Optimizing Descemet Membrane Endothelial Keratoplasty Using Intraoperative Optical Coherence Tomography

Philipp Steven, MD; Carolin Le Blanc; Kai Velten, PhD; Eva Lankenau, PhD; Marc Krug, PhD; Stefan Oelckers, PhD; Ludwig M. Heindl, MD; Uta Gehlsen, PhD; Gereon Hüttmann, PhD; Claus Cursiefen, MD

IMPORTANCE Descemet membrane endothelial keratoplasty (DMEK) is a challenging procedure for the surgeon, particularly because of deficient visibility of the delicate tissue due to the natural en face view through the operating microscope. A cross-sectional view would greatly enhance intraoperative overview and enable the surgeon to better control the procedure.

OBJECTIVE To retrospectively analyze the use of intraoperative optical coherence tomography (iOCT) for improving the safety of DMEK.

DESIGN Intraoperative OCT during DMEK was performed in 26 eyes of 26 patients. We retrospectively analyzed imaging and video data.

SETTING Department of Ophthalmology, University of Cologne.

PARTICIPANTS Seven men and 19 women aged 39 to 93 years with corneal endothelial dysfunction undergoing DMEK.

EXPOSURE Descemet membrane endothelial keratoplasty.

MAIN OUTCOMES AND MEASURES Visibility of surgical steps, overall duration of DMEK, overall time for complete intraoperative air filling of the anterior chamber, and correlation between donor age and Descemet rolling behavior.

RESULTS Intraoperative OCT enables visualization of all steps of the DMEK procedure. Overall mean (SD) duration of the DMEK procedure was 25.7 (6.9) minutes when using iOCT. Overall mean (SD) complete intraoperative anterior chamber air-filling time was 236 (108) seconds in contrast to 60 to 90 minutes for standard air-filling time. Descemet membrane rolling behavior showed significant inverse correlation between donor age (range, 39-93 years) and the extent of rolling ($R^2 = 0.5$ [$P = .006$]).

CONCLUSIONS AND RELEVANCE Intraoperative OCT enhances the visibility of graft orientation and unfolding, thereby improving safety of the DMEK procedure. Overall, iOCT is a helpful device that may support surgeons in all steps of DMEK procedures.

Author Affiliations: Department of Ophthalmology, University of Cologne, Cologne, Germany (Steven, Le Blanc, Heindl, Gehlsen, Cursiefen); Process Engineering Department, Hochschule Geisenheim University, Geisenheim, Germany (Velten); OptoMedical Technologies GmbH, Luebeck, Germany (Lankenau, Krug); Moeller-Wedel GmbH, Wedel, Germany (Oelckers); Institute of Biomedical Optics, University of Luebeck, Luebeck, Germany (Hüttmann).

Corresponding Author: Philipp Steven, MD, Department of Ophthalmology, University of Cologne, Kerpener Strasse 62, 50937 Cologne, Germany (philipp.steven@uk-koeln.de).
Descemet membrane endothelial keratoplasty (DMEK) has recently been introduced as an innovative surgical technique to selectively replace diseased endothelium in patients with Fuchs endothelial dystrophy and pseudophakic bullous endothelial keratopathy. This technique has superseded perforating keratoplasty, in many cases sparing unaffected stromal tissue. Advantages of this tissue-selective approach include better visual outcome owing to maintenance of the corneal structural configuration, faster visual recovery after initial surgery, and fewer intraoperative complications, in particular, expulsive hemorrhage. In terms of graft rejection, DMEK demonstrates a 15-times lower rejection rate, which is thought to result from the limited amount of tissue and therefore potential antigen that is transplanted. Despite all the advantages described, the overall procedure is challenging for the surgeon. Crucial yet difficult steps include preparation of the intact donor lamella, transfer of the graft into the anterior chamber (AC), unfolding and orientation of the graft, and final successful attachment after air filling. One important limiting factor in these difficulties is a deficient visibility of the delicate tissue due to the natural en face view through the operating microscope. This view hinders an estimation of the depth ratio, orientation of the transplanted graft, and drainage of the interface fluid. In this context, a cross-sectional view would greatly enhance the intraoperative overview and enable the surgeon to better control the procedure.

Recently, optical coherence tomography (OCT) has been modified to be used in an intraoperative setting. The following 2 main approaches are possible: (1) using handheld devices and (2) integrating the OCT into the operating microscope. The latter approach has several advantages, such as online visualization of all surgical steps without the necessity of interrupting the procedure and alignment of the OCT image to any given zoom and focus step of the microscope (Figure 1). To our knowledge, this study is the first to evaluate intraoperative OCT (iOCT) technology to visualize DMEK procedures, in particular, the graft during the preparation process, within the AC and during orientation and attachment to the posterior cornea.

