Influence of dextran solution and corneal collagen crosslinking on Corneal Biomechanical Parameters Evaluated by Corvis ST

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Abstract

Purpose: To analyze the influence of dextran solution and corneal collagen crosslinking (CXL) on corneal biomechanical parameters evaluated by Corneal Visualization Scheimpflug Technology (Corvis ST).

Materials and Methods: Forty porcine eyes were included in this study. Twenty porcine eyes were soaked in dextran solution for 30 minutes (10 eyes in 2% dextran

solution and 10 eyes in 20% dextran solution). CXL treatment was performed in 10 porcine eyes, the other 10 porcine eyes were regarded as a control group. Each eye was fixed on an experimental inflation platform to carry out Corvis measurements at different IOPs. Corneal biomechanical parameters were calculated based on Corvis measurement. Statistical analysis was used to analyze the influence of dextran solution and CXL on corneal biomechanical parameters based on Corvis parameters.

Results: Corneal energy absorbed area ($A_{absorbed}$) decreased after being soaked in dextran solution under IOP of 15 mmHg; Corneal elastic modulus (E) decreased after being soaked in 2% dextran solution and increased after being soaked in 20% dextran solution; SP-A1 increased after CXL.

Conclusion: Both dextran solution and CXL can change corneal biomechanical properties; SP-A1 may be used as an effective parameter for the evaluation of CXL.

Keywords: dextran solution; corneal collagen crosslinking (CXL); corneal biomechanical properties; Corneal Visualization Scheimpflug Technology (Corvis ST); intraocular pressure (IOP)

1. Introduction

Corneal Visualization Scheimpflug Technology (Corvis ST) is one of the most commonly used devices for corneal biomechanical properties evaluation in clinic. Parameters provided by Corvis have shown their value in preliminary diagnosing of corneal diseases such as keratoconus. These parameters are related to corneal biomechanics, intraocular pressure (IOP), and corneal geometrical parameters, thus we refer to them as corneal biomechanical-related parameters [1-3]. Based on the Corvis measurement, the Stiffness Parameter (SP-A1), corneal tangent stiffness coefficient (S_{TSC}) [4], corneal energy absorbed area ($A_{absorbed}$) [4], and the corneal elastic modulus (E) [5] have been calculated. These parameters made it possible to obtain corneal

biomechanical properties based on simple clinical measurements. These parameters have shown significant difference between normal and keratoconus corneas [4]. However, it is not known whether there is any change after clinical treatment, such as CXL treatment, dextran treatment in vivo / in vitro in these parameters.

Corneal collagen crosslinking (CXL) has been considered an effective treatment approach that can halt or delay the progression of keratoconus [6, 7]. Conventional CXL is considered safe and effective for the prevention of keratoconus progression. It uses the UVX 1000 system with 0.1% riboflavin solution presoaked in 20% dextran for 20 min, and 3 mW/cm^2 ultraviolet A (UVA) light for 30 min [6-9]. 20% dextran solution was used to maintain the solution iso-osmolar with respect to the corneal stroma [10]. In the treatment of keratoconus patients with a thin cornea, hypotonic dextran may be used to increase the corneal thickness by swelling of corneas in CXL [11-13]. Nevertheless, previous studies have found that the dextran solution is a vital component in the CXL treatment. Hypertonic CXL treatment results in a stiffness decrease [14], and the substitution of dextran with dextran sulfate in riboflavin solutions may result in the loss of vision and permanent corneal opacity [15].

Numerous studies that used *in vitro* experiments have reported the variations of corneal biomechanical properties after CXL [16-19], showing that corneal stiffness increased after CXL. Some researchers have reported the variation of corneal biomechanical parameters provided by Corvis, Steinberg et al find that the first applanation time (A1T) increased and the second applanation time (A2T) decreased 3 months after CXL [20]. Sedaghat et al find significant changes in radius at highest concavity and integrated inverse radius four years after CXL [21]. These studies have not reached an agreement in relation to the variation of corneal viscoelastic properties after CXL. To the best of our knowledge, only a few studies focused on the influence of dextran solution on corneal biomechanical properties. Elucidating the influence of dextran solution and riboflavin-ultraviolet CXL on corneal biomechanical properties may be helpful to the further cognition of corneal biomechanical determined by Corvis. And these will provide theoretical basis for the individual design and prognosis of CXL.

