Improvement in Outflow Facility by Two Novel Microinvasive Glaucoma Surgery Implants

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PURPOSE. To determine improvement in outflow facility (C) in human anterior segments implanted with a novel Schlemm's canal scaffold or two trabecular micro-bypasses.

METHODS. Human anterior segments were isolated from 12 pairs of eyes from donors with no history of ocular disease and then perfused at 50, 40, 30, 20, and 10 mm Hg pressures for 10 minutes each. Baseline C was calculated from perfusion pressures and flow rates. The scaffold was implanted into Schlemm's canal of one anterior segment, and two micro-bypasses were implanted three clock-hours apart in the contralateral anterior segment. Outflow facility and resistance were compared at various standardized perfusion pressures and between each device.

RESULTS. Compared to baseline, C increased by 0.16 ± 0.12 $\mu\text{L}/\text{min}/\text{mm Hg}$ (74%) with the scaffold, and 0.08 ± 0.12 $\mu\text{L}/\text{min}/\text{mm Hg}$ (34%) with two micro-bypasses. The scaffold increased C at perfusion pressures of 50, 40, 30, and 20 mm Hg ($P < 0.005$). Two micro-bypasses increased C at a perfusion pressure of 40 mm Hg ($P < 0.05$).

CONCLUSIONS. Both implants effectively increased C in human eyes ex vivo. The scaffold increased C by a greater percentage (73% vs. 34%) and at a greater range of perfusion pressures (20 to 50 mm Hg vs. 40 mm Hg) than the two micro-bypasses, suggesting that the 8-mm dilation of Schlemm's canal by the scaffold may have additional benefits in lowering the outflow resistance. The Hydrus Microstent scaffold may be an effective therapy for increasing outflow facility and thus reducing the IOP in patients with glaucoma.

Keywords: Schlemm's canal, outflow facility, glaucoma anterior segment, drainage device

Primary open angle glaucoma (POAG) remains a leading cause of blindness, affecting 60 million of people worldwide.¹ POAG is a characteristic progressive optic neuropathy in which pathologically high IOP is a major risk factor.² Although there is no cure for POAG, lowering of IOP by pharmacological or surgical methods effectively slows the progression of the disease.² One way to reduce IOP is by increasing outflow facility (C) through the trabecular meshwork (TM). This is effective because pathological changes to the TM have been shown to cause increased outflow resistance and subsequent IOP elevation.³

Drugs designed to lower IOP are effective when used as instructed, but frequent dosing, side effects, and cost create obstacles with patient compliance (24%–59% nonadherence).⁴ The traditional surgical methods available for lowering IOP include laser trabeculoplasty, trabeculectomy, and tube shunts.⁵ The nonpermanence of laser procedures, as well as the propensity for complications arising from filtering-bleb or adjuvant antimetabolite use and drainage device procedures leaves a gap in the glaucoma treatment paradigm.⁶ Microinvasive glaucoma surgery (MIGS) aims to address some of the limitations associated with these treatment options. MIGS procedures have demonstrated a high degree of safety due to an ab interno microincisional approach that minimally disrupts

the normal anatomy and physiology while effectively lowering IOP.⁶ Additionally, MIGS procedures, when successful, minimize concerns regarding medication regimen compliance and some of the complications associated with current surgical methods. Two MIGS procedures approved by the Food and Drug Administration use the conventional outflow pathway through Schlemm's canal (SC); first the Trabectome procedure (Neomedix, Tustin, CA) and more recently the iStent trabecular micro-bypass (Glaukos Corp., Laguna Hills, CA). The Hydrus Microstent (Ivantis, Inc., Irvine, CA) is the most recent addition to MIGS and is currently under clinical investigation in the United States.

The Hydrus Microstent (Fig. 1A) has been designed to bypass the TM and scaffold and dilate approximately one quadrant of SC, thus routing aqueous humor from the anterior chamber into open collector channels. In glaucoma surgeries, such as the canaloplasty, dilation of SC and increased circumferential flow is associated with IOP reduction.⁷ Moreover, scaffolding SC addresses the tenet that elevated IOP causes SC collapse and changes in aqueous humor outflow patterns.⁸ Studies in human anterior segment perfusion models with two configurations of the scaffold demonstrated significant increases in C compared with a sham control.^{9,10}

FIGURE 1. (A) Hydrus Microstent is 8 mm long with an open SC scaffold coupled with a trabecular meshwork bypassing inlet. (B) iStent micro-bypass has a snorkel with a 120- μ m lumen and a 1-mm rail fitting into SC.

