

Thermographic analysis of the corneal surface in epi-on and epi-off corneal crosslinking for keratoconus

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Abstract

Purpose: To analyse the temperature of the corneal surface in keratoconus during corneal customized crosslinking (CXL) with a preserved epithelium (epi-on) under oxygen flow, and epi-off CXL in room air, and to assess the effect of pre-heating the oxygen.

Methods: This masked, intra-individual comparing randomized study included 14 participants with bilateral progressive keratoconus treated with bilateral CXL: one eye with epi-on CXL under a flow of 2.5 L/min oxygen; the fellow eye with epi-off CXL in room air. In a second setting involving 12 healthy participants, room-tempered oxygen was flushed over one eye and oxygen pre-heated to 37°C over the fellow eye. The corneal surface temperature was assessed with infrared photography.

Results: A reduction in corneal surface temperature was seen from the pre-treatment application of topical riboflavin in the epi-off group ($-1.1 \pm 1.0^\circ\text{C}$, $p < 0.001$). The temperature increased during the first half of the CXL treatment in both groups ($+0.7 \pm 1.2^\circ\text{C}$, $p = 0.041$ for epi-on; $+0.7 \pm 0.9^\circ\text{C}$, $p = 0.023$ for epi-off CXL, respectively). In epi-on CXL an overall temperature increase was seen during the treatment ($+0.8 \pm 1.2^\circ\text{C}$, $p = 0.016$). In the second setting, pre-heating the oxygen rendered a surface temperature increase of $+1.8 \pm 0.2^\circ\text{C}$ ($p < 0.001$).

Conclusion: In epi-off CXL, the application of topical room-tempered riboflavin decreases the corneal surface temperature, likely due to increased evaporation. A slight temperature increase is seen during CXL with both epi-on and epi-off CXL, albeit far below the corneal safety limit. The corneal temperature can, however, be increased by applying pre-heated oxygen, a possible approach to modify or augment the treatment effect in CXL.

KEYWORDS

crosslinking, keratoconus, oxygen, temperature

1 | INTRODUCTION

Corneal crosslinking (CXL) with riboflavin and ultra-violet-A (UV-A) light is used for biomechanical stabilization of the cornea in keratoconus (KC) and similar conditions. A single treatment often suffices to halt the progression of KC permanently (Price et al., 2018; Seifert et al., 2022). Traditionally, CXL involves a central 7 mm corneal de-epithelization (epi-off), application of topical riboflavin and illumination of UV-A light at 3 mW/cm^2 , resulting in a total treatment dose

of 5.4 J/cm^2 (Wollensak, Spoerl, et al., 2003; Wollensak, Spoerl, et al., 2003). CXL creates cross links through two different biomechanical reactions, of which the type 2 reaction is oxygen-dependent and works via generation of reactive oxygen species (McCall et al., 2010). Complications such as keratitis and corneal scarring, albeit rare, have been reported in epi-off CXL (Ng et al., 2021). For this reason, and to limit the initial ocular discomfort after epi-off CXL, treatment regimens without mechanical epithelium debridement (epi-on CXL) have been developed (Shalchi et al., 2015). As an

intact corneal epithelium limits the oxygen bioavailability in the corneal stroma, epi-on protocols with oxygen flushed over the ocular surface have been developed to increase the stromal oxygen bioavailability (Mazzotta et al., 2020).

The reaction rate of many chemical reactions, including those in CXL, increases with increasing temperature (Kamaev et al., 2012). Since the cornea lacks blood vessels and its surface is in direct contact with the ambient air, the corneal temperature is highly affected by the ambient temperature (Matteoli et al., 2020). In CXL, the UV light is absorbed by the riboflavin and the corneal tissue, and the absorbed light energy may be converted to heat. Since the CXL reaction between UV light and riboflavin itself is endothermic, it requires external heat from the surroundings. The oxygen and riboflavin diffusion into the cornea are both temperature dependent, with 1.5 times higher diffusion rates of both substances at 37°C, compared to 25°C, and thus, higher temperatures can increase the reaction velocity (Kamaev et al., 2012). Although this complex interaction of factors is not fully understood, it is evident that corneal temperature can have effects on the photochemical reactions involved in CXL.

