Microarchitecture of Schlemm Canal Before and After Selective Laser Trabeculoplasty in Enhanced Depth Imaging Optical Coherence Tomography

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Purpose: To characterize the in vivo effect of selective laser trabeculoplasty (SLT) on the Schlemm canal (SC) in eyes with primary open-angle glaucoma (POAG).

Materials and Methods: Eighty-one serial horizontal enhanced depth imaging optical coherence tomograph B-scans (interval between B-scans, ~35 μm) of the nasal corneoscleral limbus were obtained before and 4 weeks after SLT. Fifty B-scans in the overlapping regions before and after SLT were selected for analysis based on the structures of aqueous and blood vessels as landmarks. The SC cross-sectional area (CSA) was measured in each selected B-scan and averaged to generate the mean SC CSA of the eye. SC volume in the overlapping region was calculated using commercially available 3-dimensional reconstruction software. The mean SC CSA and SC volume were compared between pre-SLT and post-SLT B-scans. Correlation analysis was performed between SC CSA changes and intraocular pressure (IOP) changes.

Results: Thirteen POAG eyes (13 patients) were included for analysis (mean age, 68.2 ± 9.2 y). After SLT, the mean IOP was reduced from 19.8 ± 7.6 to 14.4 ± 3.8 mm Hg ($P = 0.003$); the mean SC CSA increased by 8%, from 2478 ± 550 to 2682 ± 598 μm^2 ($P = 0.029$); and the mean SC volume increased from 4,304,592 ± 954,777 to 4,658,250 ± 1,039,956 μm^3 ($P = 0.029$). Increase in SC CSA had a significant positive correlation with IOP reduction after SLT ($P = 0.023$, $R = 0.622$).

Conclusions: SLT expands SC in POAG patients and even more so with greater IOP reduction after SLT. Post-SLT expansion of SC may be due to increased trabecular aqueous outflow, IOP decrease, or structural changes in trabecular meshwork resulting from SLT.

Key Words: glaucoma, optical coherence tomography, selective laser trabeculoplasty, Schlemm canal

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Selective laser trabeculoplasty (SLT) is a widely used, safe, and effective procedure for reducing intraocular pressure (IOP) in primary open-angle glaucoma (POAG) and can be used as first-line therapy.[1] It can also be used to reduce the number of antiglaucoma medications or to avoid or delay incisional surgery.[2] Despite its widespread use, its precise mechanism(s) of action, especially in regard to its effect on the trabecular aqueous outflow pathway, is not yet fully understood.

Ultrasound biomicroscopy and spectral-domain (SD) optical coherence tomography (OCT) have been used to visualize the microarchitecture of the trabecular aqueous outflow pathway. SD OCT provides high-resolution cross-sectional images of the trabecular outflow pathway in vivo and ex vivo with details comparable to corrosion casting techniques.[3–8] However, SD OCT images of the Schlemm canal (SC) are often suboptimal because SC is located deep in the corneoscleral limbus. Enhanced depth imaging (EDI) OCT, a modification to the conventional SD OCT technique, provides superior image quality of the deeper ocular tissues.[9] In this study, we characterized the in vivo effect of SLT on the SC microarchitecture and examined the trabecular outflow pathway structure in POAG patients using EDI OCT before and after SLT.

MATERIALS AND METHODS

This study was approved by the New York Eye and Ear Infirmary of Mount Sinai institutional review board. Written informed consents were obtained from all subjects and the study adhered to the tenets of the Declaration of Helsinki.

Participants

POAG patients scheduled to have SLT were consecutively enrolled after obtaining a detailed medical history and complete ophthalmologic examination. Patients were

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required to have best-corrected visual acuity of 20/50 or better, spherical and cylindrical refractive error <6 and 3 D, respectively, axial length <26.5 mm, no previous intraocular surgery other than uncomplicated small incision cataract extraction performed more than 12 months before enrollment, and no previous SLT in the study eye. We excluded participants with conditions known to affect conventional outflow pathway structures other than POAG (eg, angle closure glaucoma, neovascular glaucoma, iridocorneal endothelial syndrome, anterior segment congenital anomalies, etc.) or reduce anterior segment OCT image quality (eg, pterygium, pinguecula, limbal opacities, nystagmus, etc.). All participants underwent slit-lamp biomicroscopy, Goldmann applanation tonometry, and EDI OCT of the trabecular outflow pathway before and 4 weeks after undergoing SLT.