The iStent trabecular micro-bypass is an L-shaped titanium implant that is inserted through the trabecular meshwork into SC (Fig. 1B).¹¹ Although the use of a single micro-bypass has shown IOP-lowering potential in clinical studies, there appears to be benefit to implanting multiple micro-bypasses.⁶ Experiments with cultured human anterior segments and clinical studies suggest that two or more micro-bypasses may be required to achieve the lowest final IOP.^{11–13} However, three and four iStents reportedly are not much more effective than 2 iStents.¹¹ Some effects of the devices may be due to establishing circumferential flow beyond the area of implantation. Hence, two micro-bypasses and one scaffold were thought to access one quadrant of SC.¹⁴ Use of two iStents covering the same area of the SC as one Hydrus was considered to be a fair comparison of the two devices. Therefore, the current study compared implantation of two micro-bypasses against one scaffold. Twelve pairs of healthy donor eyes were used to evaluate quantifiable differences in C between the scaffold and two micro-bypasses. In addition, histological cross-sections were examined for morphological differences between the scaffold and micro-bypass.

MATERIALS AND METHODS

Test Articles

The Hydrus scaffold used in this study was composed of Nitinol (nickel-titanium) and was 8 mm in length with an inlet to maintain an opening in the TM of 4 to 5 times the natural cross-sectional area of SC. The iStent L-shaped trabecular micro-bypass was composed of titanium with a 0.25-mm $\times$ 120- μ m (bore diameter) snorkel and a 1-mm rail that fit into SC.

Eye Preparation

Twelve pairs of human globes from donors with no history of ocular disease were obtained from Lions Eye Institutes in

Minneapolis, Minnesota and Tampa, Florida. Eyes were shipped in moist chambers on ice and received within 48 hours of death. The project was approved by the University of Nebraska Medical Center Institutional Review Board. The eyes were dissected along the coronal equator and the anterior segments were prepared as described previously.^{9,10} The anterior segment specimens used for the experiments consisted of the cornea, anterior sclera, and TM. All other ocular tissue was discarded. All experiments were completed in a short period of time, beginning immediately after receipt of the globes and not exceeding 7 hours after the start of the experiments.

Perfusion System

The perfusion fluid was prepared by mixing an isotonic solution of 5.5 mM D-glucose in Dulbecco's PBS. A perfusion apparatus for human anterior segments was set up as described previously.⁹ Fluid columns of a fixed diameter (4 mm) and set fluid height were used to control the perfusion pressure. Calibrations were performed before each experiment to ensure demarked fluid heights corresponded to desired pressures as detected by the transducer. Each pair of anterior segments was mounted on custom-made fixtures that were coupled to the fluid column system. During the perfusion, the eye fixtures contained 10 to 12 mL perfusion fluid kept at 34°C by partial submersion in a temperature-regulated water bath. Pressure transducers, PowerLab 8/30 receiver (ADInstruments, Bella Vista, Australia) and LabChart 7 software (ADInstruments Pty. Ltd., Richardson, TX) recorded perfusion pressures throughout the experiment.

Calculation of Outflow Facility

The volume of fluid exiting the system was linearly proportional to reductions in pressure. Stabilized flows were calculated from the slope of pressure recordings in the LabChart software over the set time interval of 10 minutes. Stabilized flows and average perfusion pressures for each

FIGURE 2. Representative photos of implants in the inferior nasal quadrant of anterior segments. *Left column:* Anterior segment (OS) with implanted scaffold. *Arrows* indicate flanks of scaffold. *Right column:* Anterior segment (OD) receiving two micro-bypasses. *Arrows* indicate a single stent. S, superior; N, nasal.

interval were used to calculate C in the anterior segments using the Goldmann equation. It was assumed that episcleral venous pressure and uveoscleral outflow were zero and stabilized flow rates represented trabecular outflow. Thus, $C = \frac{f}{p}$, where C is outflow facility, f is flow of fluid through the column, and p is the pressure in the anterior segment. Outflow resistance (R) was the inverse of C .

