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Title: Evaluating the forces involved in bubble management in DMEK surgery – a mathematical and computational model with clinical implications

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Running Head: Modelling forces involved in bubble management in DMEK

Synopsis- 30 words

We have quantitatively and qualitatively modelled forces involved in DMEK adherence and have shown bubble release can abruptly reduce DMEK tissue support via the negative effect on surface tension forces.

Abstract:

Purpose: To model post-operative forces involved in DMEK tissue adherence and bubble management, including the impact of surface tension on graft support, with a view towards clinical applications.

Setting: Tennent Institute of Ophthalmology, Glasgow, and James Watt School of Engineering, University of Glasgow, Glasgow, UK

Design: Mathematical modelling and computer simulation

Methods: Theoretical modelling of biphasic flow and interaction of gas, liquid and tissue within the anterior chamber for static horizontal Scenario A (adherent DMEK with mobile bubble) and dynamic vertical Scenario B (release of bubble due to pupil block following DMEK).

Results: The model assumed incompressibility for both fluids within realistically achievable pressure ranges. Cahn-Hilliard Navier-Stokes equations were discretised through the application of the Finite Element Method.

Mathematical modelling and computer simulation showed bubble size, corneal curvature and force intensity influences surface tension support for DMEK tissue in Scenario A. Scenario B demonstrated complex, uneven distribution of surface pressure on the DMEK graft during uncontrolled bubble release. Uneven pressure concentration can cause local tissue warping, with air/fluid displacement via capillary waves generated on the fluid-air interface adversely impacting DMEK support.

Discussion: We have quantitatively and qualitatively modelled the forces involved in DMEK adherence in normal circumstances. We have shown releasing air/gas can abruptly reduce DMEK tissue support via generation of large pressure gradients at the liquid/bubble/graft interfaces, creating negative local forces. Surgeons should consider these principles to reduce DMEK graft dislocation rates via optimised bubble size to graft size, longer acting bubble support and avoiding rapid decompression where possible.

Word Count: 250 (max 250)

Evaluating the forces involved in bubble management in DMEK surgery – a mathematical and computational model with clinical implications

Introduction

Ophthalmic corneal transplant surgery has been revolutionised and refined following the development of specific lamellar techniques. Endothelial dysfunction is now commonly addressed by endothelial transplantation in the form of Descemet Membrane Endothelial Keratoplasty (DMEK).[1] DMEK is less invasive, with faster recovery and greater visual improvements, in part due to the absence of full-thickness incisions or corneal sutures as associated with Penetrating Keratoplasty (PK).[2,3] In order for DMEK to be effective, this fine 15μm thick donor tissue needs to be adherent to the posterior corneal stroma, which has been bared following surgical removal of the patient's diseased Descemet's membrane/endothelium. Anatomical apposition is commonly achieved through the use of air or gas, left in the anterior chamber at the end of surgery to act as a scaffold support for the DMEK graft. This air/gas will be resorbed over the following days to weeks.[4,5]

It is unclear which intra-operative and post-operative factors directly contribute to graft adherence and subsequent success. Refinements in intra-operative techniques have suggested matching donor size to recipient, removal of residual stromal tags, full air fill at time of surgery for 15 minutes before reduction in bubble size, and use of longer acting gases amongst others.[6,7] Post operatively, there is debate regarding management of the air/gas bubble, and both the requirement for and duration of posturing.[8] Some reports suggest the presence of an adequate inferior iridectomy greatly reduces the risk of acute pressure rises after nearly full anterior chamber air tamponade in DMEK, but this intervention is not universally performed. [9,10]

Cases of partial DMEK detachment have been evaluated for indications for re-bubbling, with >33% detachment or posterior stromal folds being implicated on OCT studies.[11]

It has been our clinical observation that releasing air/gas intra- or post- operatively can abruptly shallow the anterior chamber depth through volume loss, and so could have a rebound effect on the cornea. Air release performed at the slit-lamp has been reported previously to be unpredictable and excessive on occasion, potentially leading to sub-optimal post-operative air fill, exacerbating anterior chamber shallowing, which may increase the likelihood of graft detachment. [12,13]

We wondered if these post-operative acute surgical decompressive interventions were unintentionally creating negative forces contributing to subsequent DMEK dislocation. In light of this, we decided to model the forces involved in DMEK surgery and air/gas bubble management with a view towards clinical applications.