SLT Technique

A frequency doubled, Q-switched Nd:YAG laser emitting at 532 nm, with a pulse duration of 3 ns, a spot size of 400 μm and pulse energies ranging from 0.2 to 1.4 mJ, coupled to a slit-lamp delivery system with a He-Ne aiming system, was used in all SLT procedures (Selectra Duet; Lumenis, Dreieich, Germany). The treatment parameters and technique were very similar to those originally described by Latina et al.[10]

Immediately before treatment, topical anesthesia was instilled on the eye. Although the patient was in a sitting position, a single mirror goniolens was used to focus the laser on the pigmented trabecular meshwork. Using a 400 μm spot, the entire width of the trabecular meshwork was treated with each pulse. The laser energy was initially set at 0.8 mJ. If cavitation bubbles ("champagne bubbles") appear, the energy was reduced by 0.1 mJ until there was minimal or no bubble formation and treatment was continued at this energy level. If no cavitation bubbles occurred, the energy was increased by 0.1 mJ until bubble formation and then decreased as described above. Some patients were treated over 180 degrees of trabecular meshwork circumference (50 nonoverlapping spots on the nasal half) and others over 360 degrees (100 nonoverlapping spots). Postoperatively, steroid or nonsteroidal anti-inflammatory drops were prescribed for 5 to 7 days. Patients continued to take their preoperative antiglaucoma medications.

EDI OCT

The method for serial EDI OCT of the SC has previously been described.[11] The repeatability and reproducibility of this method have been demonstrated in a previous report.[12] In brief, serial horizontal EDI OCT B-scans [Spectralis OCT (Anterior Segment Module); Heidelberg Engineering GmbH, Heidelberg, Germany] of the nasal corneoscleral limbal area were obtained before and 4 weeks after the SLT procedure. The OCT device was set to image a 15×5-degree rectangle (81 EDI OCT B-scans; interval between scans, ~ 35 μm) (Fig. 1). Conjunctival vessels and iris anatomy were used as landmarks to scan the same limbal area before and after SLT. All scans were performed by the same experienced operator. After acquisition of EDI OCT scans, the aqueous and blood vessels in each B-scan were carefully reviewed to identify the overlapping region between the 2 sets of volumetric scan (before and after SLT).

Measurement of SC Cross-sectional Area (CSA)

Patients with an incomplete set of EDI OCT B-scans due to poor cooperation (eg, excessive eye or head movement, excessive blinking) or with poor quality scans in which SC could not be reliably delineated were excluded from analysis. The CSA of SC was measured in each scan in the overlapping region between the 2 sets of volumetric scan, by manually delineating the hyporeflective SC lumen using commercial software (Amira, version 5.4.5; Visage Imaging Inc., San Diego, CA). The SC in the overlapping region was reconstructed 3-dimensionally after manually aligning the EDI OCT B-scans using the same software, and SC volume in this region was calculated. SC in each EDI OCT image was delineated by an experienced investigator and SC delineations were reviewed and adjudicated by 2 additional investigators. All the investigators were masked to the clinical status of patients, including the time-order of the EDI OCT images with respect to the SLT (pre-SLT or post-SLT). When the investigators disagreed on the delineation, a mutual conclusion was reached after discussion.

Statistical Analysis

Statistical analysis was performed using a paired t test to compare IOP, SC CSA, and SC volume between pre-SLT and post-SLT. Correlation analysis was performed (1) between SC CSA changes and IOP changes; (2) between SC CSA percentage changes and IOP changes; and (3) SC CSA changes and baseline SC CSAs. A P value of <0.05 was considered statistically significant. Data were analyzed using Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA) and SPSS software version 13.0 (SPSS Inc., Chicago, IL).