In this study, we used porcine eyes as research objects and corneal biomechanical parameters were determined based on Corvis ST. Porcine corneas were assigned to four groups, and two groups were soaked in 2% and 20% dextran solution respectively, to analyze the influence of dextran solution on corneal biomechanical parameters. CXL was performed in another group of porcine eyes to evaluate the variation in corneal biomechanical parameters after CXL. Besides, each porcine eye was measured with Corvis ST under several different IOPs to evaluate the influence of IOP on the variation of corneal biomechanical parameters after dextran immersion or CXL. The results of this study will provide a theoretical basis for the design and prognosis of CXL.

2. Materials and Methods

2.1 Materials and measurements

Forty porcine eyes were enrolled in this study. Porcine eyeballs were acquired from a local slaughterhouse and maintained in 0.9% normal saline at 4 ℃ before testing. The porcine eyes were randomly divided into four groups. Porcine corneas were instilled with 2% and 20% dextran solution every 3 minutes for 30 minutes in Group 1 (2% dextran group) and Group 2 (20% dextran group), respectively. Conventional corneal collagen crosslinking was performed in Group 3 (CXL group), and Group 4 (control group) was regarded as the control group. Before the experiments, the whole epithelium was removed from the cornea.

The procedure of conventional CXL is as follows: Prior to irradiation, riboflavin 0.1%–dextran 20% solution (Ricrolin Sooft Italia, Montegiorgio Fermo, Italy) was instilled on the central cornea every 3 mins for 30 minutes. Next, the cornea was exposed to UVA emission for 30 minutes (370 nm, 3 mW/cm2), at the same time, instilling the riboflavin 0.1% - dextran 20% solution every 3 minutes.

Before the Corvis measurements, the corneal central thickness was measured with Pachymeter SP-3000 (TOMEY, Japan) for three times. After that, every porcine eyeball was fixed on the self-built experimental inflation platform, as shown in **Figure 1,** and

Corvis measurements were carried out when the IOPs were stable at 15, 20, 25, 30 mmHg. All Corvis measurements tests were controlled within 5-8 minutes, and no significant dehydration was found. The tests were taken by the same technician and captured by automatic release to ensure the absence of user dependency. Corvis results on “Alignment” and “Pressure Profile” reading “OK” were accepted; otherwise measurement was repeated until the reading was “OK”.

All the specimens were tested within no more than 24 hours after death. All of the experiments were approved by the ethics committee of Capital Medical University. The experiments were performed in accordance with the ARRIVE guidelines and NIH guidelines.

2.2 Determining corneal biomechanical parameters

In addition to parameters provided by Corvis software, corneal tangent stiffness coefficient (S_{TSC}), corneal energy absorbed area ($A_{absorbed}$), and corneal elastic modulus (E) were also determined based on the air-puff forces-corneal apical displacement curve provided by Corvis following the methods reported in our previous studies. The typical air-puff forces-corneal apical displacement curve is shown in **Figure 2**. A specific fitting line was selected on the loading curve to represent the tangent stiffness coefficient (S_{TSC}). The area between the loading and unloading curves was defined as the energy absorbed area ($A_{absorbed}$). When Corvis measurements were regarded as indentation experiments and cornea as a shallow spherical shell, the corneal elastic modulus was determined based on the relation between force and spherical apical displacement.