Infrared (IR) thermographic analysis is a non-invasive method to measure infrared light emission, and thereby the temperature of a surface. It does not require touching the surface to be measured and is safe, which makes it suitable to measure the corneal surface temperature in vivo (Acharya et al., 2009; Matteoli et al., 2020).

In healthy individuals, the temperature of the central cornea is lower than the body temperature, on the average between 32 and 36°C (Acharya et al., 2009). Results from studies on rodent corneas have shown that an outer temperature of 45°C for <15 min is well tolerated, while a temperature of 50°C for <10 s causes stromal damage (Corvi et al., 2006). Previous studies have shown that the corneal temperature during conventional or accelerated CXL (3 mW/cm², 5.4 J/cm²; 18–30 mW/cm², 5.4–7.2 J/cm², respectively) does not exceed 40°C, which is considered to be the cornea's thermographic limit (De Ortueta et al., 2019; Mencucci et al., 2005, 2007, 2015).

As mentioned, oxygen augments the CXL effect, and oxygen diffuses more rapidly into the cornea at higher temperatures, but on the other hand, flushing room-tempered oxygen over the ocular surface might have a cooling effect, directly or from increased evaporation, which could slow the crosslinking reaction. This study aimed to analyse the temperature of the corneal surface during epi-on CXL under oxygen flow and epi-off CXL in room air and—in a second setting—to assess the effect on the corneal surface temperature from the application of 2.5 L/min oxygen pre-heated to 37°C.

2 | METHODS

2.1 | Study design

The first setting of this single-masked, intra-individually comparing study involved participants with bilateral progressive keratoconus requiring treatment. All

participants were treated in both eyes at the same visit; one eye with epi-on CXL employing 2.5 L/min room-tempered oxygen flushed over the ocular surface, the other eye with epi-off CXL in room air. Which eye received which treatment was randomized and was masked to the participants.

A second setting involving healthy volunteers was performed under similar conditions but without UV light and with riboflavin substituted for lubricant eye drops. Oxygen was flowed over the ocular surface at 2.5 L/min, room-tempered in one eye and pre-heated to 37°C in the fellow eye. Which eye received which oxygen temperature was randomized.

Both settings included male and female participants aged 18–35 years. Individuals with past or present disease, allergy, surgery, or any medication with ocular effects that could affect the procedure's outcome were not included. In addition, the use of contact lenses or eye drops within 24 h of the intervention, or a clinical state of dry eyes were used as exclusion criteria. A total of 14+12 individuals were included (28+24 eyes). Written informed consent was obtained from each participant prior to inclusion according to the tenets of the Declaration of Helsinki, and ethical permission was obtained from the Swedish Ethical Review Authority (diary numbers: 2019-00298 and 2021-01697).

2.2 | CXL treatment, first setting

After 3 drops of Tetracaine 1% in the eye to be treated and application of a lid speculum and an oxygen mask (Glaukos, Corp.), the 7-mm central corneal epithelium was debrided using a foreign body instrument in the epi-off eye; in the epi-on eye the corneal mucin film was gently removed with a cellulose sponge soaked in riboflavin (ParaCel Part 1; 0.25% riboflavin solution; Glaukos, Corp.). Room-tempered ParaCel Part 1 was applied every 90 s during 4 min, followed by ParaCel Part 2 (0.22% Riboflavin solution, Glaukos, Corp.) at the same rate for 6 min. The oxygen, 2.5 L/min, was started at 8:00 during the riboflavin application in the epi-on eye. Pulsed UV-A illumination was applied according to a pre-specified, customized protocol for 16 min and 40 s (Nordstrom et al., 2017). Infrared images of the cornea were taken in triplicate with a IR camera FLIR C2 (Teledyne FLIR LLC., Wilsonville, OR, USA) at four time points during the treatment: before riboflavin eye-drops, at 00:00 (baseline, just before UV illumination), at 08:20 and at 16:40. The oxygen concentration over the cornea was measured after finishing the riboflavin application and after the illumination at 16:40, using a Model 901 Headspace Oxygen Analyser (Quantek, Inc.) to certify an oxygen concentration above 90%.

