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Modeling Floppy Iris Syndrome and the Impact of Phenylephrine on Iris Buckling

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Abnormal iris movement (floppy iris syndrome) during intraocular surgery is associated with an increased risk of intraoperative complications. We have previously investigated this scenario with respect to intracameral air in corneal endothelial transplantation, and described the concept of iris buckling. As a number of clinical interventions are recommended for addressing floppy iris syndrome, we wished to evaluate the impact of intracameral phenylephrine on iris buckling and so refine our mathematical model. We considered the stability of an iris structure under a uniform pressure loading. We performed mathematical and computational simulations to demonstrate iris buckling, and then altered the parameters to assess the impact of phenylephrine on the model. We elucidated a number of buckled iris configurations which become unstable as the intraocular pressure increased, for transversely isotropic iris material properties, and identified a positive correlation between the critical pressure and the iris stiffness. A mechanical analysis with a dilated pupil (mimicking phenylephrine use) was also conducted, and demonstrated a significant increase in the critical pressure required to induce iris buckling. We have shown that iris buckling can arise at lower pressures when the iris stiffness is reduced, as in floppy iris syndrome. The use of phenylephrine was shown to prevent iris movement (buckling) by increasing the required critical pressures. This refined model demonstrates the positive effectiveness of phenylephrine in the management of floppy iris syndrome and gives evidence to the clinical practice of using this as a preventative measure.

Keywords: Floppy iris syndrome; cataract surgery; intraocular surgery; phenylephrine; buckling stability.

1. Introduction

Current strategies to improve the outcomes of cataract surgery focus on risk stratification by identifying any pre-existing conditions and peri-operative situations which could significantly increase the risk of intraoperative complications [Day *et al.*, 2015; Narendran *et al.*, 2009; Sparrow *et al.*, 2011]. One of these risk factors is abnormal intraoperative iris behavior, known as floppy iris syndrome. This condition was first described by Chang and Campbell in 2005 and consists of a triad of signs: poor pupillary dilation, iris billowing and subsequent iris prolapse through the corneal wounds [Chang, 2008, 2009; Chang and Campbell, 2005; Chang *et al.*, 2008a, 2008b; Neff *et al.*, 2009]. This condition was originally described in association with previous systemic use of oral alpha blockers (such as Tamsulosin), but there are now an increasingly long list of associated medications [Chang, 2008, 2009; Chang and Campbell, 2005; Chang *et al.*, 2008a, 2008b; Neff *et al.*, 2009].

There are a range of mechanical devices in use to address abnormal iris behavior, such as iris hooks or rings, but these are not necessary in all cases, and can result in localized iris sphincter trauma. While there are concerns regarding the accumulative effects of unlicensed intracameral adjuncts causing inflammation and toxic anterior segment syndrome [Lockington *et al.*, 2010], it has been our clinical experience and common practice that the use of intracameral phenylephrine can both dilate and stiffen the floppy iris, and so result in a reduction and normalization of the iris movement arising from the intraoperative fluidics [Carifi and Kopsachilis, 2013; Gurbaxani and Packard, 2007; Lockington and Gavin, 2009; Lorente *et al.*, 2012; Manvikar and Allen, 2006; Nguyen *et al.*, 2007]. The relationship between phenylephrine and porcine pupil diameter has been quantified *ex vivo* in Whitcomb *et al.* [2009] and found to cause an increase of modulus in the iris tissue by approximately a factor of two.

In our previous work, normal iris behavior was modeled in the setting of an air bubble in the anterior chamber during endothelial graft surgery [Lockington *et al.*, 2012]. We hypothesized that the reason for pupil block/angle closure which can arise following such surgery was due to iris buckling, and proceeded to develop a three-dimensional elastic isotropic model to demonstrate this scenario. In that study, we accounted for the isotropic material properties and predicted deformation of the iris under pressure. Our model was solved using finite element method and used to investigate the critical intraocular pressure (IOP) required to cause the iris buckling. However, the iris material properties were assumed to be oversimplified and we did not go on to evaluate the impact of the intrinsic iris properties on the model for other types of intraocular surgery (of which cataract surgery is the most common), or any potential clinical solutions to this situation.

