, Temse, Belgium). Concentrations in tissue homogenates were expressed as mass versus volume after multiplication by a homogenization dilution factor of 11.[21] Serum IgE and SE-IgE were measured with the UniCAP system (Uppsala, Sweden). Serum periostin was measured using the clinical trial version of the Elecsys Periostin assay on the e 601 module of the cobas 6000 system.[22,23]

Statistical Methods

GraphPad Prism 7 for Mac OS X (GraphPad Software, Inc., La Jolla, CA) and the Statistical Package for Social Sciences, version 25.0 (SPSS, IBM Corp., Armonk, NY) were used for statistical analyses. Differences in cytokine levels between the groups were analyzed with the nonparametric Kruskall-Wallis test; correction for multiple comparisons was made. Recurrence rate and differences in comorbidities between the groups were calculated with Fischer exact test and Chi^2-test. The recurrence rates of polyposis were estimated using Kaplan-Meier statistics. The log–rank test was used to compare the differences in the Kaplan-Meier estimates for the recurrence rates between control, partial reboot, and full reboot. Changes in SNOT-22 scores were assessed with the Mann-Whitney test. Baseline VAS scores in the different groups were compared using the Kruskall-Wallis test, and pre- versus postoperative VAS scores within each group were compared with the Wilcoxon test. A P value <0 .05 was considered significant.

RESULTS

Patients Characteristics

A total number of 84 patients who were operated for CRSwNP at UZ Gent Hospital between 2015 and 2017 have been reviewed. Patients who were lost for follow-up

TABLE II.
Median Concentrations and Interquartile Ranges of Inflammatory Parameters in Nasal Polyp Tissue.

	Full Reboot	Partial Reboot	Non-Reboot	*P* Value
Tissue markers				
IgE median (IQR)	624.1 (425.9;929.4)	516.5 (267.5;902.6)	746.8 (309.2;1267)	ns*
SE-IgE median (IQR)	2.9 (1.9;6.1)	1.9 (1.9;4.6)	1.9 (1.9;8.8)	ns*
ECP median (IQR)	25315 (13206;34015)	16378 (8844;24965)	25852 (16129;50940)	ns*
IL-5 median (IQR)	493.3 (177.2;797.5)	290.8 (79.6;834.7)	317.5 (123.9;673.7)	ns*
SE-IgE ± (%)	6/6 (50)	5/13 (27.8)	8/12 (36.8)	ns†
Serum markers				
IgE median (IQR)	115.3 (26.4;228)	76.9 (32.6;157.9)	79 (25.6;231.8)	ns*
SE-IgE median (IQR)	0.3 (0.05;0.4)	0.2 (0.05;0.4)	0.05 (0.05;0.05)	ns*
Periostin median (IQR)	46 (38.8;70.7)	75.4 (47.1;89.9)	56 (46.1;77.2)	ns*

*Kruskal Wallis test. Number of patients being positive for SE-IgE in nasal polyp tissue.
†Chi^2-test.
ECP = eosinophilic cationic protein; IgE = immunoglobulin-E; IL-5 = interleukin-5; IQR = interquartile range; ns = non significant; SE-IgE = staphylococcal enterotoxin-immunoglobulin-E.

before 7 months, patients with specific syndromes such as Kartagener syndrome or cystic fibrosis, or patients who were involved in other therapeutic studies including monoclonal antibody treatment, were excluded. The remaining 50 patients had a male predominance (34 males, 16 females) with an average age of 47 years. Thirty-three of the subjects had in total 76 previous sinus surgeries before inclusion into the study (Table I). Thirty-two of 50 patients had a history of bronchial asthma; AERD was reported in four cases. Baseline Davos polyp score was comparable between all three groups.

Inflammatory Biomarkers

Nasal polyp tissues were analyzed for total IgE, SE-IgE, ECP, and IL-5, whereas serum samples were analyzed for total IgE, SE-IgE, and periostin. There were no significant differences in any inflammatory parameters in nasal polyp tissue or serum between the groups. The number of patients who were IL-5– or SE-IgE–positive in tissue or had elevated levels of serum periostin did not differ between the groups (Table II). Therefore, all patients were considered to equally suffer from type 2 inflammatory nasal polyp disease.

Clinical Outcome

Patients undergoing the reboot approach, with or without the frontal sinus, had significantly reduced relapse rates compared to patients undergoing the classical FESS approach (13% vs. 45%, $P = 0.02$). Furthermore, there was a significant difference between all three groups ($P = 0.038$) (Table III). The time from surgery to relapse was shorter in the classical FESS group compared to the reboot group. The survival analysis showed superior results for the full reboot group concerning number and timing of recurrence, followed by the partial reboot and the non-reboot groups (Kaplan-Meier survival plot) (Fig. 1).