Methods

Devices
For iOCT, we used a microscope-mounted, commercially available spectral-domain OCT camera (iOCT; OptoMedical Technologies GmbH) with an 840-nm central wavelength that performed 10,000 A scans per second. The iOCT device was connected to the camera port of an OCT-compatible microscope (Hi-R900 ANIR; Moeller-Wedel) (Figure 1). The OCT image was displayed on a separate touch screen in front of the surgeon’s visual field to enable easy exchange between the microscopic and OCT images. Intraoperative OCT imaging included recording of high-resolution videos and images of approximately 10-μm axial resolution. Image size was 4.2 mm axially in air, 3.2 mm axially in water, and from 5 to 29 mm in the lateral direction, depending on the microscopic zoom factor used. We analyzed retrospectively all video and imaging data obtained during surgery.

Patients
We used iOCT in 26 consecutive patients (7 men and 19 women) aged 39 to 93 years with corneal endothelial dysfunction undergoing DMEK. Fifteen patients with pseudophakic eyes and 9 patients with phakic eyes underwent DMEK in combination with conventional phacoemulsification and posterior chamber lens implantation (triple DMEK). In 1 case, DMEK was combined with pars plana vitrectomy and membrane peeling for treatment of impending macular hole. Retrospective evaluation variables included iOCT visualization of Descemet membrane (DM) rolling behavior immediately after preparation, DM rolling inside the eye, and attachment to the posterior stroma after insertion and air insufflation.

Donor Tissue
Eight grafts were organ cultured in modified minimal essential medium (MEM) (Eagle MEM; Biochrom) at 30°C. All grafts were deswelled in the modified MEM containing 5% dextran at 30°C for 24 hours. Three grafts were organ cultured in MEM (CorneaMax R; Eurobio Laboratoires) at 31°C. Grafts were deswelled in MEM containing 5% to 6% dextran (CorneaJet R; Eurobio Laboratoires) at 31°C. Fifteen grafts were organ cultured in MEM at 30°C and deswelled in MEM containing 5% dextran at 30°C. No information was obtainable on the exact postmortem time from the provider eye bank; however, owing to legal requirements, all donor eyes were collected within 24 hours post mortem. Donor ages ranged from 26 to 88 years.
(7 men and 19 women), and no previous eye diseases were reported. Donor tissue was accepted for DMEK when endothelial cell counts were greater than 2200 cells/mm².

Procedure
Descemet membrane endothelial keratoplasty was performed as described previously.\textsuperscript{13} Briefly, the donor tissue was placed endothelial side up into a Hanna punch block obtained using a trephine (Moria SA). After staining with trypan blue solution (VisionBlue; Dutch Ophthalmic Research Center International), an 8-mm-diameter DM graft was stripped and transferred into culture medium for definite transplantation. For grafting to the recipient, the central 9 mm of the recipient’s DM was removed, in some cases preceded by conventional phacoemulsification and posterior chamber lens implantation (ie, the triple DMEK procedure). The donor DM was injected into the AC of the recipient using a conventional lens injector cartridge (Acritec GmbH). The graft was then unfolded and oriented using air-bubble injection and blunt strikes on the corneal surface.\textsuperscript{14,15}

Complete air filling of the AC was performed by pressing the DM graft toward the recipient’s corneal stroma. All patients received a peripheral iridectomy to prevent pupillary block. At the end of the procedure, two-thirds to four-fifths of the AC remained filled with air. Patients were instructed to maintain a postoperative supine position for 24 hours, and postoperative medication was applied as described previously.\textsuperscript{6,14}

Modeling and Statistics
Estimation of the mean curvature of the DM was based on the tomographic images as follows. First, a data set of coordinate points describing the membrane shape was derived using image-processing software.\textsuperscript{16} This data set was used to compute a parametric cubic smoothing spline curve \((x(t), y(t))\) following the procedures described by Green and Silverman\textsuperscript{17} and Venables and Ripley.\textsuperscript{18} The curvature \(\kappa(t) [1/mm]\) of the spline curve was then obtained using the following previously described equation\textsuperscript{19}:

\[
\kappa(t) = \frac{|x''(t) \times y''(t) - y''(t) \times x''(t)|}{(x'(t)^2 + y'(t)^2)^{1.5}}
\]

From this, the mean curvature \(c [1/mm]\) of the membrane was derived using the arc length parameterization factor \(s [mm]\) and the membrane length \(L [mm]\) as follows:

\[
c = \frac{1}{L} \int_{0}^{L} \kappa(s) ds
\]

All computations, including the regression analysis, were performed using R software.\textsuperscript{20}