Developing a detailed mathematical model of mechanical behavior of the normal iris and understanding the subsequent impact from floppy iris syndrome or intracameral pharmacological agents can help guide the clinician towards effective management of this intraoperative scenario. In this current paper, we wish to propose a

refined mathematical model of the human iris as an orthotropic elastic material. We then use this updated model to study the effect of floppy iris syndrome by looking at the stability of the normal and abnormal iris structure under pressure loading. We also evaluate the impact of phenylephrine in a clinical scenario.

2. Methods

2.1. *Geometry and reference configuration*

We modeled the iris as an axisymmetric annular disc with a central aperture (mimicking the pupil). The lens is a fixed posterior structure and so is presented as an analytical rigid body below the iris plate. The external edge of the iris tissue is also fixed peripherally to the ciliary body and sclera. Based on the published averaged human data [Amini and Barocas, 2010; Leung *et al.*, 2010], we assumed that the iris has a uniform thickness of 0.34 mm with a hemispherical tip, the anterior chamber width is 12.37 mm and the lens diameter is 9.0 mm, see in Fig. 1. The iris has no concavity and the iridolenticular contact distance is 0.77 mm [Liebmann *et al.*, 1995]. The iris-zonule distance is 0.69 mm. The pupil diameter, based on porcine iris tissue, is between 5 mm to 6.2 mm after pharmacological pupil dilatation [Whitcomb *et al.*, 2009].

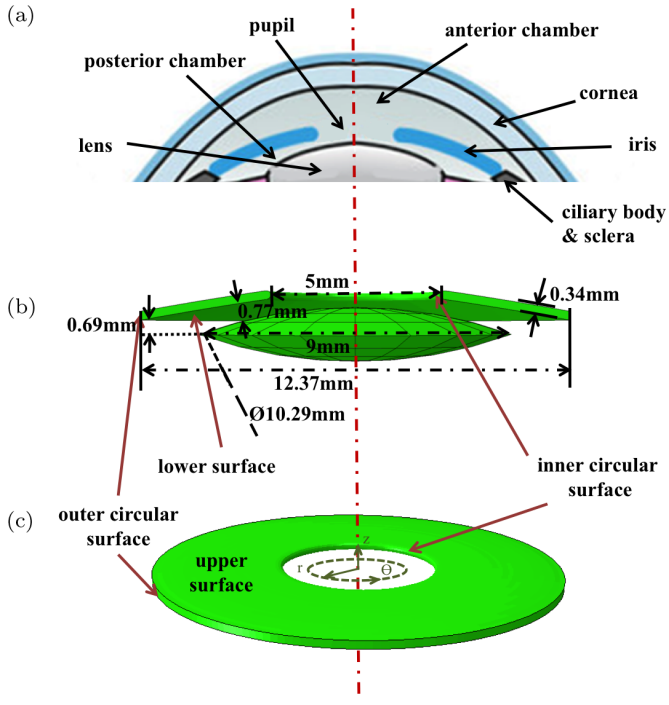

Fig. 1. (a) The side view of the eye structure; (b) the iris structure with the geometric information, and (c) the three-dimensional model of the iris, its relation with (b) is indicated.

2.2. *Linear bifurcation analysis*

We defined the reference configuration described by a cylindrical coordinate system (r, θ, z), and assumed that the iris behaves as an elastic material occupying volume V with boundary Γ. We then assumed that all free surfaces of the iris are subject to a constant IOP of P. In the absence of an external body force, the total excess potential energy of the iris structure is

$$\Pi = \frac{1}{2}\int_V \boldsymbol{\varepsilon}^T \mathbf{C}\boldsymbol{\varepsilon}\, dV - \int_\Gamma \mathbf{u}^T P\mathbf{n} dS, \tag{1}$$

where $\mathbf{C}$ is the fourth-order elasticity tensor (the tensor form is discussed below), $\mathbf{n}$ is the unit normal vector at the boundary Γ, and $\boldsymbol{\varepsilon}$ is the finite strain tensor.

Using the principle of virtual displacement method, we obtained the equilibrium equations from Eq. (1). With the finite element discretization, i.e. using the nodal displacement vector $\mathbf{U}$ to represent $\mathbf{u}$ and $\boldsymbol{\varepsilon}$, we can express the system in the matrix form

$$\mathbf{KU} = \mathbf{R}, \tag{2}$$

where $\mathbf{K}$ is the stiffness matrix and $\mathbf{R}$ is the discretized load vector (for details see in Bathe's book [Bathe, 2006]).

