**Objective:** To assess the medium- to long-term histopathological changes after coblation (cold ablation) inferior turbinate (IT) reduction (CITR) surgery for refractory IT hypertrophy.

**Design:** Two-center, prospective, nonrandomized, controlled histological study.

**Setting:** University-affiliated hospitals.

**Patients:** The coblation-treated group included 22 samples from 16 men with IT hypertrophy in whom CITR had failed and who underwent endoscopically guided mucotomy. The control group included 18 samples from 14 men who had nasal obstruction due to refractory IT hypertrophy and who had undergone inferior turbinectomy.

**Main Outcome Measures:** After processing the samples of both groups, we assessed the general histopathological features, the area fraction of various soft-tissue constituents, and the epithelial integrity.

**Results:** Qualitative analysis showed marked fibrosis and depletion of submucosal glands and venous sinusoids in the lamina propria after CITR. Compared with the control group, the coblation-treated group showed a significantly increased area fraction of connective tissue and significantly decreased area fraction of submucosal glands and venous sinusoids ($P < .001$ for all 3 comparisons). A significantly decreased relative proportion of intact epithelium and a significantly increased relative proportion of partial epithelial shedding were also found in the coblation-treated group ($P = .03$ and $P = .04$, respectively).

**Conclusions:** The long-term histological effects of CITR were significant fibrosis, glandular and venous sinusoid depletion, and partial epithelial shedding. The latter probably resulted from vascular damage, causing a reduction in epithelial perfusion. Questions remain concerning the long-term implications of the histopathological changes of CITR on nasal physiology.

PATIENTS AND TISSUE COLLECTION

Thirty men with a history of prolonged nasal obstruction due to refractory bilateral IT hypertrophy were included in the study. They received conservative therapy with antihistamines, systemic decongestants, topical nasal corticosteroid sprays, and mast-cell stabilizers for at least 2 months. When these measures did not provide adequate relief of symptoms, surgery was suggested. Immunotherapy was ineffective or refused. Otherwise, participants were generally healthy individuals. Given that allergy tests were not performed for all patients, no differentiation was made between patients with and without allergies. None of the patients received topical or systemic corticosteroids or had symptoms of upper respiratory tract infection during the month before surgery. Patients who had septal deviation with contralateral compensatory IT hypertrophy were excluded from the study.

Twenty-two hypertrophic ITs (10 singles and 6 pairs) were removed from 16 men ranging in age from 18 to 55 (mean [SD], 31 [13]) years, in whom CITR surgery had failed and who had undergone endoscopically guided IT mucotomy after 4 to 33 (mean [SD], 14 [10]) months. In 13 of 16 patients (81%), CITR surgery provided no relief of nasal obstruction, whereas improvement was reported in the remaining 3 patients and lasted for 6, 9, and 18 months before symptoms recurred. Both procedures were performed at the Department of Otolaryngology–Head and Neck Surgery, Tel-Aviv Sourasky Medical Center, between July 1, 2003, and March 31, 2007. The remaining 18 hypertrophic ITs (10 singles and 4 pairs) were removed from 14 men ranging in age from 18 to 45 (mean [SD], 27 [8]) years who had undergone inferior turbinectomy alone. These hypertrophic ITs, which form part of the existing collection of IT preparations of the Ear, Nose, and Throat Histopathologic Research Laboratory, served as a control group. Surgeries were performed at the Department of Otolaryngology–Head and Neck Surgery, Meir Medical Center, between July 1, 1997, and March 31, 2002. The patients of the 2 groups were matched according to sex and age (P=.49).

Written informed consent was obtained from all patients after they were instructed about the known benefits, risks, and complications of the procedures. The study protocol was approved by the institutional review boards of Tel-Aviv Sourasky Medical Center and Meir Medical Center and conducted in conformity with the ethical and humane principles of research established by the Helsinki Declaration.