Implant Study Design

Perfusions were performed sequentially at pressures of 40, 30, 20, 10, 20, 30, 40, and 50 mm Hg. Baseline outflow facilities were calculated for each anterior segment at each perfused pressure. After baseline measurements, one Hydrus scaffold was placed in the inferior nasal quadrant of SC of one randomly selected eye out of each pair. The scaffold was advanced approximately 3 clock-hours, leaving 1 to 2 mm protruding into the anterior chamber. Two micro-bypasses with intracanalicular rails pointing away from each other were implanted 2 to 3 clock-hours apart in a similar quadrant of the paired anterior segment (Fig. 2). Of the paired eyes, the one that received the scaffold was assigned using a software randomizer. The anterior segments were remounted as described above after the placement of the devices and the flow experiments repeated as described above.

Training of insertion technique for the iStent micro-bypass was done by an ophthalmic surgeon certified in the micro-bypass insertion procedure. Training of insertion technique for the scaffold was done by a design engineer from Ivantis. Using delivery systems designed for clinical use, all implants were inserted into SC in the nasal quadrant previously marked on the cornea, which was easily visualized in the anterior segments when the cornea was facing downward. The insertion procedure was subjectively graded on a scale of 1 to 3, with 1 being insertion with one to two punctures of TM, 2 being insertion with three to five punctures, and 3 being improper placement or insertion failure after five punctures of the meshwork. At the end of the experiment, the tissues were reexamined to ensure that no implant had any noticeable shift in position during the measurement. Verification of implant placement was recorded with photographic documentation. The experiments were successfully completed in all 12 pairs (24 eyes).

Statistical Analysis

No differences in C values were observed at perfusion pressures of 20, 30, and 40 mm Hg, between the initial pressure decrements and their equivalent pressure increments. Hence, the two values at these pressures were averaged. These

TABLE 1. Characteristics of Donors

Sex	Cause of Death	Age, y	Postmortem Time, h
M	Cardiac arrest, sepsis	51	33
M	Subarachnoid hemorrhage	60	24
M	Alzheimer's disease	82	41
M	Respiratory arrest	63	43
M	Leukemia, lymphoma	69	39
M	Multisystem organ failure	34	29
M	Heart failure, sepsis	65	44
F	Pancreatic cancer	72	44
F	Subarachnoid hemorrhage	75	37
F	Breast and lung cancers	52	33
F	Myocardial infarction	80	43
F	Ovarian cancer	58	48

Mean $\pm$ SEM for age was 63 ± 4 years and for postmortem time was 38.2 ± 2.1 hours.

* Calculated as hours between time of death and baseline perfusion.

three average values and the single values from the 10- and 50-mm Hg perfusion pressures were then averaged to calculate an overall average C value for the anterior segment. Per the protocol, any C value greater than $1.0 \mu\text{L}/\text{min}/\text{mm Hg}$ was taken as evidence of a system leak and the data to be excluded from the calculations; however, this did not occur with any of the anterior segments used in these experiments. When C was observed to be greater than $1.0 \mu\text{L}/\text{min}/\text{mm Hg}$ at multiple perfusion pressures (four occurrences), the fixture screws were tightened further or globes remounted on the fixture (in that order), and experiments restarted for that eye. With these actions, the presumed leak resolved in all four eyes. In one eye that was randomized to micro-bypass implant, the calculated baseline C at perfusion pressure of 10 mm Hg was greater than 1.0. This data point was not used in the

calculation of baseline C of the eye concerned. All other individual data points for C (total of 383) were less than $1 \mu\text{L}/\text{min}/\text{mm Hg}$. Average outflow resistance (R) was calculated as for C by calculating as the inverse of each individual C value. A two-way ANOVA was used to evaluate the influence of perfusion pressures and implant type (and their interaction) on the two variables C and R. One-way ANOVA was used to evaluate differences within a group. Data are presented as mean $\pm$ SD unless otherwise noted. Values of *P* less than 0.05 were considered statistically significant.

Histology

Histological processing was done with one anterior segment containing a scaffold and one segment containing two iStents. The anterior segments were immersion fixed in a solution consisting of 8 mL glutaraldehyde, 20 mL formaldehyde, and 72 mL 0.1 M Sorensen's Phosphate Buffer. The tissue was dehydrated and embedded in Spurr (Sigma-Aldrich, St. Louis, MO) resin. Serial sections of 0.5-mm- to 1-mm-thick plastic wafers were cut using diamond saw equipment (Exakt, Norderstedt, Germany) and then ground and polished to a thickness of 60 to 80 μm . The tissue sections were stained with hematoxylin and eosin (Alizée Pathology, LLC, Thurmont, MD), and examined under a light microscope.