The iris tissue was modeled as an orthotropic material, and $\mathbf{C}$ has nine independent parameters and can be expressed in cylindrical coordinates as

$$\mathbf{C}^{-1} = \begin{pmatrix} \frac{1}{E_r} & -\frac{\nu_{r\theta}}{E_\theta} & -\frac{\nu_{rz}}{E_z} & 0 & 0 & 0 \\ -\frac{\nu_{\theta r}}{E_r} & \frac{1}{E_\theta} & -\frac{\nu_{\theta z}}{E_z} & 0 & 0 & 0 \\ -\frac{\nu_{zr}}{E_r} & -\frac{\nu_{z\theta}}{E_\theta} & \frac{1}{E_z} & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{1}{G_{\theta z}} & 0 & 0 \\ 0 & 0 & 0 & 0 & \frac{1}{G_{zr}} & 0 \\ 0 & 0 & 0 & 0 & 0 & \frac{1}{G_{r\theta}} \end{pmatrix},$$

where E_i $(i = r, \theta, z)$ are the elastic moduli in the three mutually orthogonal directions, ν_{ij} $(i, j = r, \theta, z)$ represent the Poisson's ratios, $\nu_{ij}/E_i = \nu_{ji}/E_j$, and G_{ij} are the corresponding shear moduli [Timoshenko and Gere, 1961].

We used linear buckling analysis to assess the stability characteristics of the iris structure [Wittrick and Williams, 1973]. It involved finding the critical pressure load for which the stiffness matrix $\mathbf{K}$ becomes singular in the following eigenvalue problem. An incremental loading pattern, $P = P^{\text{base}} + \lambda_k P^{\text{inc}}$, is defined, where λ_k is the scaling factor, which becomes the eigenvalue when the critical conditions

are reached

$$(\mathbf{K}_0^{\mathrm{cr}} + \lambda_k \mathbf{K}_\Delta^{\mathrm{cr}})\mathbf{U}_k^{\mathrm{cr}} = \mathbf{0}, \tag{3}$$

where $\mathbf{K}_0^{\mathrm{cr}}$ is the stiffness matrix corresponding to the base state, $\mathbf{K}_\Delta^{\mathrm{cr}}$ is due to the incremental loading, and $\mathbf{U}_k^{\mathrm{cr}}$ are the eigenvectors of the kth buckling mode [Bathe, 2006; Systémes, 2013].

Following a grid independence test by refining mesh size sequentially, we constructed a finite element mesh with 19,610 nodes and 14,245 hexahedral elements. The finite element model was implemented using the commercial package ABAQUS 6.13 (SIMULIA, Providence, RI).

2.3. *Elastic properties*

The iris, like many biological tissues, was assumed to be nearly incompressible with Poisson's ratio equal to 0.499 [Heys and Barocas, 1999; Miller, 2005].

Based on the tests of porcine iris tissue, the iris material has its azimuthal elastic modulus E_θ to be 2.97 kPa, and the radial elastic modulus E_r to be 4.00 kPa, presenting a clearly orthotropic behavior [Whitcomb *et al.*, 2009]. The longitudinal modulus E_z is assumed to be the same as E_r, and $G_{rz} = G_{\theta z} = G_{r\theta} = E_r/2(1 + \nu_{rz})$. Simulating the clinical scenario of exposure to intracameral phenylephrine, the radial moduli becomes 6.9 kPa.

The typical IOP in humans is around 10–20 mmHg (1 mmHg≈0.13 kPa) in normal subjects [Lockington *et al.*, 2012; Heijl *et al.*, 2002] but can exceed 50 mmHg due to intraocular fluidics [Lockington *et al.*, 2012]. To mimic the increase in IOP during intraocular surgery, we applied a pressure loading incrementally from $P^{\mathrm{base}} = 10.00$ mmHg onwards. The loading was applied simultaneously to the upper, lower and inner circular surfaces of the iris as indicated in Fig. 1(c). The displacements of the outer circular surface were fully constrained to mimic the anchoring by the ciliary body. Surface tension and shear forces due to aqueous flow were considered to be negligible.