RESULTS

Eighteen eyes of 18 POAG patients were initially recruited. Five eyes were excluded due to poor patient cooperation or poor EDI OCT image quality. The remaining 13 eyes were included for measurement and analysis [mean age = 68.2 ± 9.2 y (range, 50 to 83 y)]. Demographic and clinical characteristics of participants are shown in Table 1. Mean IOP was significantly reduced 4 weeks after SLT (19.8 ± 7.6 to 14.4 ± 3.8 mm Hg; $P = 0.003$). The number of overlapping EDI OCT B-scans varied from patient to patient, ranging from 50 to 78. To maintain consistency among patients, 50 best-matched scans from before and after SLT were selected for analysis. Therefore, the SC CSA was measured in 50 pre-SLT B-scans and 50 post-SLT B-scans.

Four weeks after SLT, the mean SC CSA increased significantly by 8%, from 2478 ± 550 to 2682 ± 598 μm^2 ($P = 0.029$; Table 2). Representative EDI OCT B-scans before and after SLT are shown in Figure 2. SC volume of the analyzed region (approximately 1.7 mm of circumferential length in the nasal limbus) increased significantly from 4,304,592 ± 954,777 to 4,658,250 ± 1,039,956 μm^3 ($P = 0.029$).

Changes in the mean SC CSA had a significant correlation with IOP reduction after SLT ($P = 0.023$, $R = 0.622$; Fig. 3): SC expanded more with greater IOP reduction. Percentage changes in the mean SC CSA also had a significant correlation with IOP reduction after SLT ($P = 0.027$, $R = 0.610$). SC appeared to expand less in patients with older age ($R = -0.468$) but there was no

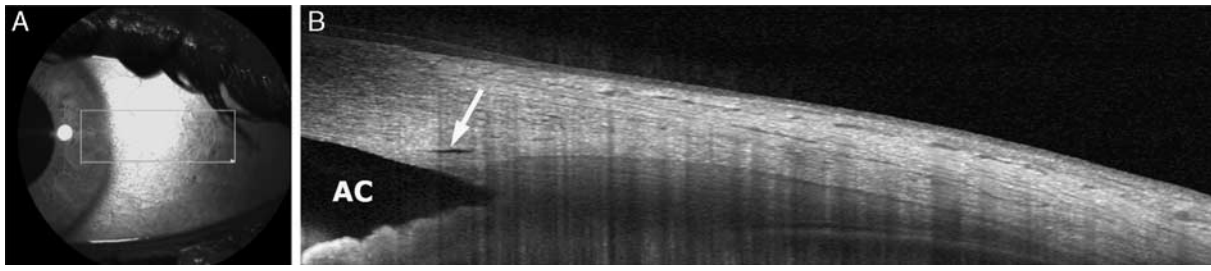

FIGURE 1. A, A 15 × 5-degree rectangular area in the nasal limbus for 81 serial horizontal enhanced depth imaging optical coherence tomography (EDI OCT) B-scans. B, A horizontal EDI OCT B-scan with a clear visualization of Schlemm canal (white arrow). AC indicates anterior chamber.

significant correlation between changes in the mean SC CSA and age ($P = 0.11$). Changes in the mean SC CSA changes had no significant correlation with the baseline SC CSA ($P = 0.75$).

In the 10 phakic eyes, the CSA increased from 2458 ± 583 to 2683 ± 643 μm^2 ($P = 0.040$) and SC volume increased from 4,268,833 ± 1,012,964 to 4,660,004 ± 1,118,884 μm^3 ($P = 0.040$). In the 3 pseudophakic eyes, the SC CSA increased from 2546 ± 523 to 2678 ± 532 μm^2 and SC volume increased from 4,423,789 ± 907,993 to 4,652,401 ± 924,897 μm^3, but these increases were not statistically significant (all $P = 0.58$) possibly due to the small sample size (n = 3).