Results

Monitoring of All Surgical Steps of DMEK
During donor tissue preparation, high-resolution imaging of the donor cornea enabled reliable identification of DM stripping (Figure 2A). Graft rolling behavior could be monitored without the necessity of restaining the graft with trypan blue (Figure 2B). Cross-sectional imaging further allowed reliable identification of the endothelial side of the graft by exact real-time observation of inward rolling of graft edges. During DMEK, DM stripping from the recipient cornea was depicted, including the stripped membrane and remnants at the posterior part of the cornea (Figure 2C). The DMEK grafts were imaged within the AC of the recipient eyes (Figure 2D). Inward rolling behavior of DM allowed for precise and correct localization of the endothelial side, even in opaque corneas. In addition, DM apposition to the stroma could be reliably depicted during air filling (Figure 2E). This visualization allows for detection of interface fluid, which could be drained. Control of graft attachment at the end of surgery was enabled by cross-sectional view of the entire posterior cornea (Figure 2F). These steps could reliably be identified in 26 of 26 studied eyes and the donor tissues.

Correlation of Rolling Behavior of Stripped DM With Donor Age
Rolling behavior of stripped DM was monitored in all donor tissues (Figure 3). A correlation of rolling behavior and donor age could be conducted in 12 of 26 cases because the shape of the DM could be obtained from the raw data (Figure 4). For the other 14 cases, rolling behavior could be monitored within video recordings only, without data on actual geometric shape. Tissue from donors younger than 60 years demonstrated the strongest inward rolling activity and multimellar shape (Figure 3A). Donor tissues from individuals 60 years and older featured less rolling activity and an open-spiral shape (Figure 3B). No sex dependency in rolling behavior was observed.

The dependence of the mean curvature \(c\) of the DM on age can be seen in Figure 4. The regression analysis of these data showed that the mean curvature \(c\) depends significantly and inversely on age \(\left( R^2 = 0.5 \ P = .0061 \right)\). This dependence allows choice of the optimal donor tissue for each patient and surgeon.

Visualization of Precise Membrane Unfolding and Correct Orientation
After injection of the graft into the AC, unfolding and correct orientation of DM rolls could be visualized in all patients (Figure 5). Exact imaging of the entire graft was enabled even when recipient corneas exhibited much reduced transparency. Intraoperative OCT further allowed us to identify the endothelial side of the graft by reliably depicting rolling tendency in concordance with the rolling behavior after initial preparation.

Evaluation of Interface Fluid Drainage
Unfolding and attachment of the DM to recipient cornea was visualized and controlled by iOCT (Figure 6). Real-time OCT imaging allowed reliable detection of not yet attached areas during air-filling time. Overall, iOCT enabled us to control the entire attachment of the graft and allowed for more exact determination of time necessary for complete AC intraoperative air fill.
Complete AC Air-Filling Time
Air-filling time during DMEK was measured in 21 of 26 patients (81%). In 5 patients, only screenshots were obtained with no real-time videos recorded. Air-filling time measurement was started when the entire AC was filled with air for attaching the DM graft and finished at the end of surgery, when the amount of air was reduced to two-thirds to four-fifths of the AC volume. The overall mean (SD) air-filling time was 236 (108) [range, 86-480] seconds.

Overall Duration of DMEK Using iOCT
We compared the overall duration of DMEK in the triple DMEK and DMEK-only procedures. The mean (SD) duration of the triple DMEK procedures was 36.0 (7.2) [range, 25-46] minutes. One case of triple DMEK was excluded from the calculation because of pars plana vitrectomy and membrane peeling due to an impending macular hole. In the DMEK-only procedures, the mean (SD) duration was 25.7 (6.9) [range, 17-44] minutes. Donor graft preparation time was not included in the calculation.

Discussion
Descemet membrane endothelial keratoplasty has been demonstrated to reliably replace diseased corneal endothelium, thereby maintaining corneal topography and allowing fast visual recovery. In addition, DMEK leads to better visual acuity and less immune reaction compared with Descemet stripping automated endothelial keratoplasty.\textsuperscript{3,9} Surgical challenges, partly owing to limitations in the visibility of the delicate graft tissue and lack of standardization, limit wider surgical deployment of this technique.\textsuperscript{14,15}

By using iOCT, some of these limitations can be reduced, as demonstrated in our case series. Because the OCT camera

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Figure 2. Intraoperative Optical Coherence Tomography (OCT) Enables Real-Time Visualization of All DMEK Steps