3. Results

3.1. *Buckling analysis for orthotropic control case*

We conducted the stability analysis of the normal iris under loading. The iris was modeled as a homogeneous orthotropic material with an azimuthal elastic modulus of 2.97 kPa, and a radial elastic modulus of 4.00 kPa. We chose $P^{\mathrm{base}} = P^{\mathrm{inc}} = 10.00$ mmHg and increased the IOP (i.e., increased the scale factor λ_k) until the critical condition was reached.

The critical load P_c when the iris first buckles was found to be 17.42 mmHg for the chosen elastic moduli. With further increases in IOP, higher buckling modes also occurred. We labeled each buckling mode according to the number of local maxima across the structure, for example, mode $n = 2$ has 2 maxima as shown in Fig. 2(c).

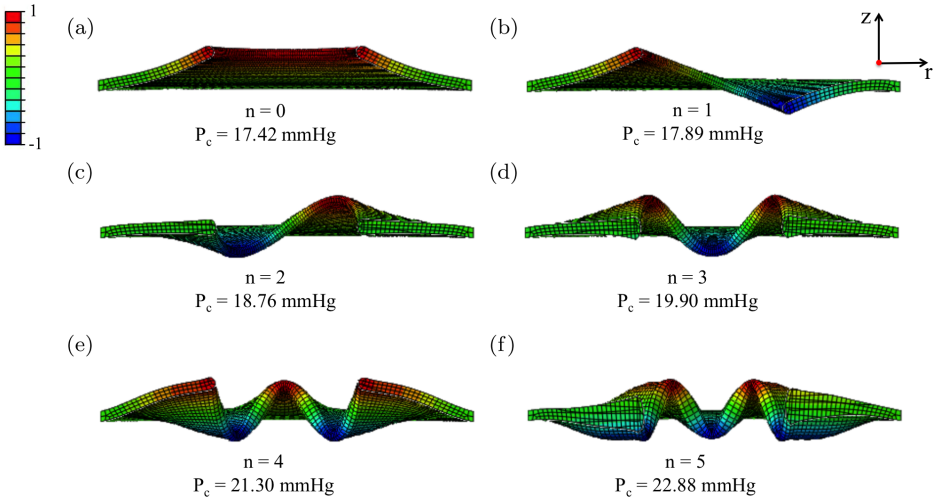

Fig. 2. The first six buckling modes in the $r\theta$-plane view, in which $E_r = E_z = 4.00\,\text{kPa}$, $E_\theta = 2.97\,\text{kPa}$. The color indicates the mode's longitudinal displacement. Note that the magnitude is unified from eigenvalue analysis.

The $n = 0$ mode is axisymmetric while for $n > 0$, mode n has n symmetries. As in the analytical solution [Bloom and Coffin, 2000], the annular plate always buckles into the axisymmetric form regardless of the hole size. The subsequent increase in fluidics behind the iris will exacerbate the buckling shapes/tissue instability, eventually leading to prolapse of tissue through the incision wounds during cataract surgery.

3.2. *Buckling analysis for phenylephrine-activated iris tissue*

We have previously noted that the elastic properties/stiffness of the iris can be very different in abnormal clinical situations: for example, in floppy iris syndrome or a traumatized tonic pupil, the elastic moduli is significantly decreased, and conversely, the introduction of intracameral phenylephrine has been shown to have a positive clinical effect by stiffening the iris (modulus). We wondered if this mechanical effect combined with iris dilatation could increase the critical pressure, and hence, reduce the potential for the iris buckling.

To further investigate the dilated pupil diameter and iris stiffness variance due to intracameral phenylephrine use, we repeated the analysis with different dilated pupil sizes and material stiffness. We changed the elastic moduli in the orthotropic iris model using a proportion factor η, so that the elastic moduli becomes ηE_i, $(i = r, \theta, z)$. With $\eta < 1$, the iris becomes soft (floppy), while with $\eta > 1$, the iris is stiffened by phenylephrine.

The relationship between the critical pressures and η is summarized in Table 1, highlighting how a uniform augmentation/reduction in stiffness can increase/reduce the critical pressures. In addition, the differences in critical pressure between the

Table 1. The critical pressures (mmHg) for the first six modes with different material stiffness factor η. The bold values are the critical pressures for the first buckling mode.