TABLE III.
Recurrence Rates Between Different Groups.

		Procedure			Total	*P* Value
		Non-reboot	Partial Reboot	Full Reboot		
Recurrence	0	11	15	11	37	
	1	9	3	1	13	0.038*
Total		20	18	12	50	
Earliest time for recurrence (months)		2	4	12		
		Non-reboot	Total Reboot			
Recurrence	0	11	26		37	
	1	9	4		13	0.02†

*Chi^2 test.
†Fisher exact test.

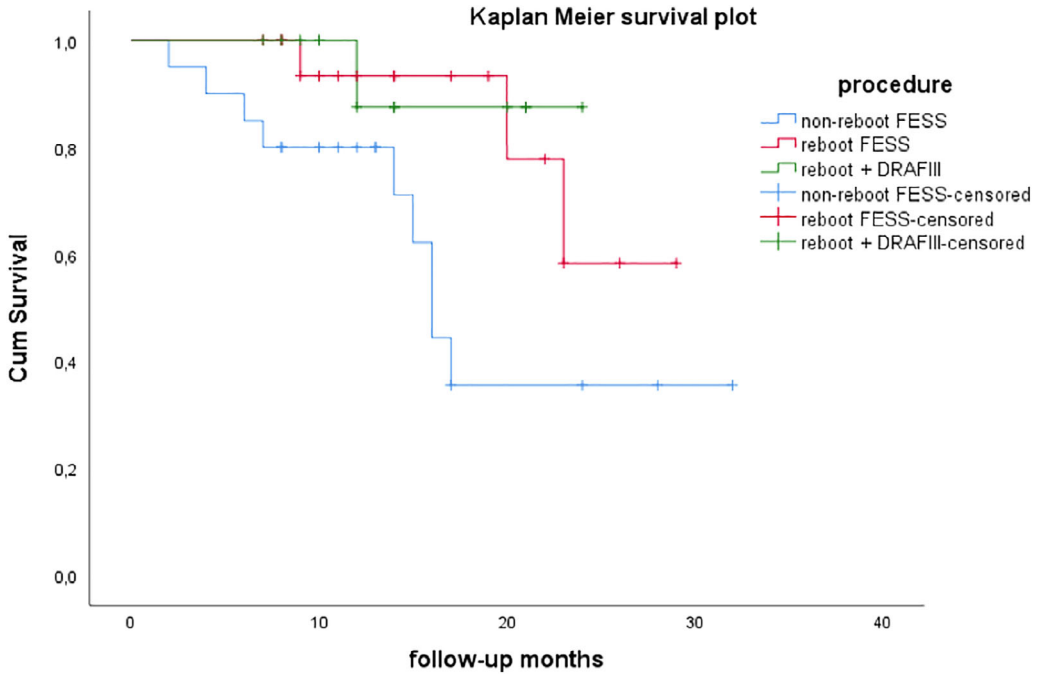

Fig. 1. Kaplan-Meier survival plot for the three groups. Relapse rates were 13% for the reboot group versus 45% for the non-reboot group (P = 0.02). Notice the least number of relapses (n = 1) and the latest time of recurrence (12 months) for the full reboot group, followed by the partial reboot with (n = 3) relapses and 4 months for the earliest recurrence, whereas the non-reboot group comes last with (n = 9) relapses and 2 months for the earliest recurrence (P = 0.038).

At baseline, the VAS scores did not show any significant difference between groups. Comparing the changes between the preoperative and the postoperative VAS scores, there also was no significant differences for the postoperative VAS scores between all groups. The postoperative total SNOT-22 score was significantly lower in the combined reboot group versus the non-reboot group (P = 0.03) (Fig. 2).

In the postoperative follow-up time, it took up to 8 weeks for the mucosa to fully re-epithialize all sinuses. The mucosa general looked healthy and moisturized, of normal thickness without edema or scar formation. No dryness of the mucosa was noticed by either the investigators or the patients. The random biopsy taken 28 months after surgery shows normal aspects of ciliated epithelium with goblet cells. There were no complications reported in the three study groups.

DISCUSSION

We here show for the first time that polyp recurrence was significantly lowered by the complete removal of the sinus mucosa using the partial and full reboot techniques compared to the classical FESS approach in type 2 biased inflammatory nasal polyposis (CRSwNP). Moreover, the full reboot approach including the frontal sinuses (Draf III access and removal of all frontal sinus mucosa) showed superior results compared to partial reboot and non-reboot approaches, leading to even lower relapse rates and longer time to relapse.

