Segmental Uveoscleral Outflow and its Relationship with Trabecular Outflow in Monkey Eyes

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Purpose
Segmental trabecular outflow has been observed in various species, and segmental uveoscleral outflow was recently found in mouse eyes by our research group. However, the existence of the segmental flow pattern in uveoscleral outflow and its correlation with trabecular outflow in other species remain unknown. This study investigated the flow pattern along the uveoscleral outflow pathway and its correlation with trabecular outflow in monkey eyes.

Methods
Intraocular pressure (IOP) was measured in the eyes of five adult female cynomolgus macaques. After administering anesthesia with ketamine (10 mg/kg), a fixed volume of tracer (50 µl) was injected into the anterior chamber. The tracers were allowed to diffuse and reach the outflow systems for 45 minutes, and the eyes were fixed with 4% paraformaldehyde (PFA) *in situ*. After euthanasia, the eyes were enucleated and immersion-fixed with 4% PFA for 48 hours. The eyes were dissected into 12 radial segments based on clock hours. Images of both sides of each segment were captured by a confocal microscope after nuclear counter-staining and analyzed using ImageJ. The normalized tracer intensity (tracer intensity at different locations/total intensity of each eye) was calculated and compared.

Results
The average IOP was 19.7±1.9 mmHg. Segmental uveoscleral outflow was observed where the normalized tracer intensity was the highest at 11 o'clock and lowest at 3 o'clock. Concurrently, in the trabecular outflow pathway, the normalized tracer intensity was the highest at 2 o'clock and lowest at 5 o'clock. Overall, a high-flow region was identified at the superior quadrant in the uveoscleral and the nasal quadrant in the trabecular outflow pathway. Both outflows were uncorrelated ($p>0.05$). Four different tracer patterns were found: 1) Low flow in both outflow pathways (Figure A); 2) High flow in both

outflow pathways (Figure B); 3) High flow mainly in the trabecular outflow pathway (Figure C); and 4) High flow mainly in the uveoscleral outflow pathway (Figure D).

Conclusions

Uveoscleral outflow is segmental and uncorrelated with the segmental flow patterns in the trabecular outflow pathway in monkey eyes, similar to mouse eyes. Future studies of segmental uveoscleral outflow patterns in human eyes will provide a better understanding of the optimal location for the placement of drainage devices and drug delivery systems targeting this pathway.

Layman Abstract (optional): Provide a 50-200 word description of your work that non-scientists can understand. Describe the big picture and the implications of your findings, not the study itself and the associated details.

Aqueous humor (AH) is the liquid in the front part of the eyes. It provides nutrients and removes wastes inside our eyes. When the drainage (outflow) pathway of AH is damaged, the outflow resistance increases and the eye pressure rises, which is one of the risk factors for glaucoma. While enhancing drainage can lower IOP and slow the progression of glaucoma, understanding the drainage pattern around the eyes is crucial. In our previous research, we found that AH leaves the eyes non-uniformly via two routes: trabecular and uveoscleral outflow pathways in mouse eyes. However, the outflow patterns, especially in uveoscleral outflow pathway in other species, remain unknown. We repeated the experiment in monkey eyes. After injecting a fixed amount of dye into the eyes, the dye distribution around the eyes was measured. Similarly, we found that both outflows were non-uniform and uncorrelated. The improved knowledge of the outflow patterns and correlation is essential to identify the best location in the uveal outflow pathway for injecting medication in different eye diseases and implanting drainage devices to lower eye pressure in glaucoma patients.