Steps are described in order of performance. A, Graft preparation. DM indicates Descemet membrane; EP, epithelium; ST, stroma. B, Graft rolling behavior. C, DM stripping (arrows). D, Graft localization within the anterior chamber (arrows demonstrate inward rolling behavior of DM edges, with correct graft positioning). E, Graft localization and shape after initial air filling (arrows indicate graft). Virtual inversion of the cornea was caused by an OCT imaging artifact, in which the imaged tissue depth partly exceeded the range in which OCT can uniquely determine the axial position of the scattering structures. Frequency-domain OCT then folds all tissue structures above the upper image margin downwards. F, Control of graft attachment during air-filling time (arrowheads indicate complete attachment; arrow, interface fluid).
is attached to the operating microscope and also embedded into the microscope’s optical setup, real-time cross-sectional imaging at high resolutions is enabled. Intraoperative OCT aids the surgeon to identify remnants of DM during the stripping process (Figure 2C), thus avoiding membrane rests remaining at the posterior surface of the recipient’s cornea. Because the rolling behavior can be followed, correct unfolding of the graft is enabled by online visualization, avoiding accidental attachment of the endothelial side. As anecdotally reported in personal communications with other surgeons, rolling behavior of the graft inversely and significantly correlates with donor age. Dependence of DM shapes on age was analyzed with a mathematical model that was derived from 2-dimensional tomographic cross-sections. Because the real DM shapes are 3-dimensional, better results and less variability of the data in Figure 4 can be expected if 3-dimensional mathematical models are used, such as 3-dimensional finite-element models describing the structural mechanical behavior of the DM.21 These models, however, would have to be based on more detailed 3-dimensional tomographic data and on data describing

**Figure 4. Mean Curvature \( c \) Correlation With Age**

Increasing age is inversely correlated with decreasing curvature of donor graft roll (regression line, \( c = -0.0323 \times \text{age} + 3.28; R^2 = 0.5 \)).

Donor age less than 60 years is correlated with strong rolling activity (multilamellar shape), whereas donor age 60 years and greater is correlated with less rolling activity (open-spiral shape).
In summary, young donor grafts demonstrate the strongest inward rolling behavior, which is reduced with increasing age. However, we did not observe any sex dependence. We hypothesize that differences in rolling behavior result from an age-dependent decrease of elastin levels and from changes in collagen composition or an increase in nonenzymatic glycosylation, thus increasing the rigidity of the DM. Because membranes featuring an open-spiral shape are faster to unfold, a preferential use of tissues from donors 60 years and older is desirable if they are available, especially for surgeons beginning to adopt this technique.

Visualization of the graft was performed under reduced transparency of the recipient cornea, thereby allowing for better orientation of the graft (even in very opaque host corneas), limiting dislocation and misalignment under these circumstances. Air filling of the AC is a crucial step to initiate graft attachment of the entire membrane. Although partial or circumscribed graft nonattachments due to interface fluid are normally impossible to detect by conventional use of the surgical microscope, only a cross-sectional view at high resolutions enables us to image remaining interface fluid. Air refilling, smoothening of the surface, or extension of the air-filling time can be chosen to secure a best possible surgical result at the end of the procedure. In this context, air-refilling procedures sometimes result in partial detachment owing to fluid circulation into the interface. Intraoperative OCT enables reliable detection of such artificial detachment and thereby aids in avoidance of intraoperative complications. In addition, when iOCT was used, the mean (SD) duration of procedures was 25.7 (6.9) minutes in DMEK-only procedures and 36.0 (7.2) minutes in triple DMEK procedures. This measurement included a mean (SD) overall air-filling time of 236 (108) seconds until no interface fluid could be detected in each quadrant and the procedure was safely terminated. Therefore, using iOCT increases the effectiveness of DMEK by reducing in particular air-filling time; this finding differs from previously published intraoperative air-filling times of as long as 60 minutes. Also, air-reinjection rates were 68%, which is in the range of

Figure 5. Real-Time Visualization of Descemet Membrane (DM) Grafts Within Anterior Chamber

A-F, Real-time visualization of DM grafts within anterior chamber in 6 representative cases. Intraoperative optical coherence tomography enables the surgeon to control graft location and unfolding even when recipient corneas exhibit reduced transparency. Arrows indicate the endothelial side of the DM.
Optimizing DMEK by Using iOCT

During air-filling time, localized graft nonattachment (arrows) is monitored and reduced by drainage maneuvers until intraoperative optical coherence tomography ensures attachment of the entire graft at the end of surgery. This monitoring helps to reduce time of complete anterior chamber air fill.

This challenging technique and especially in larger corneal training centers, iOCT might represent a helpful procedure to steepen the individual learning curve. In particular, visualization of crucial steps such as graft rolling, unfolding, and orientation and monitoring of graft attachment are better visualized, leading to better surgical performance and shortening of operation time by reducing complete intraoperative air-filling time.

Previously published rates. Overall, iOCT increases safety through decreased visibility and correct positioning of DM grafts, without decreasing surgical performance in terms of air-reinjection procedures.

In summary, iOCT is a helpful procedure that supports the surgeon in all steps of DMEK procedures. For surgeons new to this challenging technique and especially in larger corneal training centers, iOCT might represent a helpful procedure to steepen the individual learning curve. In particular, visualization of crucial steps such as graft rolling, unfolding, and orientation and monitoring of graft attachment are better visualized, leading to better surgical performance and shortening of operation time by reducing complete intraoperative air-filling time.

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