2.3 | Thermographic measurements, second setting

One eye was randomized to receive 2.5 L/min room-tempered oxygen; the fellow eye received 2.5 L/min oxygen pre-heated to 37°C. Local anaesthesia, a lid speculum

and an oxygen mask were applied as detailed above. Oxygen was flowed at 2.5 L/min through a 3-mm plastic hose into a humidifier bottle with sterile water, from which an insulated 3-mm plastic hose led the oxygen to the applicator mask. Room-tempered moisturizing drops (Systane Ultra, Alcon Inc., Geneva, Switzerland) were applied every 90 s for 10 min to mimic the application of topical riboflavin used in CXL treatment. After 10 min, the oxygen was turned on and continually flowed through the mask, always starting with the eye randomized to room-tempered oxygen to avoid residual heat in the system.

Infrared images in triplicate were taken at baseline (00:00) and 12 subsequent time points: 8:00; 11:00; 13:00; 15:00; 17:00; 19:00; 21:00; 23:00; 25:00; 26:40; 27:40 and 28:40. Oxygen was turned off after 26 min and 40 s. Thus, the oxygen application time was 16:40, as in the CXL protocol above.

For the eye randomized to pre-heated oxygen, the humidifier bottle was placed in a water bath at 52°C, and the procedure was repeated. The temperature 52°C was chosen to get a temperature of 37°C on the oxygen entering the mask. The oxygen concentration over the cornea was measured as detailed above, and the temperature inside the oxygen mask was measured after 3:00, 9:00 and 15:00 of oxygen application, using a Model 5110 type K digital thermometer (PeakTech, Ahrensburg, Germany). A predetermined safety limit of 38°C was set for the latter readings with termination of the procedure should any measurement exceed this value.

2.4 | Thermographic image analysis

The images were analysed using the FLIR Thermal Studio software (Teledyne FLIR LLC., Wilsonville, OR, USA): a circular area limited by the limbus was plotted, and the software calculated an average temperature for the marked area. The analysis was repeated for each of the 3 images taken at each measurement time point, and the mean values of the 3 measurements were used in subsequent statistical analyses. The noise equivalent temperature difference (NETD) of the camera is <70 mK and the accuracy specification 2% of the temperature reading at 30°C.

2.5 | Statistical analysis

A repeated measures ANOVA with Mauchly's test for sphericity was performed to assess changes in temperature over time, and a pairwise *t*-test was used for comparison between the two eyes at individual time points.

A power analysis showed that a temperature change of 0.5°C could be detected with 90% certainty and an alpha value set to 0.05 with 12 eyes in each group, using pairwise analysis and assuming a standard deviation of 0.47°C (Matteoli et al., 2020).

IBM SPSS statistics and R were used for statistical analyses. A *p*-value of <0.05 was considered statistically significant. Data are presented as means ± standard deviations unless stated otherwise.

3 | RESULTS

3.1 | Participant data

The first setting involved 14 study patients treated bilaterally for keratoconus (28 eyes), 3 females and 11 males, age 26 ± 5 years, range 18–35 years. Twelve healthy individuals (24 eyes), 3 females and 9 males, were included in the second setting, age 28 ± 4 years, range 23–33 years. The participants in the two settings did not differ in age or gender (*p*=n.s.).

3.2 | Thermographic data

3.2.1 | First setting

The corneal surface temperature at baseline was 34.1 ± 1.6°C and 34.2 ± 1.6°C for epi-on and epi-off eyes, respectively (*p*=0.89). After riboflavin application, the temperature had dropped to 33.0 ± 1.5°C in the epi-off group (*p*<0.01) but remained at 33.8 ± 1.2°C in epi-on eyes (*p*=0.29). A repeated measures ANOVA revealed that the corneal temperature changes over time were significant in both groups (*F*=3.65; *p*=0.021 and *F*=4.25; *p*=0.011 for epi-on and epi-off CXL, respectively). The temperatures were increased compared to baseline in epi-on eyes at all subsequent time points (+0.8 ± 1.1°C at 00:00, *p*=0.016; +0.9 ± 1.5°C at 08:20, *p*=0.046 and +1.1 ± 1.6°C at 16:40, *p*=0.018; Figure 1), tested with repeated measures ANOVA and post hoc pairwise *t*-test.