η	P_c [mmHg]					
	$n=0$	$n=1$	$n=2$	$n=3$	$n=4$	$n=5$
0.6	**16.54**	17.28	/	/	/	/
0.7	**16.82**	17.47	18.38	19.28	/	/
0.8	**17.04**	17.62	18.49	19.46	20.60	/
0.9	**17.20**	17.73	18.61	19.66	20.93	22.36
1	**17.42**	17.89	18.76	19.90	21.30	22.88
1.5	**19.52**	19.54	20.40	22.06	24.19	26.53
2	24.61	**23.61**	24.07	26.20	28.99	31.91
4	72.21	59.13	**50.13**	50.24	53.03	56.62

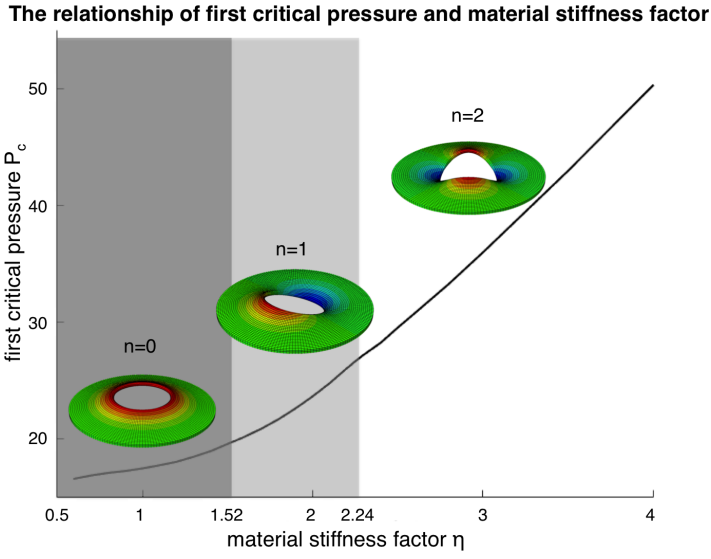

Fig. 3. The plot of first critical pressures with respect to the material stiffness factor η. In the dark gray region, the iris first buckles into mode 0, while it buckles into mode 1 in the light gray region and mode 2 in the white region.

individual modes become greater with the increased material stiffness except for the behaviors of mode 0 which are more sparse. We noticed that as η reduces, the structure became very soft and yielded large deformation. As the result, it is harder to obtain converged solutions when loading is high. We also noted from Fig. 3 that a stiffer material is more likely to lose stability to higher buckling modes first. For example, the iris becomes unstable at mode 1 when $\eta \geq 1.52$ at the critical pressure of 19.65 mmHg, instead of mode 0 in the softer cases; at $\eta > 2.24$, the iris becomes unstable to mode $n = 2$ at a critical pressure of $P_c = 26.50$ mmHg.

Table 2 shows the critical pressure P_c for the first six buckling modes with different dilated pupil diameter d_p and the corresponding iris thickness t_i. Note

Table 2. Values of P_c, d_p, t_i for the first six buckling modes. The bold values are the critical pressures of the first buckling.

d_p [mm]	t_i [mm]	P_c [mmHg]					
		$n=0$	$n=1$	$n=2$	$n=3$	$n=4$	$n=5$
5.00	0.3400	**17.42**	17.89	18.76	19.90	21.30	22.88
5.50	0.3488	**18.31**	18.62	19.29	20.19	21.45	22.91
6.00	0.3583	**19.99**	20.06	20.47	21.20	22.20	23.45
6.50	0.3686	22.02	**21.81**	21.85	22.34	23.17	24.27