DISCUSSION

SLT is widely used to lower IOP in patients with POAG.[1,2,13–16] The exact mechanism by which SLT lowers IOP is not yet fully understood and a number of hypotheses have been proposed. Most researchers believe that the decrease in IOP is the result of cellular activity stimulated by the laser energy. The SLT laser emits a single ultra-short duration low fluency (energy/area) pulse that selectively targets pigmented trabecular meshwork cells.[17,18] Alvarado et al[19] showed that the number of monocytes/macrophages in the trabecular meshwork increases substantially after SLT and monocytes augment both trabecular outflow facility and SC endothelial cell conductivity. The same group also demonstrated that SLT, in a manner similar to prostaglandin analogs, regulates the permeability of cultured human SC cells by inducing intercellular junction disassembly.[20] SLT caused a 3-fold increase in SC cell conductivity, emphasizing the role of intercellular junctions in regulating trans-endothelial fluid flow across SC cells.[20] The intercellular junctions between SC endothelial cells are assumed to be the last control point regulating the egress of aqueous humor from the intraocular fluid compartment into the venous compartment[21] and therefore determining the IOP level. Another publication[22] suggested that laser trabeculoplasty induces the expression and secretion of both interleukin-1β and tumor necrosis factor-α within the first 8 hours after treatment. These cytokines then mediate increased trabecular stromelysin expression.[22] Putatively, this initiates remodeling of the juxtacanalicular extracellular matrix, a likely site for the aqueous outflow resistance, and thus improves outflow facility thereby decreasing IOP. We demonstrated a significant increase in mean SC CSA and SC volume after SLT in POAG patients and a significant correlation between this increase and IOP reduction. Our study provides the first in vivo evidence consistent with increased trabecular aqueous outflow in human eyes after SLT and is

TABLE 1. Demographic and Clinical Characteristics of Participants

Patient #	Age (y)	Sex	24-2 VF MD (dB)	Pre-SLT IOP (mm Hg)	Post-SLT IOP (mm Hg)
1	71	M	−1.2	22	15
2	50	F	−4.2	15	11
3	77	M	−7.3	10	12
4	70	F	−1.2	21	14
5	67	M	−2.8	22	22
6	77	F	−4.1	18	14
7	83	F	−18.7	13	10
8	65	M	−1.9	30	17
9	57	M	−27.6	22	13
10	62	M	−8.3	18	12
11	70	F	−0.8	38	22
12	77	F	−7.6	16	13
13	61	F	−6.4	12	12
Mean ± SD	68.2 ± 9.2		−7.1 ± 7.8	19.8 ± 7.6	14.4 ± 3.8

F indicates female; IOP, intraocular pressure; M, male; MD, mean deviation; SLT, selective laser trabeculoplasty; VF, visual field.

TABLE 2. Mean Schlemm Canal Cross-sectional Area Before and 4 Weeks After Selective Laser Trabeculoplasty

Patient #	Before SLT (μm^2)	After SLT (μm^2)
1	2472 ± 724	2424 ± 674
2	3075 ± 824	3613 ± 844
3	2801 ± 783	2539 ± 762
4	1542 ± 468	1825 ± 973
5	3618 ± 1276	3686 ± 1155
6	2176 ± 746	2125 ± 601
7	1945 ± 830	2229 ± 1244
8	2168 ± 769	2681 ± 800
9	2500 ± 825	3273 ± 635
10	2620 ± 832	2688 ± 845
11	2893 ± 1022	3266 ± 836
12	1909 ± 790	2132 ± 617
13	2500 ± 945	2384 ± 789
Mean ± SD	2478 ± 550	2682 ± 598

Values are described as mean ± SD.
SLT indicates selective laser trabeculoplasty.