Methods

We chose a static and then a dynamic scenario to model the forces involved in DMEK surgery and air/gas bubble management. Scenario A was the static initial immediate post-operative period following uneventful DMEK surgery, where the graft is well positioned centrally, the patient is posturing horizontally flat on their back, and the supporting air/gas bubble is mobile and resolving over time. This stable scenario is consistent with commonly recommended guidelines in the immediate post-operative period to maximise bubble support on the DMEK graft.[9] This 'horizontal' scenario also enables us to describe the total static effect of buoyancy and surface tension on the DMEK graft.

Scenario B was the dynamic management of an acute post-operative complication, where air/gas overfill in the immediate recovery period had resulted in pupil block glaucoma, necessitating a release of air/gas from the anterior chamber via a needle paracentesis. This dynamic scenario is often addressed with the patient sitting up at a slit lamp in a vertical position, and can result in uncontrolled, unpredictable and excessive release of the bubble.[12,13]

To achieve this, our reduced model operated on the assumption of incompressibility for both fluid and air/gas within realistically achievable intra-ocular pressure ranges.

Other assumptions within our model included DMEK graft tissue as a thin plate incompressible structure, corneal thickness to be uniform, and the iris tissue as a rigid posterior structure. Despite gas compressibility being significantly greater than that of liquid, the effect of inertia can be considered secondary in our reduced modelling due to the wide range of clinical pressures and given that the density of gas is two orders smaller than that of liquid.

Cahn-Hilliard Navier-Stokes equations were used to model the biphasic flow and interaction of gas and liquid within the eye through the application of the Finite Element Method. Both of these chosen scenarios simplified the equations of the discretised system down to two dimensions.[14] We employed MoFEM, an open-source Finite Element software that is accessible in the public domain.[15]

Corneal parameters as related to DMEK were chosen from published average Caucasian measurements.[16,17] [See Figure 1] As Scenario A was a static analysis, it was idealised as axisymmetric to enable quantitative analysis. A surface tension of 73 g/s^2 and a wetting angle of 16 degrees was considered, with a primary emphasis on the net lift generated through surface tension.[18]

Scenario B was a dynamic analysis, using the same parameters as Scenario A, and was idealised as a planar problem, yielding qualitative results. Since the model did not account for tissue deformability, we defined a fluid flow rate that achieves the displacement of the air/gas within the anterior chamber as one second (via a needle paracentesis decompression effect).

Results

Cahn-Hilliard Navier-Stokes equations were discretised through the application of the Finite Element Method. Mathematical modelling and computer simulation were used to demonstrate forces and interactions between DMEK tissue, internal corneal curvature and air/gas and fluid interactions.

Scenario A: Static Analysis of the Immediate Post-Operative Period

In Scenario A the corneal graft is orientated horizontally as the patient is posturing on their back. Mathematical modelling and computer simulation showed that bubble size and force intensity influenced surface tension support for DMEK tissue.

Figure 2 shows the surface pressure on the graft due to air/gas bubble. These forces were integrated to give the total net lift provided to the DMEK tissue by the air bubble in the immediate post-operative period. As the size of the air/gas bubble is seen clinically to reduce over time, our model demonstrated different supporting lift forces on the DMEK graft. For example, an air/gas bubble which covered the entire 8mm DMEK graft (163 mm^3) resulted in a 14 grams positive net lift effect due to surface tension. However, once the air/gas bubble was less than 120 mm^3 in size (approx. 70%), the model suggested a negative net lift force due to surface tension. This support continued to reduce with lower bubble volumes. [See Figure 2 – where the green lines demonstrate the bubble, the blue arrows show lifting forces due to surface tension alone on the DMEK tissue in yellow]

Scenario B: Dynamic Analysis of Acute Post-Operative Release of Pupil Block

In Scenario B the corneal graft is orientated vertically as the patient is positioned on the slit lamp for intervention. Mathematical modelling and computer simulation showed that as the bubble size was reduced abruptly due to the release of air/gas, the resultant loss of force intensity due to the changing curvature of the air-fluid interface significantly reduced surface tension support for the DMEK tissue. For example, evaluation of forces acting on the DMEK tissue, cornea and within the residual anterior chamber fluid due to the uncontrolled release of the air bubble at “snapshot” moments in time in Figure 3 demonstrates localised traction forces (black arrows on bottom left figure), which could potentially lead to local displacement or wrinkling of the graft.   Scenario B also demonstrated the complex, uneven distribution of surface pressure on the DMEK graft during uncontrolled bubble release. This triggered local tissue warping and air/fluid displacement was observed via capillary waves generated on the fluid-air interface. [See supplementary online video animation, with black arrows representing tractional forces exerted on the DMEK tissue and corneal surface following bubble release in the horizontal and vertical directions, as illustrated by their size and direction]