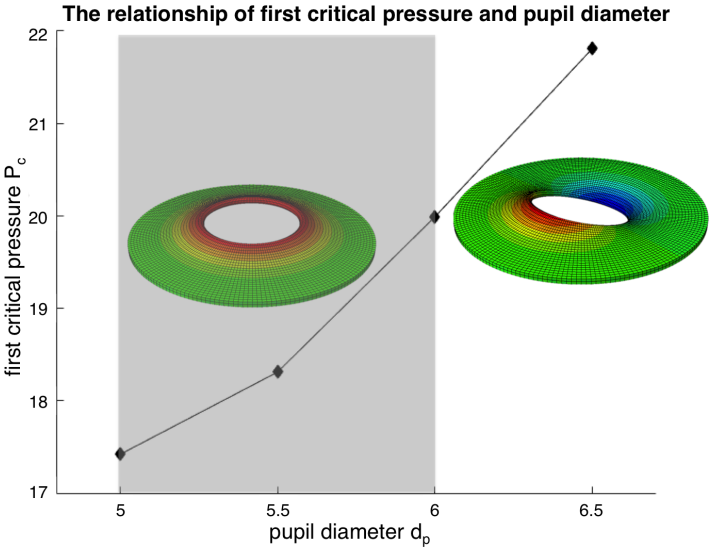

Fig. 4. The plot of the first critical pressure with respect to the degree of dilation/pupil size. In the dark gray region, the iris first buckles into mode 0, while it buckles into mode 1 in the light gray region.

that the addition of phenylephrine causes the pupil to dilate, and since the iris volume is conserved, the iris thickness has to increase.

We note the positive correlation between the buckling pressures and the dilated pupil length in Table 2: a large/dilated pupil hole increases the critical pressure. The first critical pressure against the pupil size is also plotted in Fig. 4, showing the more dilated the pupil, the higher the buckling modes that become unstable first.

The critical pressure at different degrees of the pupil dilation is shown in Fig. 5. Clearly, dilatation increases the critical pressure for all buckling modes, and therefore stabilize the system. This is because dilation reduces the surface area and thus the iris thickens. This in turn, increases the critical buckling pressure.

The critical IOP required for each buckling mode is significantly lowered when the material becomes less stiff (floppy), as might be expected from other studies of buckling in elastic tissue [Han, 2007; Townsend *et al.*, 1975]. However, the use of intracameral phenylephrine has a synergistic effect to minimize intraoperative iris

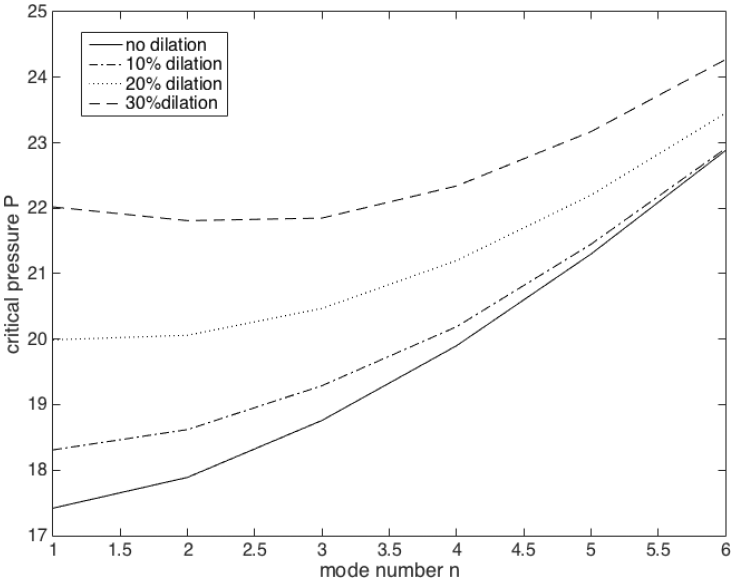

Fig. 5. The critical pressures for different degree of dilations of the pupil.

buckling by (a) increasing the material stiffness moduli and (b) dilating the pupil aperture. We note that these two factors are highly correlated, as is demonstrated in Figs. 3 and 4.

4. Discussion

This study aimed to study abnormal iris movement during intra-ocular surgery using a finite element mechanical model of iris. Our 3D finite element model showed that the iris tissue instability found during the surgery is due to iris buckling. The reason for the buckling is, because the outer ring of the iris is clamped, although the pressure is applied to all sides, the pressure on the top and bottom surfaces do not produce much net effect, and the pressure on the inner surface of the iris is responsible for the buckling. This is different to placing a round disk of finite thickness with a circular hole in the bottom of a swimming pool; since the disk is not clamped on any side, it will not buckle even if the pressure is huge. We also identified the key parameters in iris buckling, the IOP loading and the impact of floppy iris behavior.