3.2.2 | Second setting

The corneal surface temperature at baseline, before application of oxygen, was 35.5 ± 0.7°C. A repeated measures ANOVA revealed that the corneal temperature changed over time in both groups (*F*=17.86; *p*<0.001 and *F*=71.86; *p*<0.001 for room-tempered and pre-heated oxygen, respectively). Repeated measures ANOVA showed higher temperature increase in corneas subjected to pre-heated oxygen from timepoint 3, after 3:00 of oxygen application, onwards (Table 1; Figure 2). The difference in temperature between the two groups increased gradually over time, and the corneas subjected to pre-heated oxygen had a temperature increase of +1.8 ± 0.6°C at the end of the oxygen application, at which time point the corneal surface temperatures ranged from 36.8 to 38.3°C in this group. With room-tempered oxygen the initial temperature increase levelled off after 5:00 of oxygen application and remained largely stable after this time point (Figure 2).

3.2.3 | Other measurements

In the first setting the room temperature during the treatments was 21.9 ± 1.3°C, whereas in the second setting the room temperature was 22.9 ± 0.6°C. A gradual increase in the temperature inside the oxygen mask was seen in the second setting in the eye treated with

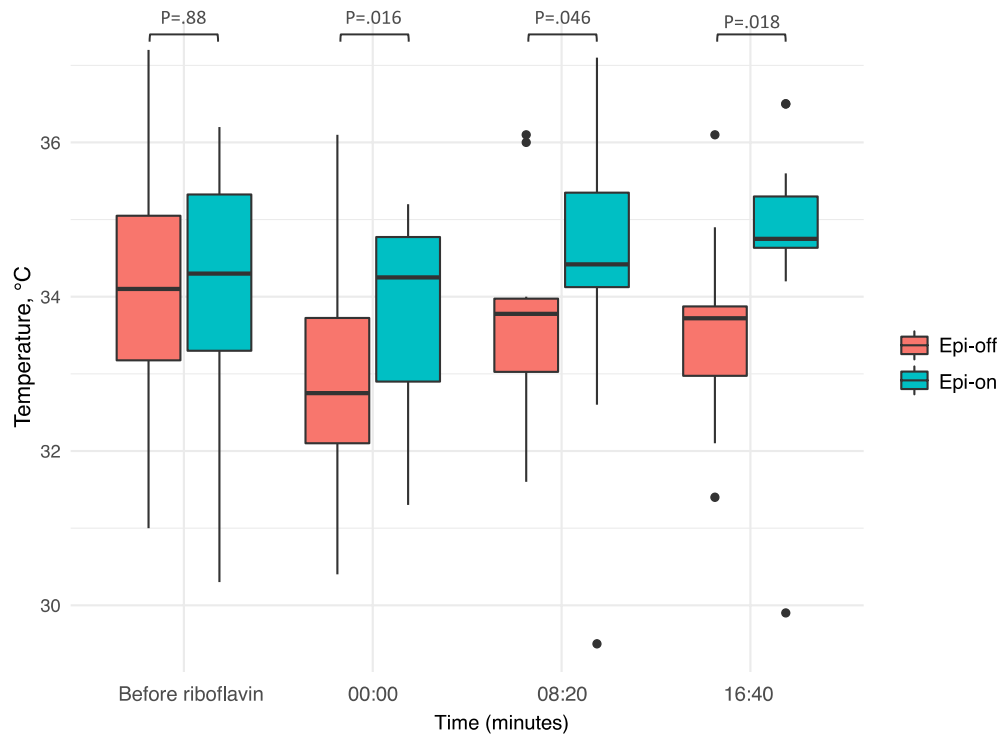


FIGURE 1 Box-plot (means, standard deviations and ranges, °C) of corneal surface temperature in epi-on CXL for keratoconus with 2.5 L/min supplemental oxygen and epi-off CXL in room air. 00:00=baseline, just before UV illumination; 08:20=middle of CXL treatment; 16:40=end of CXL treatment.

TABLE 1 Corneal surface temperature at different time points with room-tempered and pre-heated oxygen, respectively.