RESULTS

Demographic and clinical information on donors is presented in Table 1. The mean age was 63 ± 14 years, and 7 were male. The average interval between time of death and time of start of experiments was 38.2 ± 7.1 hours. Donor sex did not affect baseline outflow facilities (*P* = 0.14).

There was no significant difference in C at baseline between the anterior segments randomized to the two implants (*P* =

FIGURE 3. Calculated outflow facilities (C) for anterior segments with implanted scaffold or two micro-bypasses. Bars represent SEM. **P* < 0.05 for scaffold versus baseline 1. †*P* < 0.05 for two micro-bypasses versus baseline 2. Baseline measurements from contralateral eyes were not significantly different (NS).

TABLE 2. Summary of Outflow Facilities Before and After Device Implantation

PP, mm Hg	Scaffold				2 Micro-Bypasses			
	Pre	Post	Change	P	Pre	Post	Change	P
10	0.34 ± 0.19	0.45 ± 0.19	0.07 ± 0.12	0.053	0.29 ± 0.14	0.37 ± 0.12	0.09 ± 0.16	0.09
20	0.28 ± 0.08	0.41 ± 0.13	0.13 ± 0.13	0.003	0.30 ± 0.13	0.35 ± 0.11	0.05 ± 0.15	0.27
30	0.28 ± 0.11	0.46 ± 0.15	0.18 ± 0.14	0.001	0.31 ± 0.16	0.39 ± 0.15	0.08 ± 0.18	0.17
40	0.24 ± 0.12	0.47 ± 0.17	0.23 ± 0.14	<0.001	0.26 ± 0.10	0.38 ± 0.15	0.12 ± 0.13	0.01
50	0.25 ± 0.12	0.41 ± 0.16	0.16 ± 0.15	0.003	0.29 ± 0.09	0.35 ± 0.16	0.06 ± 0.11	0.09
Mean	0.28 ± 0.10	0.44 ± 0.13	0.16 ± 0.12	0.001	0.29 ± 0.09	0.37 ± 0.12	0.08 ± 0.12	0.046

Data are mean ± SD. Statistical significance between before and after device implantation was determined by paired *t*-tests. *n* = 12 pairs. PP, perfusion pressure.

0.36, Fig. 3). The scaffold-implanted tissue showed an increase in mean C from 0.28 ± 0.10 $\mu\text{L}/\text{min}/\text{mm Hg}$ to 0.44 ± 0.13 $\mu\text{L}/\text{min}/\text{mm Hg}$ ($P = 0.001$, Table 2). The tissues with two iStent micro-bypasses showed an increase in mean C from 0.29 ± 0.09 $\mu\text{L}/\text{min}/\text{mm Hg}$ to 0.37 ± 0.12 $\mu\text{L}/\text{min}/\text{mm Hg}$ ($P = 0.046$, Table 2). The mean percent increase from baseline in C of 73%

± 71% for the scaffold implanted eyes was greater than the increase of $34\% \pm 38\%$ ($P = 0.03$) for the two micro-bypass implanted eyes. Compared with baseline, the increase in C of 0.16 ± 0.12 $\mu\text{L}/\text{min}/\text{mm Hg}$ in the scaffold implanted eyes was greater than the increase in C of 0.08 ± 0.12 $\mu\text{L}/\text{min}/\text{mm Hg}$ ($P = 0.03$) in the two micro-bypass eyes.

FIGURE 4. Changes in outflow facility (top graph) and resistance (bottom graph) from baseline by the scaffold or two micro-bypasses. Data are represented as mean ± SEM. * $P < 0.05$ change by scaffold versus change by micro-bypasses.

FIGURE 5. Combined baseline outflow facilities of both Hydrus and iStents receiving eyes ($n = 24$) at five perfusion pressures. Outflow facility at a perfusion pressure of 40 mm Hg was less than at 10, 20, and 30 mm Hg. * $P < 0.05$ compared with outflow facility at 40 mm Hg.