COBLATION IT REDUCTION

The treatment was performed on an outpatient basis. We used a plasma surgery system with a turbinate handpiece (ENTec Coblator with the ReFlex Ultra 45 wand; Arthrocare Corporation, Austin, Tex). The patient was in a supine position, and the nasal cavity was topically anesthetized with cotton pledgets soaked in tetracaine hydrochloride and ephedrine hydrochloride. With the use of a spinal needle, each IT was infused with 4 mL of 1% lidocaine hydrochloride and 1:100,000 epinephrine. Under direct vision, the bipolar electrode was inserted into the mucosa at a 90° angle to achieve as small an entry as possible. With the wand in position for 10 to 15 seconds at a power level of 6 mV, 3 passes were performed submucosally along the medial aspect and 1 pass along the inferior aspect of both turbinates. Care was taken not to penetrate the mucosa posteriorly. Packing was not necessary. The patients were followed up every 3 months for a year and then as needed.

ENDOSCOPICALLY GUIDED IT MUCOTOMY

Surgery was performed on an outpatient basis. Topical anesthesia of the nasal cavity was administered in the manner described for CITR. Under endoscopic guidance and with the use of a scalpel and then turbinectomy scissors, a 1.5- to 2.0-cm full-thickness mucosal piece was harvested unilaterally or bilaterally from the anteromedial aspect of the IT and sent for processing to the Ear, Nose, and Throat Histopathologic Research Laboratory. Subsequently, mucotomy was accomplished under endoscopic guidance and using a straight microdebrider, and the medial and inferior portions of the mucosa were removed throughout the entire turbinate length. Care was taken not to injure the bony surface of the turbinate. Packing was left for 2 days. Follow-up was performed as per protocol for CITR.

TISSUE PREPARATION

All 40 samples underwent standard histological processing. Care was taken not to break the delicate mucosal surface of the epithelium, ensuring the integrity of the samples at the time of retrieval and preparation. The sections were fixed in 10% buffered formaldehyde, and the bone of the control group samples was separated by sharp dissection. Thereafter, the samples were dehydrated with increasing concentrations of ethanol and embedded in paraffin blocks. Serial 5-µm-thick tissue sections were cut at a plane perpendicular to the mucosal surface. Representative sections from the anteromedial aspect were stained with hematoxylin-eosin. The Masson trichrome stain was used to identify fiber collagen. The samples were coded at random and analyzed blindly under light microscopy.

QUALITATIVE AND QUANTITATIVE ASSESSMENT

A qualitative assessment of the sections was performed to indicate the type of epithelium, the presence of inflammation and fibrosis, and the population of submucosal glands and venous sinusoids. The quantitative assessment included standard stereological and morphometric methods to measure the area fraction (ie, relative proportion) of the following soft-tissue constituents: epithelium, connective tissue, glands, arteries, and venous sinusoids. A grid composed of 10×10 squares corresponding to a 4-mm² surface area (2×2 mm) at magnification ×40 was superimposed on the medial mucosal layer. The soft-tissue constituent that appeared at the upper left intersection of each square was recorded. This method allowed 100 hits on each sample. The area fraction of each constituent was calculated as the number of its cross points divided by the total points of the sample. Additional measurements to determine the epithelial integrity included the length of the basement membrane that was (A) covered with intact pseudostratified ciliated columnar epithelium, (B) covered with a single layer of basal cells (ie, indicative of partial epithelial shedding), and (C) devoid of epithelial cells. The total length of the basement membrane was measured by adding the length of the corresponding areas of each of the 3 measurements. The numerator for calculating the relative proportion (expressed as a percentage) of the basement membrane covered by each of these length was the sum of lengths of the corresponding areas, and the denominator was the total length of the basement membrane. For example, the relative proportion for measurement A was A/(A+B+C). The length of the reticule at magnification ×100, used for the quantitative assessment, was 0.8 mm.10
STATISTICAL ANALYSIS

The data were analyzed with SPSS for Windows statistical software (version 14.0; SPSS Inc, Chicago, Illinois). Given that the data were not normally distributed, the Mann-Whitney non-parametric test was used to compare age and various histopathological and morphometric characteristics of the 2 study groups (coblation-treated vs control). Intergroup comparisons of mucous and serous glands were determined using the Wilcoxon rank sum test. Measurements are expressed as mean (SD). The statistical significance level was set at .05.