CRSwNP is characterized by a high risk of disease recurrence, especially in patients with comorbid asthma. We have previously demonstrated that recurrence is linked to type 2 inflammation in the polyp tissue with elevated levels of type 2 mediators in nasal polyp tissue.[8] In this study, all subjects suffered from type 2 inflammatory disease, as demonstrated by the expression of type 2 biomarkers in nasal polyp tissue harvested during surgery and in serum. In line with type 2 inflammation, 66% of patients had at least one; 40% of the subjects had undergone an average of three surgeries in the past; and 64% had comorbid asthma. Thus, judged by the inflammatory parameters and clinical disease expression, the selected patients in all groups can

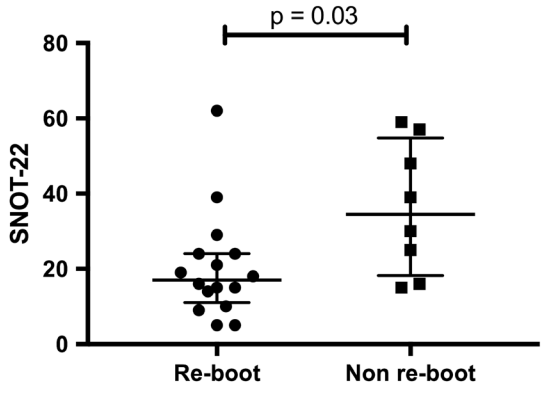

Fig. 2. Comparison of the SNOT-22 postoperatively between the two main groups.

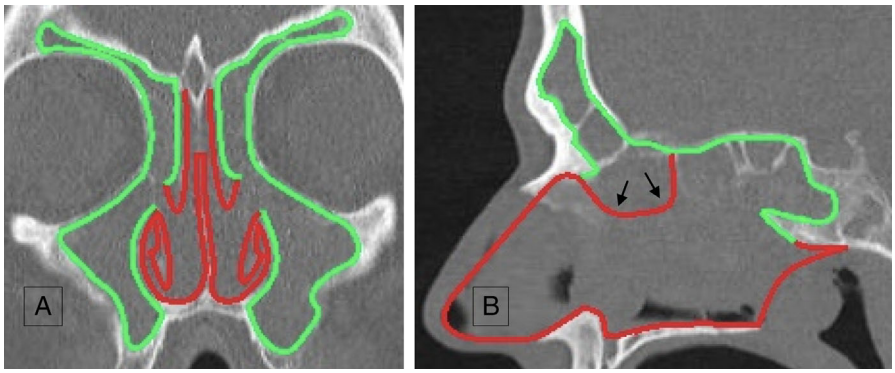

Fig. 3. Green lines show the mucosal areas removed during the reboot surgery; red lines show the mucosal areas that are kept untouched. (A) Coronal view. Notice the untouched parts of middle turbinates kept as important suppliers for epithelial regrowth and surgical landmarks. (B) Sagittal view (black arrows point to the septal area that is removed during Draf III procedure).

be characterized as moderate-to-severe polyposis subjects. Inflammatory patterns and comorbidity in the three groups did not differ, indicating that the differences in outcome were due to the applied surgical techniques rather than severity of disease at baseline.

Type 2 inflammation in nasal polyps is associated with dysfunctions at several mucosal levels, involving the colonizing microbiota,[24] the epithelial barrier function,[25] innate and adaptive immunity,[26] and finally the intramucosal presence of germs.[27] Typically, type 2 biased nasal polyp mucosa is inadequately responding to viral infections due to a deficit in IFN-γ production.[28] This results in an inability to defend the mucosa against viruses and to bacterial invasion due to the alternative activation of macrophages, which impairs the phagocytosis and the killing of germs including *S. aureus*.[29] As a result, the sinus mucosa is heavily colonized by pathologic germs such as *S. aureus*, *H. influenza*, and others[30,31]; bacteria can even persist intramucosally and release immunogenic proteins into the tissue.[30]

We therefore hypothesised that the complete removal of the sinus mucosa, together with the microbiota, the intramucosal germs, and the significant immune dysfunction, would present a possibility to impact on the natural course of the disease. Furthermore because type 2 cytokines such as IL-4 and IL-13 impair epithelial tight junction expression and barrier formation,[25] the eradication of the type 2 inflammation may allow better wound healing postoperatively, starting from the nasal mucosa of the inferior and middle turbinates as well as the septum; over the sinus walls under noninflamed conditions.