The scaffold implanted tissue showed an increase in C from baseline at individual perfusion pressures of 20, 30, 40, and 50 mm Hg ($P < 0.003$; Table 2, Fig. 3). The two micro-bypass implanted tissue showed a statistically significant increase in C from baseline at the 40 mm Hg perfusion pressure only ($P < 0.01$; Table 2, Fig. 3). The increase in C from baseline for the scaffold implanted tissue was greater than the two micro-bypass implanted tissue at perfusion pressures of 30, 40, and 50 mm Hg ($P < 0.05$; Table 2, Fig. 4).

The scaffold implanted tissue showed a decrease ($P = 0.0016$) in mean R from 4.30 ± 1.91 mm Hg/ μ L/min to 2.68 ± 1.16 mm Hg/ μ L/min. The micro-bypass implanted tissue showed a decrease ($P = 0.004$) in mean R from 4.05 ± 1.42 mm Hg/ μ L/min to 3.17 ± 1.18 mm Hg/ μ L/min. The mean decrease in R from baseline for the scaffold implanted tissue (1.62 ± 1.35 μ L/min/mm Hg) was more than that of the two micro-bypass implanted tissue (0.89 ± 0.85 μ L/min/mm Hg, P

$= 0.035$). The scaffold implanted tissue showed a larger decrease in R than the two micro-bypass implanted tissue at individual perfusion pressures of 30, 40, and 50 mm Hg perfusion pressures (Fig. 4). There was a negative correlation between the change in R and baseline R in the scaffold implanted tissue ($R^2 = 0.68$, $P = 0.002$) (i.e., the higher the baseline R the larger the decrease in R). This correlation was not significant in the tissue with two micro-bypasses ($R^2 = 0.31$, $P = 0.06$).

When baseline measurements, including both Hydrus and iStents receiving eyes, were analyzed in the absence of device, C values were borderline significantly different among perfusion pressures ($P = 0.06$; one-way repeated measures ANOVA). Post hoc tests found in the undisturbed eyes that C at 40 mm Hg was less than C at 10 mm Hg perfusion pressure ($P = 0.04$, Tukey post hoc test, Fig. 5). Resistance was different among pressures ($P = 0.01$); R at 10 mm Hg was less than R at 40 mm Hg ($P < 0.05$). The decrease in C with higher perfusion pressure was not seen after the implantation of the scaffold ($P = 0.86$), or micro-bypasses ($P = 0.79$). The scaffold and the two micro-bypasses both achieved the greatest increase in C at 40 mm Hg perfusion pressure (Table 2).

On histological examination (Fig. 6), the scaffold was noted to dilate SC and stretch the TM around its window region. No breaks or discontinuity to the TM were identified in the sections examined. The micro-bypass also dilated SC, but due to the wall thickness and diameter of the rails, the lumen of SC was not distinct and dilation was not as apparent as with the scaffold in the histopathology sections. The TM was stretched around the micro-bypass and no breaks or other physical injury to the TM were noted in the sections examined. When lined up side-by-side, the extrascleral tissue with the scaffold is wider than the tissue with the micro-bypass potentially from the high volume of fluid that flowed from the collector channels into the sclera and conjunctiva (Fig. 6).

DISCUSSION

The Hydrus Microstent scaffold and two iStent micro-bypasses both significantly increased C in human anterior segments ex vivo; however, there are several qualitative and quantifiable differences between the implants that warrant discussion. The overall mean C increase in the scaffold implanted tissue was twice that of the two micro-bypass implanted tissue. In addition, the scaffold implanted tissue showed up to a 2-fold increase in C from baseline at individual perfusion pressures of 20, 30, 40, and 50 mm Hg. The current study is the first direct

FIGURE 6. (A) Histological section of the scaffold window region in situ showing significant TM stretch and SC dilation. (B) Histological section of the micro-bypass rail in situ showing placement inside SC.

comparison of the scaffold and the micro-bypass in paired eyes. Procedural differences in previous anterior segment perfusion protocols precluded interstudy comparisons.