2.3 Statistical analysis

The Kolmogorov-Smirnov test was used to check for a normal distribution of quantitative data, which were reported as the mean and standard deviation (SD). Coefficient of variation (CV) was calculated to evaluate the repeatability of corneal biomechanical parameters. The influence of dextran solution, CXL, and IOP on corneal

biomechanical parameters were evaluated by multivariate analysis of variance (ANOVA). All statistical analyses were performed using SPSS statistical software version 21.0 (SPSS Inc., Chicago, Illinois, USA), and an alpha value of $p < 0.05$ was considered as statistically significant.

3. Results

K-S test results showed that all of the corneal Corvis parameters had normal distribution ($p>0.2$). The coefficient of variation (CV) of Corvis parameters related to corneal biomechanics were no more than 10%, which suggested that these parameters had good repeatability.

The porcine central corneal thickness (CCT) measured by Pachymeter SP-3000 showed no significant difference among different groups before CXL or dextran solution immersion ($p>0.05$). The CCT and *R* of the different groups after treatment are shown in **Table 1**. The obtained results showed no significant difference among different groups ($p>0.05$) in *R*. The CCT significantly increased after being soaked in 2% dextran solution ($p<0.001$) and was significantly reduced after being soaked in 20% dextran solution ($p<0.001$). There was no significant variation in CCT and *R* after CXL.

Figure 3 and Table 2 presents the corneal biomechanical parameters in different groups under different IOP. S_{TSC} showed no significant difference among different groups; $A_{absorbed}$ decreased after being soaked in dextran solution under IOP of 15mmHg, and no significant difference was found at other IOPs. *E* decreased after being soaked in 2% dextran solution and increased after being soaked in 20% dextran solution at each IOP value. SP-A1 increased after being soaked in 2% dextran solution and decreased after being soaked in 20% dextran solution under IOP of 15mmHg, while increased after being soaked in 20% dextran solution, decreased after being soaked in 2% dextran solution under other IOPs. Compared to Group 3 and 4 in Figure 3, SP-A1 increased after corneal collagen cross-linking, and there was no significant variation in other parameters after CXL. In all of the four groups, SPA1, S_{TSC}, and E increased with IOP,

while $A_{absorbed}$ decreased with IOP. The results of multivariate analysis of variance showed no interaction among these three factors in the four parameters above.

4. Discussions

In this paper, we studied the influence of dextran solution and CXL on corneal biomechanical parameters determined from Corvis measurements. The obtained results showed that both dextran solution and CXL had an influence on corneal biomechanical properties. The results of this study may provide an important theoretical basis for the design and prognosis of CXL.

Numerous studies have reported on the corneal biomechanical properties after CXL, whilst failing to reach consensus on the variations of corneal biomechanical parameters after CXL. Dias *et al* assessed the corneal anterior and posterior stromal elasticity after CXL using Atomic Force Microscopy (AFM) [16], showing that the stiffness of corneal anterior stroma increased after CXL, while the posterior stroma was not affected by CXL. Zhang and colleagues studied the corneal biomechanical properties after CXL with a uniaxial tensile test [19], and they found that corneal elastic moduli significantly increased after CXL. Matteoli *et al* measured porcine corneal biomechanical properties with corneal inflation experiments [18] and found that corneal elastic modulus increased after CXL under high IOP, while no significant difference was found within the physiological range of IOP (15-30mmHg).

Clinical results showed that SP-A1 increased significantly 6 months after CXL [22], and no significant changes was found 4 years after CXL [23]. In this study, SP-A1 was increased immediately after CXL, which was in agreement with the reported increase of corneal elastic properties from a short-term evaluation in vivo after CXL. In the current study, we found no significant changes in S_{TSC}, and corneal elastic modulus (E) after CXL, which may be due to the CXL surgery was carried out in vitro and the corneal elastic modulus was measured under a physiological range of IOP [18]. Liu et al found corneal viscosity decreased significantly after CXL by stress relaxation experiments [24]. While $A_{absorbed}$ was also found no significant variations after CXL in

this study. This difference may be due to the 30 ms duration of air-puff test which was too short to achieve thermodynamic equilibrium [25].