Figure 3 shows the changing size of the air bubble over time as illustrated at 4 individual time points (snapshots) and a graph of how the resultant horizontal and vertical forces change over time within 1 second. The reducing size and pressure effect of the bubble is significantly influenced by the changing curvature of the air-liquid interface, which in turn leads to varying forces on the DMEK graft. It can be seen locally that these forces can have a negative action on the DMEK tissue within 0.3 seconds.

Discussion

Mathematical and computational modelling can serve as powerful tools for enhancing our understanding of intraocular surgery such as cataract surgery and endothelial transplant surgery, specifically the biphasic fluid interactions and the structural behaviour of the iris and corneal tissues.[19,20]

Previous publications in this field have sought to establish optimum conditions for graft coverage by exploring a combination of likely factors, such as bubble characteristics, patient positioning, anterior chamber morphometrics and lens status. Two recent studies have identified that patient positioning and volume of gas fill were more critical for graft coverage in pseudophakic eyes, due to the increased anterior chamber depth in comparison to phakic eyes. Between 85%-92% graft contact was achieved with a 70% gas fill in the phakic eyes, but this was more variable in pseudophakic eyes with a range of 63%-94%.[21,22] However, no significant distinction was found comparing gas (SF6) versus air fill in the phakic eye model. The practice of performing pre-operative inferior peripheral iridotomies (PIs) and 80% bubble sizes to reduce the risk of bubble-induced pupil block glaucoma has also been encouraged in the literature.[4,9] However, patent PIs can still become occluded, requiring release of the bubble.[10] Furthermore, several deep learning algorithms utilising anterior segment OCT data have been developed to examine a variety of pivotal questions, such as predicting risk of graft detachment, requirement for re-bubbling, and precise localisation of detachments.[23–25] One model was able to predict graft detachment with 92% sensitivity, in comparison to a senior ophthalmologist (31%) on the basis of pre-operative OCT data, albeit the ophthalmologist's specificity was superior (64% v 45%).[23] The integration and implementation of these systems have the potential to offer valuable data-driven insights relevant to clinical practice, informing decision-making and aiding in the personalised management of endothelial grafts.

Our research represents our initial effort to develop a comprehensive DMEK model that incorporates the factors of biphasic fluid interactions with air/gas bubbles and the structural behaviour of the corneal DMEK tissue and recipient's posterior cornea. This static model was then tested via a dynamic scenario involving bubble release and the changing forces on the DMEK tissue.

The results for Scenario 1 highlight the complexity of competing forces within DMEK surgery, and clarify the link between three factors: the size of the bubble, the curvature of the tissue surface, and the intensity of forces applied to the graft surface. We have shown the crucial role of surface tension, as it creates a difference in pressure gradient that provides structural support for the DMEK tissue to be in contact with the recipient's posterior cornea. The effect of air/gas buoyancy within the fluid in the anterior chamber, which results from the difference in density of these two, is a secondary effect. The results also indicate that the optimal size of the bubble should correspond to the size of the DMEK graft it is intended to support. It was of interest to note that larger air bubbles lose their spherical shape due to buoyancy or the force of gravity within the boundary restrictions of the iris, lens and cornea of the anterior chamber. Previous clinical publications have recommended a large but mobile bubble to avoid pupil block, and use of longer duration gases to prolong the support for the DMEK graft tissue.[4,10,26] Our modelling confirms these clinical recommendations.

The results for Scenario 2 demonstrate a complex, uneven distribution of surface pressure on the DMEK graft on release of the bubble. This pressure appears to traverse the graft surface from bottom to top, possibly triggering local warping, displacement, or even graft separation, impacting DMEK graft stability. Furthermore, the results suggest that reducing the negative interaction effects associated with the rapid release of air could be beneficial, such as through a controlled air-fluid exchange. This quick release can generate capillary waves on the water-air interface, impacting graft stability. However, it is important to note that the component of force associated with surface tension remains, regardless of inertia effects.