Earlier anterior segment studies with 15-mm and 8-mm canal scaffolds also showed increases in C over baseline when compared with sham procedures.^{9,10} A recent study¹⁰ of the 8-mm scaffold showed a 54% increase in C from baseline; a change similar to the current study finding a 73% increase from baseline. Changes in resistance to outflow calculated during the current study also are comparable with those changes observed in the earlier 8-mm scaffold study.¹⁰ The time between death and start of measurement was not correlated with C in this experimental model.¹⁰

A previous study¹¹ of the micro-bypass ex vivo reported on changes in IOP after implantation using a method involving a constant controlled aqueous flow. By extrapolation from the IOP changes, increases in C in anterior segment models were noted with the micro-bypass.¹¹ In the earlier study, the final reported C after implantation of a single micro-bypass was 0.22 $\mu\text{L}/\text{min}/\text{mm Hg}$ and that calculated after implantation of two micro-bypasses was 0.20 $\mu\text{L}/\text{min}/\text{mm Hg}$. However, the earlier study differs from the current study in design and had a significantly lower baseline C at 0.12 $\mu\text{L}/\text{min}/\text{mm Hg}$, making a direct comparison with previous micro-bypass data difficult.

It is thought that drainage of aqueous humor through the TM is greatest near collector channels. The highest number of collector channels has been found in the inferior nasal quadrant of the SC.¹⁵ There is a greater pressure gradient across the inner wall of SC near the collector channels, thus the inferior nasal quadrant should be more likely to collapse at higher pressures than other quadrants, making it an ideal region for scaffold implantation.^{16,17} Implantation of micro-bypasses into multiple quadrants is thought to reduce IOP by increasing circumferential flow through the SC.¹¹ Implantation of the scaffold dilates an 8-mm portion of the SC, potentially improving access to the collector channels, a favorable characteristic supporting better efficacy when implanted in the nasal quadrant. Therefore, the devices evaluated in the current study were implanted in this region. A future study of tracer movement through eyes with SC implants should answer the question of implant's impact on drainage patterns.

When only baseline measurements were considered, C was significantly higher and outflow resistance was significantly lower at 10 mm Hg than at 40 mm Hg. This is consistent with earlier findings¹⁸ reporting SC outer wall prolapse into collector channels at high pressures, leading to increased resistance to outflow. In earlier efforts to describe the effect of IOP on the structural integrity of the SC,¹⁸ a servo-perfuser and pressure transducer were used. Resistance to outflow increased as transmural pressures and IOP increased; from which it was proposed that the increase in resistance at higher pressures was due to SC collapse.¹⁸ If this is indeed the case, as our baseline data suggest, a device continuously dilating the SC will have a greater efficacy at higher pressures. The lack of this inverse relationship between C and perfusion pressure in eyes implanted with scaffold or micro-bypass supports this hypothesis. A recent study¹⁰ also reported that decrease in resistance to outflow on scaffold implantation is linearly related to the baseline outflow resistance, providing a predictive model for the IOP-lowering potential of the canal scaffold.

Surgical insertion of either the scaffold or micro-bypasses is minimally traumatic (ab interno micro-incisional approach), appears to be safe, and may potentially require less recovery time than other surgical options, such as trabeculectomy and glaucoma drainage devices.⁶ iStent micro-bypass implantation does not result in the major postoperative complications often associated with filtering-bleb procedures.⁶ Given that the scaffold insertion is minimally invasive with negligible inflam-

mation or damage to the TM,⁶ it also potentially should reduce the postoperative recovery period as compared with conventional glaucoma surgical procedures. Future clinical trials of the scaffold may be compared with those of the micro-bypass for accurate, in vivo conclusions about the relative outflow-enhancing and IOP-lowering capacities of either device.

Several limitations to the perfusion study should be mentioned. First, this study design investigates only C changes, as there is no episcleral venous pressure in these mounted anterior segments and uveal tissue has been removed, eliminating any uveoscleral outflow. Additionally, any confounding factors, such as blood and inflammation, which may be encountered in an actual surgical implantation of the device, were not present. Thus, conclusions on the performance of the scaffold or shunt in the live subject cannot be made. Second, cell viability may be compromised before the 48-hour postmortem time limit and that may affect C. However, because this study is focused primarily on changes in C in a set of paired eyes as a result of mechanical manipulation, cell viability should not affect the results.

In summary, our study demonstrates improvement in C when the SC was implanted with two different types of implants. The scaffold was found to increase C by a greater magnitude than two micro-bypasses in an anterior segment perfusion model possibly because of greater access to collector channels.

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