RESULTS

Qualitative assessment showed marked structural changes in the coblation-treated areas compared with the treatment-spared neighboring areas. Considerable differences were also observed between coblation-treated and control samples (Figure 1). At low magnification (×40), the overall histological pattern was fairly bland and featureless. The loose connective tissue of the normal lamina propria was replaced by extensive fibrosis (Figure 2) with scattered islands of inflammatory cell infiltration under the epithelium. A marked diminution of serous and mucous submucosal glands and large venous sinusoids was observed. Numerous capillaries (average diameter, 25 µm) were seen throughout the submucosal stroma. Partial and/or complete epithelial denudation was found in large regions of the mucosa alongside normal-appearing, pseudostratified, ciliated columnar respiratory epithelium. Occasionally, the respiratory mucosa was partly or completely replaced by a metaplastic squamous epithelium. Nevertheless, in all cases, a well-defined basement membrane was present across the coblation-treated areas.

Quantitative measurements of the area fraction of the various soft-tissue constituents are shown in Table 1. Compared with the control group, the coblation-treated group had a significantly increased area fraction of connective tissue ($P < .001$) and a significantly decreased area fraction of total, mucous, and serous glands and of venous sinusoids ($P < .001$, $P < .001$, $P = .02$, and $P < .001$, respectively). In both groups, the area fraction of serous glands outnumbered that of mucous glands ($P < .001$ and $P = .02$, respectively). On the other hand, no significant difference was found in the area fraction of the epithelium and arteries ($P = .42$ and $P = .053$, respectively).

Measurements of the epithelial integrity showed a significantly decreased relative proportion of intact epithelium and a significantly increased relative proportion of partial epithelial shedding in the coblation-treated group compared with the control group ($P = .03$ and $P = .04$, respectively). The extent of complete epithelial shedding was not different between the groups ($P = .97$) (Table 2).

COMMENT

It is accepted that, although submucosal electrourgical techniques for turbinate reduction generate high temperatures (>400°C), the bipolar coblation wand operates at lower temperatures (40°C-70°C) with less thermal damage extending to adjacent tissues. These attributes were supported by animal experimentation, demonstrating greater tissue injury and slower wound healing after tongue incisions by monopolar diathermy than by coblation.11 It was also shown that application of diathermy causes obliteration of venous sinusoids accom-
panied by submucosal fibrosis and scarring as well as epithelial and glandular changes. Likewise, intense fibrosis was reported a year after radiofrequency bipolar submucosal diathermy of the IT.

To date, the statements regarding the limited collateral effect of coblation on turbinate tissue were not histologically confirmed. Our data on the medium- to long-term histopathological changes of CITR revealed for the first time marked qualitative and quantitative changes of the various IT soft-tissue constituents. The most prominent change was diffuse fibrosis of the lamina propria extending from the basement membrane superficially to the deeper parts of this layer. Other significant changes within this layer were a paucity of submucosal glands and replacement of the large venous sinuses, found in our control group, with small-caliber veins. The quantitative analysis supported this observation and showed a significantly increased area fraction of connective tissue and significantly decreased area fractions of total mucous and serous submucosal glands, as well as a significantly decreased area fraction of veins. Of note is that, although coblation uses far lower temperatures, these histopathological observations of significantly increased area fraction of connective tissue and significantly decreased area fractions of submucosal glands and venous sinuses are very much like those seen when laser application is used for IT reduction (Figure 3).

An additional morphometric hallmark of CITR surgery was a significantly decreased intact pseudostratified, ciliated, columnar respiratory epithelium and a significantly increased partial epithelial shedding manifested by a basement membrane covered with a single layer of basal cells and devoid of ciliated, nonciliated, and goblet cells. The explanation for the late damage of the epithelial integrity, occurring months after the prudent submucosal insertion of the coblation wand, is probably related to submucosal vascular injury that eventually decreased epithelial perfusion.