Clinical relevance

Understanding the forces involved in DMEK surgery should assist the surgeon in optimising graft positioning and bubble support with a view to successful tissue adherence.
Scenario 1 demonstrated the importance of sufficient bubble support relative to DMEK tissue size, which reduced as the bubble reduced in volume. It follows that using long duration gases will provide a longer period of support for the tissue, increasing the potential for successful adherence.

Scenario 2 demonstrated the impact of reduced surface tension and negative decompressive forces on reducing bubble support for the DMEK tissue. Posterior stromal folds and >33% detachment have been linked with re-bubbling in cases of partial DMEK detachment due to negative outcomes, and this would be consistent with the findings of our model and logically related to some of our assumptions regarding tissue curvature and subsequent DMEK graft support.[11,27]

Both scenarios would suggest maintaining anterior chamber stability is crucial, with leaving an initial residual mobile bubble size to cover the entire graft, and avoidance of abrupt decompression, if possible, via a controlled bubble-fluid exchange at the end of surgery. Our project has provided novel evidence via mathematical modelling and computer simulation for these clinical recommendations.

Limitations of our model and future work

Aside from the previously mentioned assumptions, our model does not incorporate corneal elasticity, nor does it delve into the relationship between deformation and fluid pressure. Reducing the DMEK to a thin plate allowed us to consider the impact of tissue buckling on movement, localised separation and subsequent detachment. We did not consider how elastic curling properties can influence the subsequent detachment. However, these positional changes can only occur when the surface tension and scaffold support of the bubble have been reduced over time. Our primary focus was on the interplay between the fluid and air/gas phases of the DMEK operation in the immediate post-operative period, with a particular emphasis on understanding the impact of surface tension on graft support. We did not account for any reduction in anterior chamber volume due to release of the bubble, which could further contribute to graft instability. Similarly, as we wanted to evaluate forces acting on the posterior cornea in a closed system (the anterior chamber), we decided to keep the volume constant through a rigid posterior structure. This also allowed us to avoid modelling any differences between a phakic or pseudophakic eye. This should not influence the model when the bubble is mobile, but it could have an even greater effect on uncontrolled volume loss during decompression, and should be considered in a more advanced analysis of fluid elastic structure interaction.

Future studies could involve comparing different needle placement locations and the resultant impact on internal forces generated through the decompressive effect. While our current model allows us to estimate the initial effect that leads to detachment, it does not yet predict what occurs after the detachment takes place. For definitive answers to this complex dynamic response, a comprehensive 3D model that includes elastic deformability and/or tissue recoil of the cornea and the graft itself would be necessary to account for the full complexity of the surgical scenario. Patient-specific models are a realistic but longer-term ambition.

Conclusion

We have quantitatively and qualitatively modelled the forces involved in DMEK adherence in normal circumstances. We have shown releasing air/gas intra- or post-operatively can abruptly reduce DMEK tissue support via the negative effect on surface tension forces. Surgeons should consider these principles to reduce DMEK graft dislocation rates via ensuring an optimised bubble size to graft size, adopting a longer acting bubble for greater support and by avoiding rapid decompression of the bubble from the anterior chamber (and subsequent shallowing) where possible.

Value Statement

What was known before:

- Descemet Membrane Endothelial Keratoplasty (DMEK) enables sutureless lamellar corneal transplantation, yet is associated with early graft dislocation.
- Debate regarding air/gas bubble management and posturing exists, related to influencing successful DMEK tissue adhesion.
- There are currently no published models for evaluating effect of bubble decompression on DMEK adherence.

What this work adds:

- We have quantitatively and qualitatively modelled the forces involved in DMEK adherence in normal circumstances and via mathematical modelling and computer simulation showed that bubble size, corneal curvature and force intensity influences surface tension support for DMEK tissue.
- We have shown releasing the air/gas bubble can abruptly reduce DMEK tissue support via the negative effect on surface tension forces.
- Surgeons should consider these principles to reduce DMEK graft dislocation rates via optimised bubble size to graft size, longer acting bubble support and avoiding rapid decompression where possible.

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Legend:

Table 1 – Table of parameters used for modelling DMEK bubble scenarios. AC = anterior chamber.