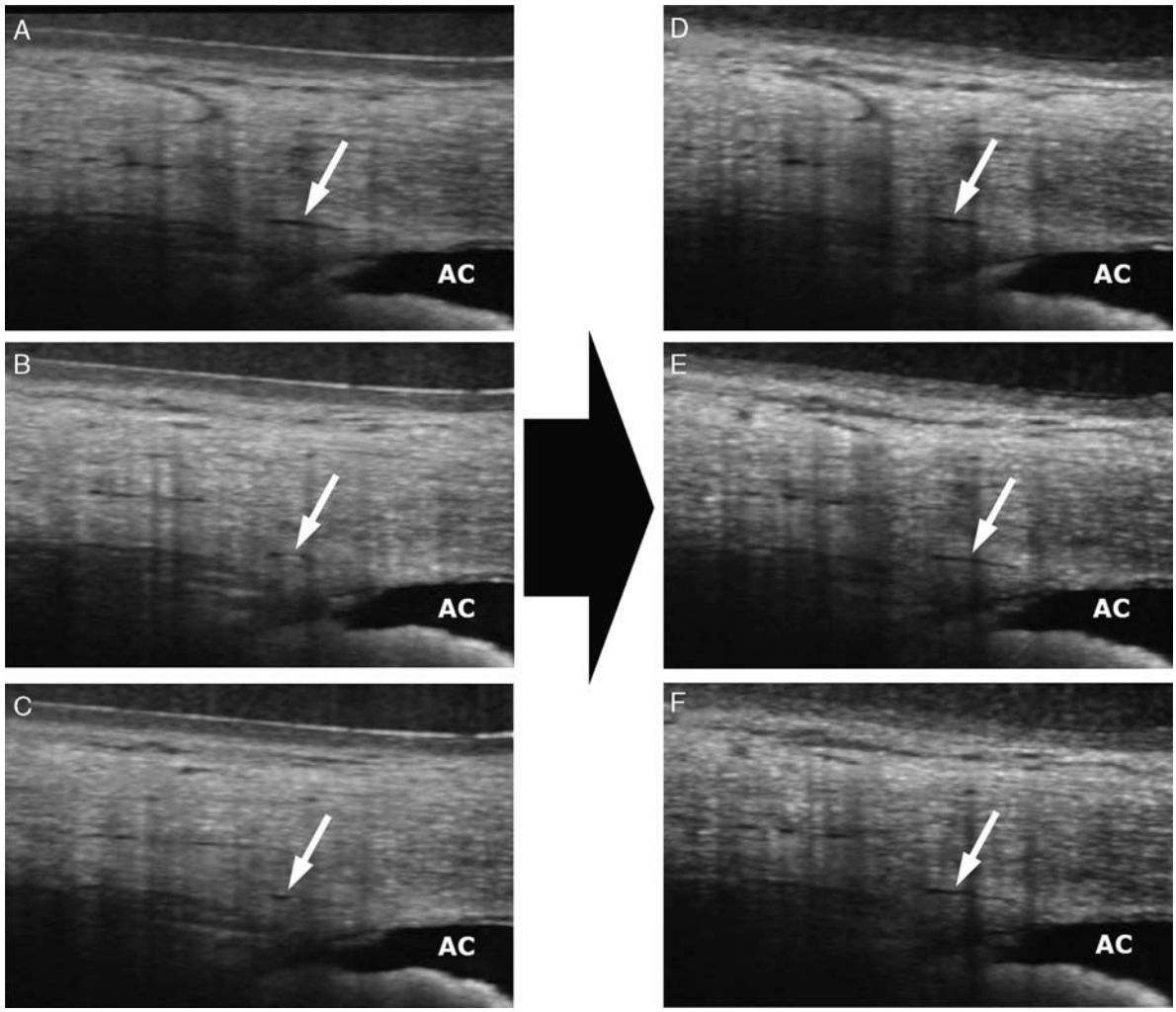

FIGURE 2. Representative serial enhanced depth imaging optical coherence tomography B-scans of Schlemm canal (SC) (white arrow) before (A-C; interval between adjacent scans = 35 μm) and 4 weeks after (D-F; interval between adjacent scans = 35 μm) selective laser trabeculoplasty. Expansion of SC is noted in (E) and (F) compared with (B) and (C), respectively. AC indicates anterior chamber.

compatible with previous studies that showed increased trabecular outflow facility,[19] increased permeability of SC cells,[20] and increased expression of cytokines which may lead to remodeling of the juxtacanalicular extracellular matrix.[22]

Patients with greater IOP reduction after SLT tended to have a larger increase in SC CSA. This suggests that the physical expansion of SC is directly related to the increased aqueous outflow and IOP reduction. A previous study[23] has reported that increasing IOP correlates with smaller SC diameter in glaucoma patients. Another study showed that acute IOP elevation significantly reduces SC CSA in healthy subjects.[24] However, it is still unclear if the increased (decreased) IOP causes the SC collapse (expansion), if the SC collapse (expansion) causes increased (decreased) IOP, or both. The temporal relationship between SC microarchitecture change and IOP change needs to be studied further. In addition, post-SLT expansion of SC may be partially due to structural changes in trabecular meshwork caused by SLT.