Composition of the riboflavin solutions is one of the obstacles in evaluating the potential efficacy of CXL [26]. 20% dextran solution is used in standard CXL to maintain the solution iso-osmolar with the corneal stroma [10]. While for keratoconus patients with thin corneas (<400μm), hypotonic dextran may be used to increase corneal thickness during CXL [11, 12]. To the best of our knowledge, only a few studies have reported on the influence of dextran solution on corneal biomechanical properties.

In this study, we found that corneal viscoelastic parameters, $A_{absorbed}$, decreased after being soaked in both 2% and 20% dextran solution under IOP of 15mmHg. Corneal elastic modulus, *E*, increased after it was soaked in 20% dextran solution and decreased after it was soaked in 2% dextran solution. The influence of dextran solution on corneal biomechanical properties may be reflected in two aspects: the influence of dextran on the corneal structure [27], and the different concentration of dextran solution, which may lead to corneal swelling or shrinking [28, 29]. Sondergaard et al compared the corneal shear moduli in riboflavin solution-treated groups and CXL-treated groups, and the results showed there was no significant difference between these groups. This remained us the immediate effects of CXL treatment may be due partly to the interaction between ground substance and riboflavin-dextran solution [30]. In Kling's study, dextran solution has been used to maintain the native corneal ultrastructure in corneal decellularization [31]. In Hatami-Marbini's study, corneal elastic modulus decreased with the increase of corneal swelling [32]. These results suggested that dextran may have an influence on corneal viscoelastic properties. The concentration of dextran may influence the corneal biomechanical because of the corneal swelling or corneal shrinkage.

Another parameter that can reflect corneal stiffness, SP-A1, was found to decrease after being soaked in 20% dextran solution and increased after being soaked in 2% dextran solution under IOP of 15mmHg, which was opposite to the variation of *E*. While SP-A1 showed similar variation trend with *E* under other IOPs. These results

maybe because SP-A1 was more influenced by corneal thickness under IOP of 15mmHg. In our previous study, we also found that *E* was less influenced by corneal geometrical parameters than SP-A1 [5].

In the current study, we also examined the influence of IOP on corneal biomechanical parameters. Our results showed that SPA1, S_{TSC}, *E* increased with IOP, and $A_{absorbed}$ decreased with IOP. Besides, $A_{absorbed}$ decreased after being soaked in dextran solution under IOP of 15mmHg, while no significant difference was found at other IOPs. These results suggest considering the influence of IOP when evaluating corneal biomechanical parameters using Corvis measurements.

Comparing the four parameters addressed in this study, we found that both dextran solution and CXL had influence on corneal biomechanical. *E* was more sensitive to corneal swelling induced by dextran solution, and SP-A1 was more sensitive to corneal thickness variation induced by corneal swelling. The variation of SP-A1 was also more significant than *E* after CXL. According to these results, we can speculate that SP-A1 may be a useful parameter to evaluate the effect of CXL. Combining *E*, SP-A1, $A_{absorbed}$ can help the ophthalmologists to design CXL procedures individually and to predict the effect of CXL whilst considering the influence of dextran solution and CXL, especially for the CXL treatment with a thin cornea.

The innovation of this study was that we evaluated the influence of CXL and dextran solution on corneal biomechanical properties by Corvis measurements. To the authors acknowledge, there was few studies that studied the influence of dextran solution on corneal biomechanical properties by Corvis measurements. the results of this study showed that both dextran solution and CXL can change corneal biomechanical properties; Corneal elastic modulus (E) was more affected by the corneal swelling induced by the dextran solution, while SP-A1 was more influenced by the variation of corneal thickness induced by the dextran solution. SP-A1 may be used as an effective parameter for the evaluation of CXL. Dextran may influence the corneal viscoelastic properties. These results may provide theoretical basis for the individualized design of

CXL. This study has some limitations that need to be pointed out. First, only two concentrations of dextran solution were used to study the influence of the dextran solution on corneal biomechanical properties. Second, standard CXL was carried out in this study during which the UV irradiation intensity and time were fixed. The results of this study revealed a significant difference between the biomechanical parameters of cornea socked in 2% and 20% dextran solution. The variation of corneal biomechanical parameters after standard UVA- riboflavin CXL was also found in this study. Future studies should use more concentrations of dextran solution, more gradients of the UVA irradiation intensity and time to achieve better clinical application.