Parameter	Value
Phakic AC Depth	3mm
Pseudophakic AC Depth	3.5mm
Phakic AC Volume	133mm^3
Pseudophakic AC Volume	186mm^3
AC Width	12.5mm
DMEK Diameter	8mm
DMEK Thickness	15µm

Figure 1 – Schematic diagram of parameters used for modelling DMEK bubble scenarios.

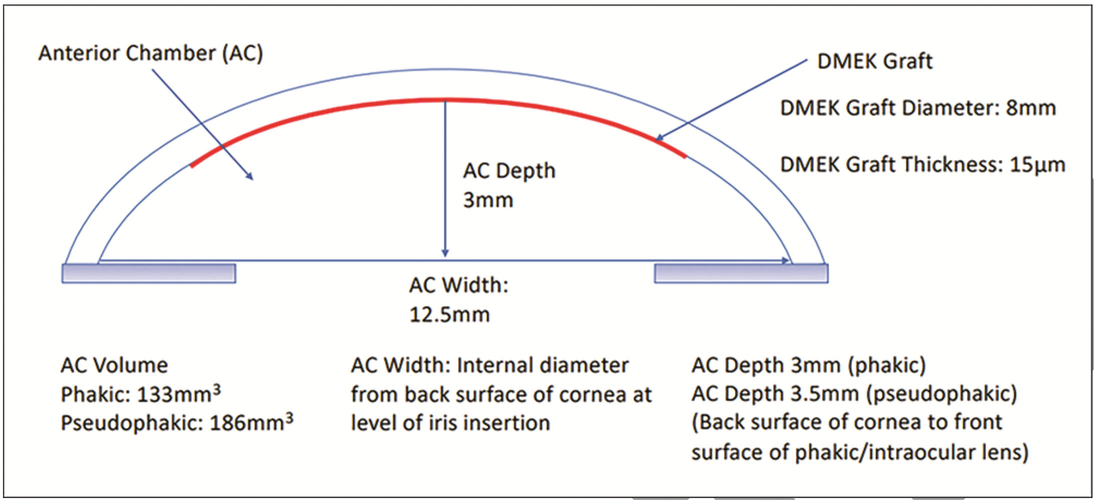


Figure 2 – Figure of DMEK and lift generated by an air bubble due to surface tension during immediate postoperative posturing in the horizontal position. The green colour corresponds to the shape of an air bubble. The arrows represent local tractions supporting graft. Note that the lift is integrated with surface pressures on DMEK graft section of the cornea (represented by the yellow line).