We demonstrated that phenylephrine is effective in reducing the movement of the iris during cataract surgery. It is worth mentioning that the effects of phenylephrine have been debated in literature. Some argued that there is no or reduced dilatation caused by phenylephrine [Gurbaxani and Packard, 2015], while others stated the opposite [Vazquez-Ferreiro *et al.*, 2017; Lorente *et al.*, 2012; Lundqvist *et al.*, 2014]. Since the injection of phenylephrine is used frequently to dilate small pupils in

cataract surgery, and phenylephrine eye drops are used in all clinics to dilate pupils, we believe it is important to study the impact of the phenylephrine. In addition, the iris tissue of patients (i.e. stiffness) may be different compared to a normal iris, and without the patient-specific iris data, we performed a parameter study looking at the effects of a range of stiffness changes. Therefore, despite the simplifications, our finding is qualitatively representative of the clinical situations, and our simulations are visually consistent with the intra-operative surgical findings.

The majority of eye modeling studies have focused on ocular fluid mechanics [Canning *et al.*, 2002; Fitt and Gonzalez, 2006; Fleck, 1990], or simplified fluid–structure interaction [Huang and Barocas, 2004, 2006]; some of the studies have considered the iris and its interaction with aqueous humour [Canning *et al.*, 2002; Fitt and Gonzalez, 2006; Heys *et al.*, 2001]. However, to the best of our knowledge, three-dimensional modeling of iris buckling under pressure loading accounting for the anisotropy of the iris tissue has not been reported. Developing a detailed mathematical model of mechanical behavior of the normal iris and understanding the subsequent impact of floppy iris syndrome can help guide the clinician to the effective management of this intraoperative complication. Compared to our previous study based on a simplified mathematical model [Lockington *et al.*, 2012], this work provides a quantitative measure for structure-based iris buckling with realistic material properties for the first time. We have shown that the critical pressure of buckling is dependent on both the iris stiffness and pupil size. We also have demonstrated how intracameral phenylephrine can reduce the instability of the iris buckling. We remark that the effect of phenylephrine to iris buckling is similar to the effect of arterial contraction and dilatation to its critical buckling pressure, i.e., higher wall thickness to radius ratio increases the critical pressure [Han, 2007; Hayman *et al.*, 2013]. We believe our model of iris buckling is the first step towards understanding and preventing this complication.

So, what does this mean for the clinician? The majority of cataract surgeons will have encountered floppy iris syndrome, and we trust our computer simulation and cross-sectional diagrams are an accurate representation of this clinical scenario. We believe our model demonstrates that floppy iris syndrome occurs due to reduced intrinsic iris stiffness properties, and that iris buckling can be induced at lower pressures/fluidics. As the clinical scenario appears to be minimized through stiffening of the iris with phenylephrine, it would be our recommendation that intracameral phenylephrine is used prior to the initiation of iris buckling, to minimize the adverse consequences. In other words, any buckling mode is unwelcome to the surgeon, as it means the iris has started to display abnormal movement behavior. This is a situation we all wish to avoid, as it can lead to iris prolapse and further complications, so we suggest the use of intracameral phenylephrine as the first preventative step.

One of the limitations of this study is the lack of specific material iris properties, which can change due to trauma or pharmacological intervention during eye surgery, and have different qualities dependent on their inherent physiological and/or pathological conditions. Since the mechanical properties of specific human

iris tissue were not available, we had to estimate our model parameters based on measurements of animal (canine and porcine) iris which were varied [Heys and Barocas, 1999; Whitcomb *et al.*, 2009]. Therefore, although our model predictions may explain the mechanism in general, it remains a challenge to provide a patient-specific prediction. In addition, our model is based on simplifications of the complex architecture of the iris and the anterior eye. In particular, the active contraction of the iris sphincter and dilator smooth muscles were ignored. Activation of iris smooth muscles can alter the iris contour and mechanical response and could therefore change the results of current model. In addition, the inhomogeneity of the iris structure may also alter the outcome. However, while these factors may change the values of the critical pressures predicted, we expect our qualitative findings will not change.

5. Conclusion

We used a finite element orthotropic iris mechanical model to understand the potential iris movements due to fluidics during intra-ocular surgery. The model predicts the critical pressure under which the iris may lose its stability. The situation is exacerbated by the degree of floppiness of the iris since the critical pressure is lower when the iris is less stiff. We suggest that iris buckling can arise at lower pressures when the iris stiffness is reduced, as in floppy iris syndrome. This model demonstrates the positive impact of phenylephrine in the management of floppy iris syndrome and gives evidence to the clinical practice of using this as a preventative measure.

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