Table 1. Area Fraction of Soft-Tissue Constituents

<table>
<thead>
<tr>
<th>Group</th>
<th>Epithelium</th>
<th>Connective Tissue</th>
<th>Glands</th>
<th>Veins</th>
<th>Arteries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coblation-treated</td>
<td>2.1 (1.9)</td>
<td>84.3 (6.1)</td>
<td>5.3 (3.6)</td>
<td>0.8 (1.7)</td>
<td>4.5 (3.2)</td>
</tr>
<tr>
<td>Control</td>
<td>1.6 (1.4)</td>
<td>59.2 (8.5)</td>
<td>11.7 (5.5)</td>
<td>4.2 (3.2)</td>
<td>7.6 (4.5)</td>
</tr>
</tbody>
</table>

Table 2. Relative Proportion of Intact Epithelium and Partial and Complete Shedding

<table>
<thead>
<tr>
<th>Group</th>
<th>Intact Epithelium</th>
<th>Partial Shedding</th>
<th>Complete Shedding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coblation-treated</td>
<td>26.6 (29.1)</td>
<td>43.7 (27.4)</td>
<td>29.7 (22.5)</td>
</tr>
<tr>
<td>Control</td>
<td>44.3 (24.3)</td>
<td>26.8 (14.4)</td>
<td>29.1 (22.9)</td>
</tr>
</tbody>
</table>

Figure 3. A resemblance between coblation-treated (A) and laser-treated (B) areas was observed and in both sections shows marked fibrosis with few glandular structures and venous sinuses (B, processed from the existing collection of inferior turbinate preparations of the Ear, Nose, and Throat Histopathologic Research Laboratory, Meir Medical Center, Kfar Saba, Israel) (hematoxylin-eosin, original magnification ×40).
patients on whom we operated and who underwent surgery elsewhere benefited from CITR surgery for at least 6 to 12 months. The diminution of submucosal glands may offer a plausible explanation for the decreased nasal discharge in these patients. However, the dwindling of glands with advancing age was already demonstrated in the normal IT and in another neighboring region of the upper respiratory tract. Given these data, it would be difficult at present to speculate on the long-term physiological effects of this phenomenon or those of the fibrosis common in electrosurgical techniques. Moreover, the finding of delayed partial epithelial shedding with submucosal vascular damage may be associated with altered defensive function of the epithelium. Considering that the long-term implications of surgery on normal nasal physiology have yet to be fully established, open questions remain on the ultimate effect of these pathological changes on normal nasal physiology.

In conclusion, the medium- to long-term histological effects of CITR included significant fibrosis, glandular and venous sinusoid depletion, and partial epithelial shedding. The latter probably resulted from a reduction in epithelial perfusion due to vascular damage. The long-term implications of these pathological changes on normal nasal physiology should be considered when assessing the need for CITR surgery.

Submitted for Publication: October 16, 2007; final revision received December 7, 2007; accepted December 19, 2007.

Correspondence: Gilead Berger, MD, Department of Otolaryngology–Head and Neck Surgery, Meir Medical Center, 59 Tchernichovsky St, Kfar Saba 44281, Israel (berger45@netvision.net.il).

Author Contributions: Drs Berger, Ophir, and Landsberg had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Berger and Landsberg. Acquisition of data: Berger and Landsberg. Analysis and interpretation of data: Berger, Ophir, and Pitaro. Drafting of the manuscript: Berger. Critical revision of the manuscript for important intellectual content: Berger, Ophir, Pitaro, and Landsberg. Obtained funding: Ophir. Administrative, technical, and material support: Berger and Landsberg. Study supervision: Berger, Ophir, Pitaro, and Landsberg.

Financial Disclosure: None reported.

Previous Presentation: This study was presented at the 2007 Annual Academy Meeting; September 18, 2007; Washington, DC.

Additional Contributions: Doron Comaheshter, MHA (Statistical Service, Tel Aviv Sourasky Medical Center), provided statistical consulting and Rachel L. Berger, BA (Kfar Saba), assisted with the writing and editing.

REFERENCES