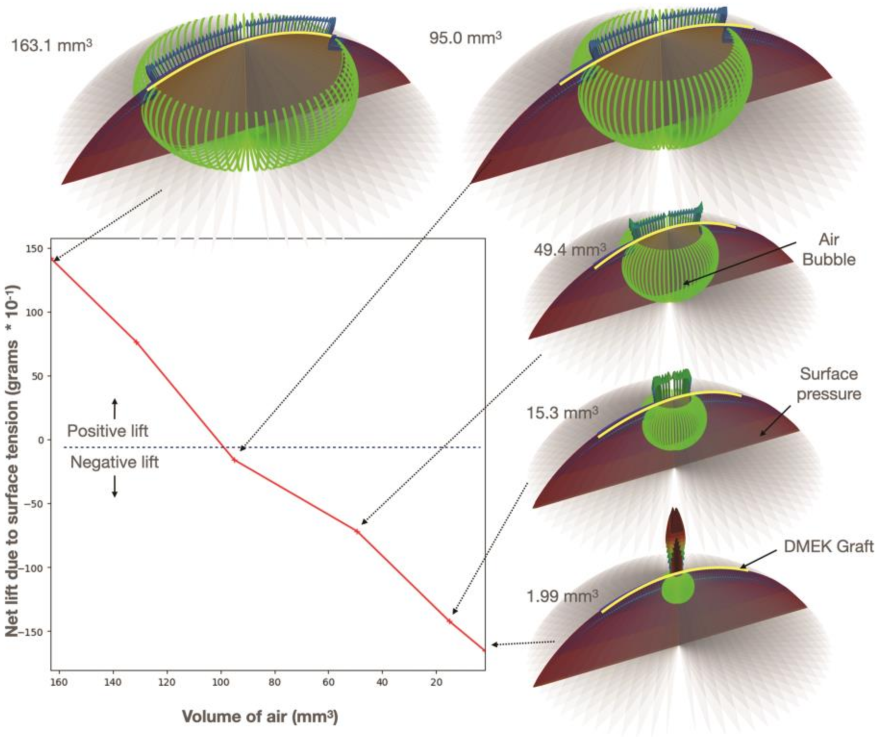
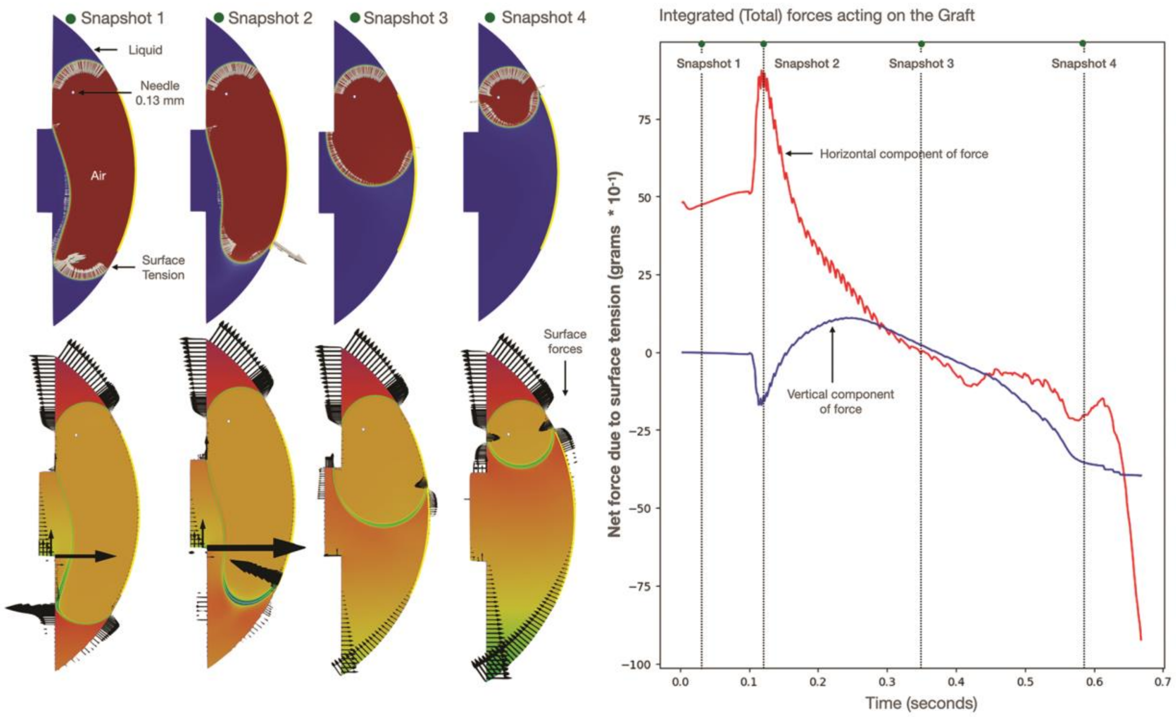


Figure 3 – Figure of DMEK graft and 4 snapshots in time of air bubble release in the vertical position, with corresponding graph showing total horizontal and vertical forces acting on the DMEK graft. Subsequent snapshots are arbitrary moments in time which represent the transition from the complete bubble-filled stage (Snapshot 1) to the final mobile bubble stage (Snapshot 4). The top left illustration shows the bubble in red and the fluid/liquid in blue. Forces on the bubble-fluid interface result from surface tension and depend on surface curvature of the air interface. The bottom left illustration shows the distribution of pressure as the bubble is released. The black arrows represent tractional forces exerted on the DMEK tissue and corneal surface in the horizontal and vertical directions, as illustrated by their size and direction, with the net force components plotted in the graph.



Online simulation video – Animation of bubble release from anterior chamber via inferior paracentesis in the vertical position following pupil block in post DMEK. The black arrows represent tractional forces exerted on the DMEK tissue and corneal surface in the horizontal and vertical directions, as illustrated by their size and direction. The first clip is in real time, then repeated at a slower speed, then finally back to real time to assist the viewer to appreciate the forces involved.