Time (min)	Pre-heated O ₂ , °C, means±SD	Room-tempered O ₂ , °C, means±SD	p-value
00:00	35.5±0.7		—
08:00	35.3±0.9	35.0±1.2	0.29
10:00	(O ₂ turned on)		
11:00	35.9±1.0	35.6±0.8	0.23
13:00	36.5±0.6	36.1±0.8	0.04
15:00	36.8±0.6	36.2±0.8	0.01
17:00	37.0±0.6	36.2±0.7	<0.001
19:00	37.2±0.5	36.2±0.7	<0.001
21:00	37.3±0.5	36.2±0.7	<0.001
23:00	37.4±0.4	36.3±0.6	<0.001
25:00	37.5±0.5	36.1±0.8	<0.001
26:40	37.5±0.4	36.1±0.7	<0.001
	(O ₂ turned off)		
27:40	37.4±0.5	36.2±0.7	<0.001
28:40	36.6±0.6	35.8±0.8	0.004

Note: Corneal surface temperature, °C, means±standard deviations, in healthy volunteers with 2.5 L/min of oxygen flushed over the cornea, pre-heated to 37°C or room-tempered.

pre-heated oxygen, from $31.8 \pm 0.6^\circ\text{C}$ after 3:00 of oxygen application to and $35.9 \pm 0.6^\circ\text{C}$ after 15:00 of oxygen application. With room-tempered oxygen the corresponding temperatures were $27.1 \pm 1.0^\circ\text{C}$ and $27.5 \pm 1.0^\circ\text{C}$, respectively.

In the first setting, the oxygen concentration in the oxygen mask was $95.3\% \pm 1.2\%$ before treatment and $95.3\% \pm 1.4\%$ after treatment. The corresponding numbers

for the second setting was $94.1\% \pm 1.7\% / 95.0\% \pm 1.7\%$ for room-tempered oxygen and $94.0\% \pm 3.2\% / 93.6\% \pm 1.8\%$ for pre-heated oxygen, respectively.

4 | DISCUSSION

Although epi-on CXL can reduce the early post-treatment ocular discomfort and possibly decrease the risk for post-treatment corneal complications, oxygen has been identified as a rate-limiting factor in epi-on CXL due to a reduced oxygen concentration in the corneal stroma with epi-on protocols (Fredriksson et al., 2020; Richoz et al., 2013). Epi-on CXL performed in a high-oxygen environment has therefore been studied in recent years, with the aim to augment the treatment effect in epi-on CXL (Mazzotta et al., 2020; Seiler et al., 2021; Wang et al., 2020). Flushing 2.5 L/min room-tempered oxygen over the cornea might, however, cool the cornea and reduce the CXL reaction rate. No previous studies have mapped the cornea's thermographic profile during CXL with supplemental oxygen, and in the present study, we wanted to analyse the thermographic profile of the corneal surface in epi-on CXL with supplemental oxygen, compared to an epi-off protocol in room air.

Applying a simplified form of the Arrhenius equation, $k_2 = k_1 \times (Q_{10})^{(\Delta T/10)}$, and the increase in oxygen consumption by a factor 1.5 from a 10°C temperature increase in an ex vivo porcine CXL model (Kamaev et al., 2012), an increase in corneal temperature of 1.8°C , as seen with the pre-heated oxygen in the present study, would increase the CXL reaction velocity with about 8%. Such an effect is not negligible, but the CXL reaction is complex, and it may be that