In a previous study,[25] phakic eyes with POAG or ocular hypertension showed a significantly greater IOP reduction at 2 weeks after SLT compared with pseudophakic eyes, whereas the longer term (3 mo or longer) effectiveness of SLT was the same between phakic and pseudophakic eyes. It was suggested that in pseudophakic eyes, the SLT response may be delayed and may not be completely achieved in the short term after SLT.[25] In the present study, there was a tendency of greater SC expansion and greater IOP reduction after SLT in phakic eyes compared with pseudophakic eyes. Considering the limitation of a small sample size (10 phakic eyes vs. 3 pseudophakic eyes), however, further studies with a larger sample size are required to compare the SC structure change after SLT between phakic and pseudophakic eyes.

Imaging SC in vivo in human eyes is challenging because of its deep location, shadowing effect of superficial blood or aqueous vessels, different light reflection properties and polarization characteristics of the adjacent tissues, and

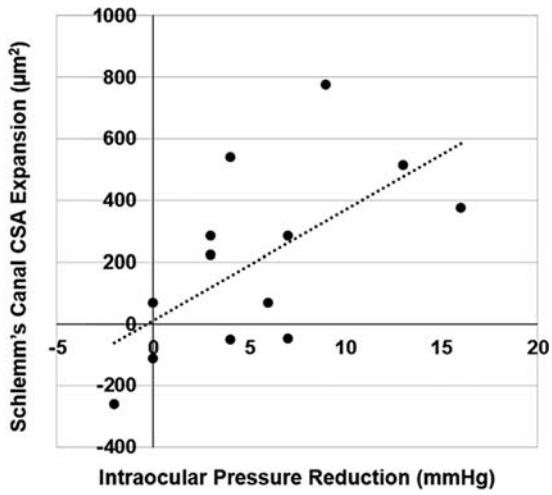

FIGURE 3. Scatter plot of intraocular pressure reduction versus the mean Schlemm canal cross-sectional area (CSA) expansion after selective laser trabeculoplasty, showing a moderate positive correlation ($R = 0.622$, $P = 0.023$).

its structural variations. If longer wavelengths are used to visualize the SC better, the axial resolution of the scans will become worse. EDI OCT provides superior imaging of the deeper ocular tissues to conventional SD OCT and is useful for evaluating in vivo microarchitecture of the trabecular outflow pathway.[11,12] In vivo SC dimensions may reflect the canal's function more accurately than SC measurements in histologic studies because artifacts during histopathologic preparation can be avoided. EDI OCT may play a future role in assessing SC with regard to glaucoma laser and microinvasive surgical procedures and pharmacologic agents that target the trabecular outflow pathway. EDI OCT-guided SC evaluation may also promote understanding of glaucoma surgical success and failure, which will in turn enable proper patient selection and improve outcomes.

This study is not without limitations. SC in the nasal area was evaluated, and it is possible that other parts of the SC may respond differently to SLT. Because of the interval between adjacent EDI OCT B-scans (approximately 35 μm), the matched pre-SLT and post-SLT scans may not be from the same location. Considering the number of EDI OCT scans analyzed per eye (50 pre-SLT scans and 50 post-SLT scans), however, we believe that this did not have a significant negative effect on the results.

In summary, we have demonstrated that SLT results in SC expansion in eyes with POAG in vivo. SC tends to expand more when IOP reduction is greater after SLT. These results provide additional insights into the SLT's mechanisms of action. EDI OCT of SC may prove useful for evaluating the mechanisms of action of laser procedures, pharmacologic agents, and surgical techniques and devices that target trabecular outflow structures. Future identification of preoperative SC anatomic features that are correlated with the amount of IOP reduction will help in selecting which patients may better benefit from SLT.

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