

# Ophthalmology Times

CUTTING-EDGE ADVANCEMENTS

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## Study: CXL for corneal ectasia requires oxygen within tissue

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### Take home

CXL protocols using high irradiance/short irradiation time or leaving the epithelium on may limit the opportunity for adequate oxygen replenishment within the cornea, resulting in unsatisfactory outcomes.

Dr. Hafezi By Cheryl Guttman Krader; Reviewed by Farhad Hafezi, MD, PhD



The success of corneal crosslinking (CXL) for ectatic disease requires oxygen within the tissue, and this dependency likely explains the limited efficiency of high-intensity (rapid) and transepithelial treatment protocols, said Farhad Hafezi, MD, PhD.

In a series of studies, Dr. Hafezi and colleagues at Geneva University, Switzerland, demonstrated that the biomechanical effect of CXL is (a) oxygen-dependent, and (b) declines in efficacy when intensity is raised and treatment time reduced, even when the total energy dose (fluence) remains the same.

"By definition, the corneal strengthening effect of treatment with riboflavin and ultraviolet A (UVA) requires oxygen because it arises from crosslinking of collagen and proteoglycans that is mediated by the generation of reactive oxygen species," said Dr. Hafezi, professor and chairman, Department of Ophthalmology, Geneva University Hospitals, Switzerland, and clinical professor of ophthalmology, Keck School of Medicine, University of Southern California, Los Angeles. "Previous research has shown that oxygen in the cornea is rapidly depleted during CXL irradiation and at a faster rate using higher intensities, raising concern that high irradiance/short irradiation time protocols or presence of an intact epithelial barrier limit the opportunity for adequate oxygen replenishment through diffusion.

"Devices offering these alternative protocols are already on the market, but without thorough clinical validation," he added. "To increase the likelihood of successful CXL for corneal ectasias, we currently

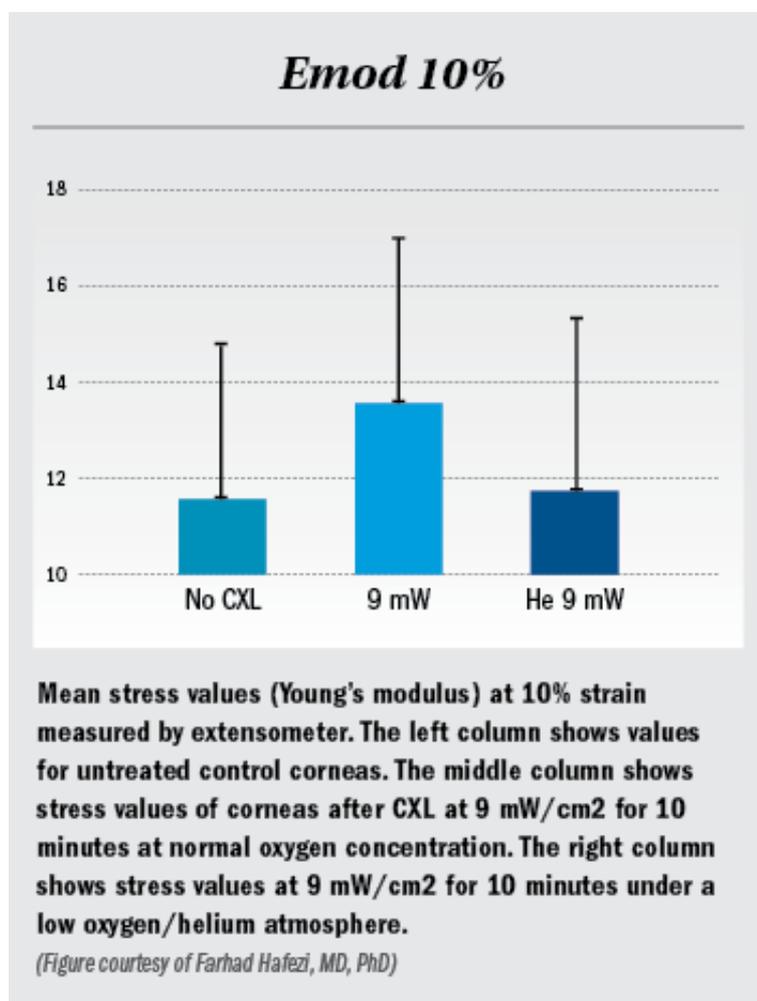
recommend using epithelium-off CXL (Dresden protocol) at 3 mW/cm<sup>2</sup> for 30 minutes or 9 mW/cm<sup>2</sup> for 10 minutes. In particular, the 3 mW/cm<sup>2</sup> protocol is well established and has been shown to provide good results over the long term.”

## Examining further

To investigate the oxygen-dependency of the biomechanical effect of CXL, Dr. Hafezi and colleagues first conducted a study where porcine corneas were treated with the epithelium-off and at a fluence of  $9 \text{ mW/cm}^2$  in normal (21%) and low-oxygen (<0.1%) atmospheric conditions.<sup>1</sup> Determinations of Young's modulus showed a significant increase in corneal stiffness in eyes treated in the normal atmosphere, but there was no difference comparing eyes treated in the low-oxygen atmosphere and untreated controls (Figure).

A second study investigated the hypothesis that high-intensity protocols provide the same biomechanical benefit as long as total fluence delivered remains the same.<sup>2</sup> A total of 200 porcine eyes were allocated into 4 groups, all being exposed to riboflavin. Three groups were irradiated with UVA at varying fluences and durations ( $3 \text{ mW/cm}^2$  for 30 minutes,  $9 \text{ mW/cm}^2$  for 10 minutes, and  $18 \text{ mW/cm}^2$  for 5 minutes), and the fourth group received no UVA treatment as a control.

The results showed the corneal stiffening effect significantly decreased as the UVA intensity increased.



"CXL approaches using higher intensities and shorter irradiation times assume—based on the Bunsen-Roscoe reciprocity law—that the biological effect from the photochemical reaction would be constant using any combination of fluence and time that results in the same total energy delivery as that achieved in the standard Dresden protocol ( $3 \text{ mW/cm}^2$  for 30 minutes)," Dr. Hafezi said. "However, as oxygen is a limiting factor for the biomechanical effect of CXL, then it would appear that the treatment needs to be done slowly, as with the original Dresden protocol, in order to give the tissue time to re-oxygenate."

"In our study, the increase in stiffness in eyes treated at  $9 \text{ mW/cm}^2$  for 10 minutes and  $18 \text{ mW/cm}^2$  for 5 minutes was significantly greater than in the controls," he continued. "However, the question remains whether the treatment effect using this approach is sufficient to provide a long-term benefit for preventing keratoconus progression. Only limited clinical data have been reported for eyes treated with higher fluences of 9 or  $18 \text{ mW/cm}^2$ , including our own report,<sup>3</sup> and

they do not show much benefit."

### **Some disappointing results?**

Dr. Hafezi noted that transepithelial CXL has also been associated with disappointing results.

In an experimental study, Spoerl and colleagues reported no difference in biomechanical stiffness comparing eyes treated with transepithelial CXL and untreated controls.<sup>4</sup> Caporossi et al.<sup>5</sup> are reporting failure of keratometric stabilization in keratoconic eyes followed for 2 years after transepithelial CXL, and a multicenter study on transepithelial CXL—currently being conducted in Geneva, London, and Dresden—will report results in summer 2014.

“Using the Dresden protocol, the epi-off CXL failure rate is no more than 5%,” Dr. Hafezi said.

“We think the explanation for the unsatisfactory outcomes with transepithelial CXL may be related to oxygen availability.”

## References

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