The reboot technique aims to accomplish a total clearance of all affected mucosa from all sinuses, leaving the periost where possible. The procedure starts with a wide antrostomy and a complete clearance of all the mucosa of the maxillary sinus, including the alveolar recess using 30° and 70° endoscopes, and then moving forward to clean the anterior and posterior ethmoids, including the lamina orbitalis, skull base, and the lateral aspects of the middle turbinate. The sphenoid sinus needs specific attention for the major structures passing along its lateral walls and roof, the internal carotid arteries, and the optic nerves; the surgeon should try to remove the diseased mucosa from the floor and medial parts of the sphenoid under endoscopic vision and create a wide access through reduction of the anterior sinus wall up to the skull base. Then the frontal recess is approached, completing the denuding of the anterior skull base. The middle turbinate is preserved as much as possible as a landmark, except for the parts that are destroyed or occupied by the disease or the anterior parts that need to be taken during the Draf III procedure. The superior turbinate mostly needs to be removed when

TABLE IV.
Sinuses, Instruments, and Points of Concern of the Reboot Procedure.

Steps	Special Instruments	Comments
1. Maxillary sinuses	70° endoscope	Total removal of the sinus mucosa including the alveolar recess
	Antrum grasping forceps (Heuwieser)	
	90° blakesley	
2. Ethmoid sinuses	45° up-biting Blakesley	Including lamina orbitalis and skull base mucosa (periost remains), lateral aspect of the middle turbinate; superior turbinate removed
	Microdebrider with a 60° blade on a 5000 $_{RPM}$ oscillation speed	
3. Sphenoid sinuses	Hajek-Kofler Sphenoid Punch Forceps 360° rotatable	Wide access remove mucosa carefully (especially from the floor, anterior, and medial walls)
	Microdebrider use on the floor and medial parts only	
4. Draf III procedure	Frontal sinus punch forceps	Wide access, complete removal of frontal sinus mucosa to the periost
	Frontal sinus high-speed Midas Rex drill (Medtronic, Gent, Belgium)	
	Frontal sinus seeker	
	Frontal sinus curette	

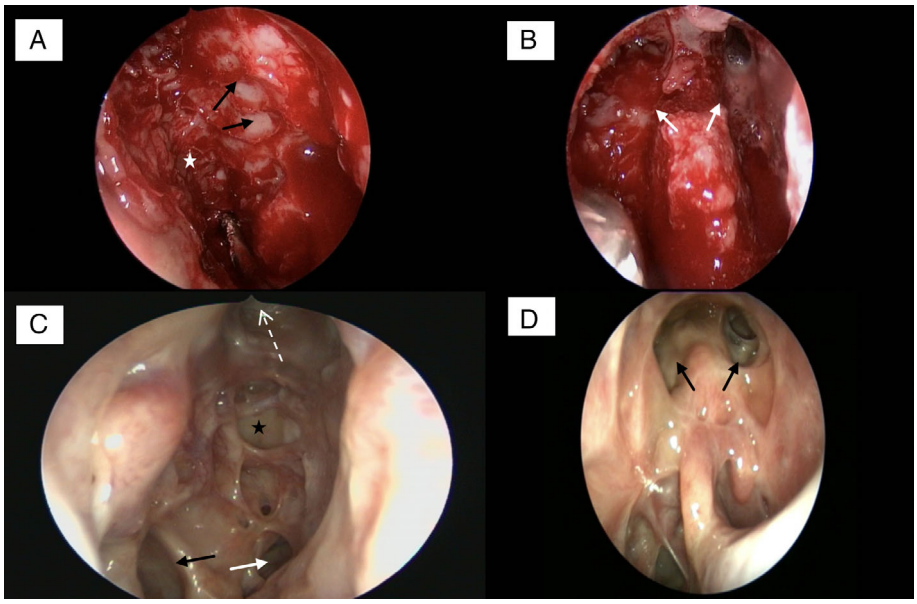

Fig. 4. Intra- and postoperative view of the reboot procedure. (A) Left-side lamina orbitalis (black arrows) and skull base (white asterisk) at the end of the procedure. Polyps and nasal mucosa have been removed down to the periost. (B) Draf III with frontal sinus reboot showing access to both frontal sinuses (white arrows). (C) Right-side posterior ethmoid cells and sphenoid (white arrow) open and clean. The opening of the right maxillary sinus (black arrow), skull base (asterisk), and right frontal recess (dashed arrow). (D) Frontal recess and the opening of both frontal sinuses (black arrows) seen after the procedure.