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Fig.1 Platform for eyeball inflation and Corvis test.

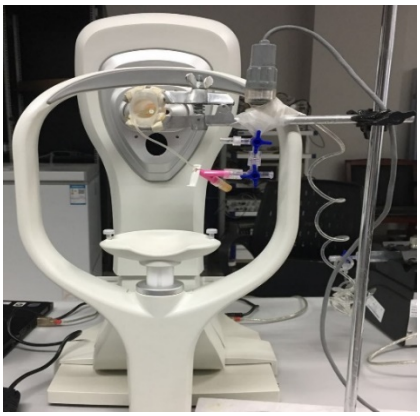

Fig.2 Air puff force – corneal apical displacement curve

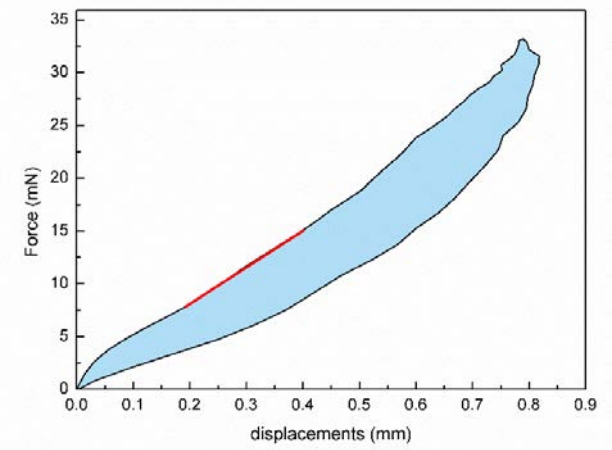

Fig.3 Variation of corneal biomechanical parameters with IOP in different groups.