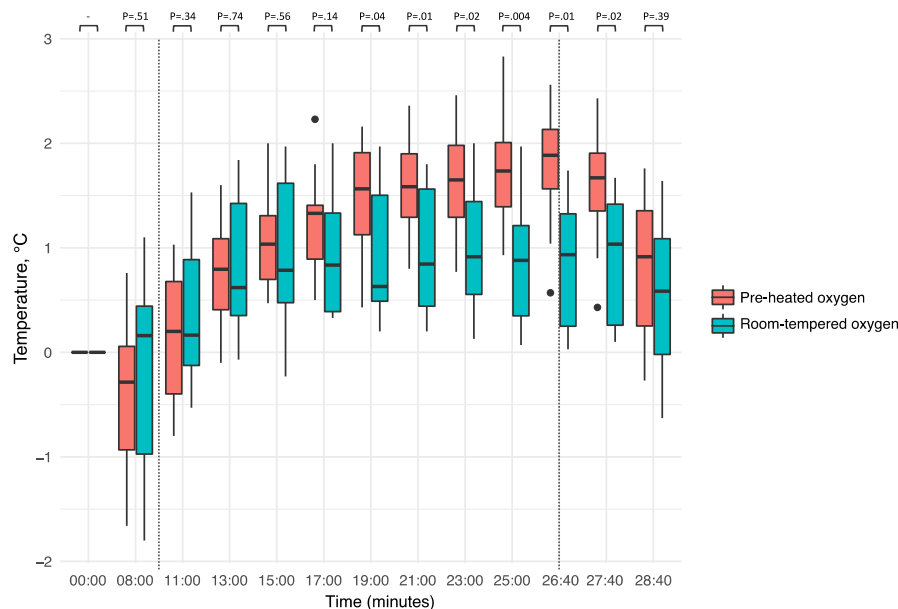


FIGURE 2 Box-plot (means, standard deviations and ranges, °C) of corneal surface temperature changes in healthy volunteers with 2.5 L/min of oxygen flushed over the cornea, pre-heated to 37°C (red) or room-tempered (green). Oxygen was turned on at 10:00 and turned off at 26:40 (dotted vertical lines).

oxygen consumption is not an optimal measure of the CXL reactions, since these reactions are only in part oxygen-dependent (Kamaev et al., 2012; McCall et al., 2010). Taking the Type 1 reactions into account as well, the effect from a temperature increase may be larger, but this remains to be elucidated.

The sample size of the present study was relatively small, but a power analysis showed that this sample size would suffice with the present study design. The initial temperature decrease seen during riboflavin application in the epi-off protocol is interpreted as an increased evaporation due to the absent corneal epithelium. Somewhat surprisingly, the temperature gradually increased during the UV illumination in the epi-on, but not in the epi-off protocol. This can likely also be explained by a continually higher evaporation in epi-off CXL. Another theoretical possibility could be that the treatment effect with epi-off CXL is significantly larger and that the endothermic CXL thereby reduces the corneal temperature more in epi-off CXL. This, however, seems unlikely in the perspective of results from recent studies, showing that supplementary oxygen allows for a potentially more efficient CXL (Seiler et al., 2021), and that the treatment effect is good also with epi-on CXL in high oxygen (Mazzotta et al., 2020). Furthermore, as mentioned, the corneal temperature in epi-off CXL decreases already before the UV illumination.

The amount of IR radiation emitted from an object depends on its temperature, but also on its emissivity, defined by how much radiation an object emits compared to a perfect blackbody—an object that absorbs all incoming radiation and emits the same amount of radiation. A blackbody has an emissivity of 1, while human tissues have an emissivity of 0.97–0.95 (Church et al., 2014). Given these numbers, the difference in temperature registered between the two treatments is not likely to be accounted for by differences in their surface properties. Our results indicate that a higher corneal temperature in

epi-on CXL, likely due to less evaporation, might add to the treatment effect with such protocols.

Notably, the corneal baseline temperature was higher in the second setting than in the first setting, but the room temperature was also higher. This indicates that the ambient temperature affected the corneal temperature in our investigation, a phenomenon well-known from previous studies (Mazzotta et al., 2020; Micheletti et al., 2022; Tan et al., 2009). Thus, the room temperature can affect the corneal temperature, and thereby potentially affect the CXL treatment effect. Too large deviations in room temperature should likely be avoided in CXL facilities, to optimize the reproducibility of the treatment results.

Previous studies have indicated that the initial riboflavin application before an epi-off CXL treatment lowers the corneal temperature, and the temperature does not return to baseline levels during the subsequent treatment (Mencucci et al., 2007, 2015). It appears the UV light itself does not increase the corneal temperature significantly. In the present study, with a treatment time of 16:40, the temperatures consistently remained well below the safety limit of the cornea for both CXL protocols. The average temperature increase in epi-on CXL was 0.6°C during the treatment. We here demonstrate that pre-heating the oxygen is a way to further increase the corneal temperature, in the present setting by 1.8°C on the average and that maintaining a constant flow of pre-heated oxygen over the cornea is likely to continually raise the corneal surface temperature during the entire time course of a CXL treatment. Whether this can be a way to augment the treatment effect remains to be seen, but given our results, pre-heating the oxygen is feasible also from a safety perspective.

We conclude that the corneal temperature is slightly higher in high-oxygen epi-on CXL, albeit well below the safety limit of the cornea, and that pre-heating of the supplemental oxygen can be a way to further increase the

corneal temperature. Modifying the corneal temperature can become a future tool in optimizing the treatment parameters in CXL.

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