approaching the sphenoid and clearing the central skull base. Finally, the Draf III procedure is performed, giving maximal access to both frontal sinuses by reducing the bony walls laterally and anteriorly and partially removing the interfrontal septum; the frontal sinus mucosa is then completely removed from the posterior and anterior walls using special instruments (e.g., a curved frontal sinus curette, frontal sinus punches) and making a wide access that will allow the surgeon to remove the whole mucosa of the frontal sinus walls (Table IV) (Fig. 3 and Fig. 4). As shown in the latter figures, it was our intention to remove all sinus mucosa; however, we cannot claim that we removed 100% of the sinus mucosa. Although we aim at complete removal of the sinus mucosa, we are aware of the fact that this may not be achieved specifically from the frontal and sphenoid sinuses and the alveolar recess of the maxillary sinus due to limitations in viewing and instrumentation. After controlling the area for bleeding and irrigating the sinuses with a 1:1 diluted 10% polyvidone iodine solution, two packs of Merocel (Medtronic, Gent, Belgium) are placed bilaterally into the middle meatus and nasal cavities and removed the next morning.

The removal of all sinus mucosa could potentially cause problems during the healing process and lead to prolonged healing and scarring due to the full-thickness mucosal injury. However, an experimental study in sheep has reported no difference in mucosal regeneration after partial or full-thickness mucosal removal, although the reciliation differed significantly.[32] In the patients in the current study, we also did not see any signs of abnormal scar formation; in contrast, the mucosa was wet and functional, without disturbance of the mucociliary clearance, and patients reported no feelings of a dry nasal cavity. A biopsy of a patient 28 months after reboot surgery showed the normal structures of a ciliated epithelium with active goblet cells, indicating the coverage of the operation field by a functional epithelium. Furthermore, well-known to ear, nose, and throat surgeons, the resection of larger areas of the sinus mucosa often is needed in cases of inverted papilloma or malignant sinus tumors, with an appropriate wound healing and closure of the mucosal lining thereafter.[33,34]

Extensive surgery might lead to increased complication rates and more severe complications. A previous study on a more extensive form of surgery compared to a minimal approach did not show any severe complications, and there were no differences in complication rates between the groups.[35,36] Also in our patients, we did not see any severe or lasting complication in relation to the applied technique. However, we advocate that this procedure should only be performed by a surgeon with excellent knowledge and experience of endoscopic sinus surgery (ESS), including Draf III procedures to minimize the risk of complications.

Although the primary outcome criterium was the polyp score, the patients have evaluated the symptoms pre- and postoperatively by VAS scores (in average 30 months after surgery). When evaluating the VAS scores at baseline and postoperatively, no significant differences could be demonstrated between groups, and the VAS scores in all three groups were reduced significantly; larger patient groups would be needed to reach significance. In support of differences between the reboot and non-reboot groups, the postoperative SNOT-22 scores were significantly different in favor of the reboot group. However, we did not record preoperative SNOT scores and therefore cannot provide the changes in SNOT-22 scores. Taken together, we here show that the reboot

surgery—more than the non-reboot surgery—improves sinusitis-related quality of life (SNOT-22) without leading to any additional adverse effects.

In summary, because there are deficits at multiple mucosal levels, the probability of restoring a normal mucosa without fully removing the diseased mucosa appears to be low; therefore, nasal polyp recurrences after sinus surgery might be a question of failed completeness of mucosal removal, especially because the removal of the frontal sinus mucosa in moderate-to-severe nasal polyposis leads to a further decrease in polyp recurrence over a partial reboot only. Furthermore, only the complete suppression of type-2 inflammation may allow for a normal wound-healing process postoperatively, with new mucosa growing from the nasal cavity into the sinuses. In contrast to sinus mucosa, the nasal mucosa is only seldomly involved in polyp formation. Our results in patients with a type-2 sinus mucosa inflammation with polyp formation in two-thirds of subjects with prior surgery and comorbid asthma suggests that the reboot approach may offer a better outcome in severely ill CRSwNP subjects than the conventional mucosa-sparing approach without increasing the risk for intra- or postoperative problems or complications.

CONCLUSION

CRS, including CRSwNP, is a disease with different endotypes that should be approached differently according to these endotypes. Type-2 eosinophilic inflammation, which represents 80% of patients with nasal polyps, at least in Western countries, has been linked to disease severity and a higher recurrence rate than other endotypes. We here introduce the reboot technique, which shows promising results in reducing polyp recurrence and in improving symptoms in a retrospective comparative study with a follow-up of 30 months over the established technique. Further prospective and long-term studies are warranted, which should include inflammatory biomarkers.

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