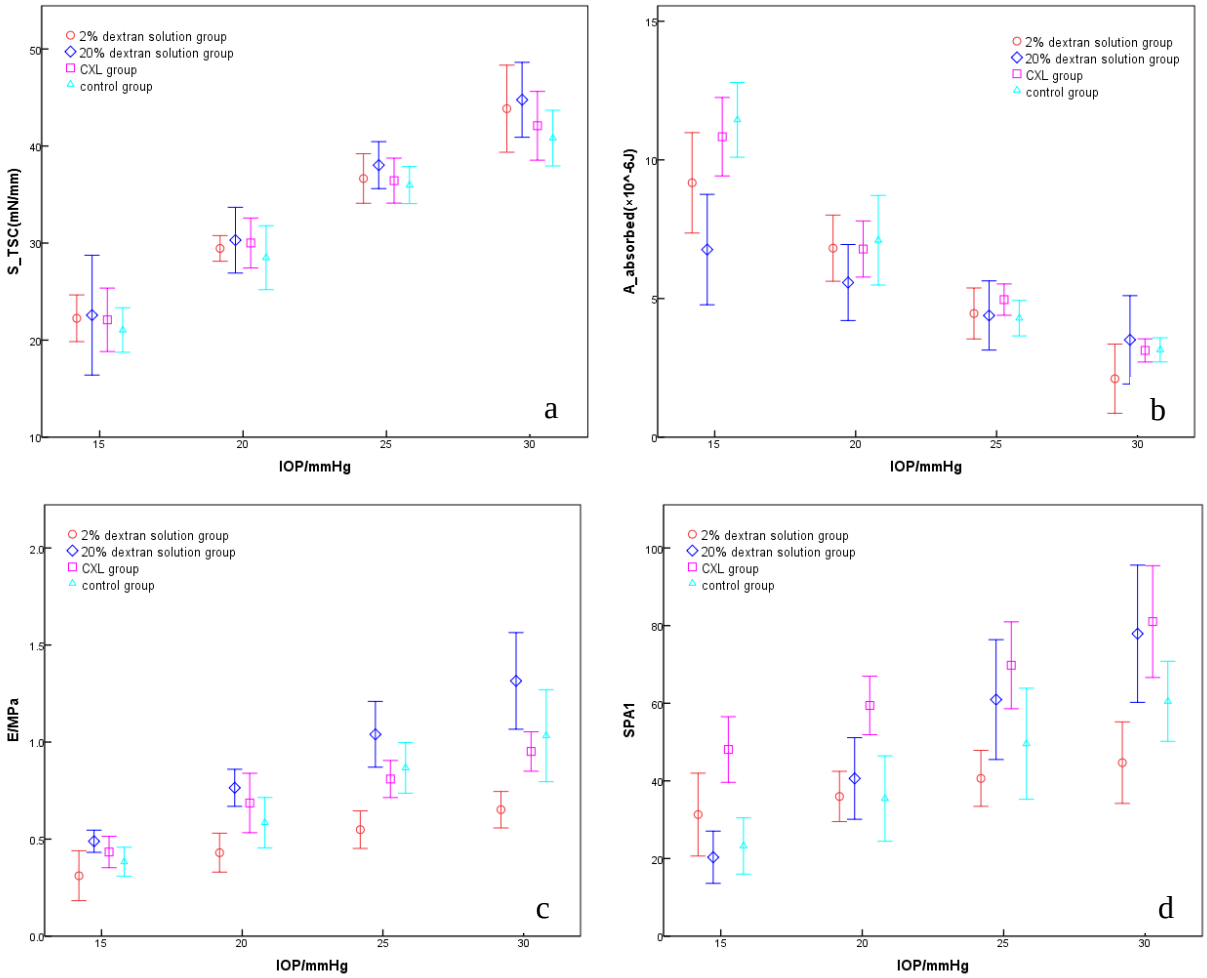

Table 1. Porcine central corneal thickness and curvature radius in different groups

	2% dextran group	**20% dextran group**	**CXL Group**	**Control Group**	***p***
CCT/μm	983±16	747±21	877±20	860±22	<0.001
R/mm	8.10±0.87	8.65±1.30	8.54±1.07	8.16±1.67	0.154

Table 2. Variation of corneal biomechanical parameters with IOP in different groups.

	IOP	K(mN/mm)	E(MPa)	SPA1	$A_{absorbed}(\times 10^{-6}J)$
2% dextran group	15	22.249±2.298	0.311±0.123	31.321±10.164	9.173±1.726
	20	29.449±1.258	0.430±0.096	35.983±6.178	6.818±1.136
	25	36.648±2.433	0.549±0.092	40.644±6.872	4.463±0.877
	30	43.848±4.277	0.652±0.089	44.692±9.999	2.108±1.189
20% dextran group	15	22.573±5.884	0.489±0.054	20.326±6.412	6.766±1.896
	20	30.301±3.230	0.765±0.091	40.633±10.018	5.577±1.306
	25	38.029±2.307	1.040±0.161	60.939±14.712	4.388±1.189
	30	44.765±3.680	1.315±0.237	77.913±16.851	3.511±1.518
CXL Group	15	22.091±4.254	0.434±0.105	48.099±11.003	10.834±1.840
	20	30.011±3.597	0.686±0.214	59.435±10.529	6.785±1.412
	25	36.430±3.243	0.810±0.134	69.783±15.651	4.961±0.792
	30	42.091±4.955	0.952±0.142	81.038±20.132	3.128±0.587
Control Group	15	21.040±3.205	0.384±0.104	23.249±10.124	11.444±1.886
	20	28.492±4.608	0.585±0.182	35.461±15.385	7.102±2.258
	25	35.972±2.668	0.867±0.182	49.553±19.996	4.293±0.894
	30	40.815±4.013	1.033±0.332	60.501±14.395	3.150±0.611