Evolution of the Critical Oxygen Tension

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Goodlaw [1948] previously surmised that the cornea required an anterior supply of oxygen to maintain its physiology and transparency, but did not quantify it. It is now well known that the cornea, like all human tissues, requires oxygen for normal metabolic function. The cornea being avascular, oxygen reaches this tissue primarily from the atmosphere and secondarily from the anterior chamber (aqueous humor) under open eye conditions. When the eye is closed (sleep), oxygen is provided both from exposure to the tarsal palpebral conjunctiva as well as from the aqueous humor [Fatt 1968, Freeman 1972]. With a reduced oxygen supply, the cornea is susceptible to hypoxic complications: corneal swelling (and loss of transparency), corneal stromal acidosis, epithelial punctate staining, limbal hyperemia, and endothelial polymegathism. Therefore, the minimum oxygen tension that allows "normal" oxygen consumption as a direct index of corneal oxygen metabolism, is a critical clinical parameter to ascertain.

To this end, Polse & Mandell at the University of California, Berkeley, School of Optometry, published their research: "Critical Oxygen Tension at the Corneal Surface" in *Archives of Ophthalmology* in 1970. This landmark study proposed that human corneas would swell if exposed to anterior oxygen tensions below 11-19 mmHg, while "normal" corneal thickness would be maintained as long as anterior corneal oxygen tension remained above this threshold. The implication was that there was a specific, well-defined or "fixed" oxygen value in humans below which corneal metabolism would begin to suffer (leading to corneal swelling among other complications) if only we could properly identify it.

Over the following several decades many investigators spent much time, effort, thought, and money in an effort to definitively quantitate that "critical" oxygen value (if in mmHg or tension, it was called the "COT"). Efron & Brennan [1987] published a meta-analysis documenting and discussing many potential values, ranging from the original Polse/Mandell 11-19 mmHg metric through Brennan et al's [1987] finding of 137 mmHg for swelling, to 100 mmHg [Hamano et al 1983] to maintain epithelial mitosis. In a meta-analysis, Efron & Brennan speculated that the real figure might even be the sea-level room air oxygen tension of 21% or 155 mmHg.

Quantification of the COT is important clinically as contact lens materials continue to evolve. Contact lens designers (material chemists, engineers etc) found it helpful over the years to have a precise and definitive oxygen goal. Once this goal is achieved in a lens design they then focus on other aspects such as lubricity of surfaces, anti-soiling, and anti-microbial properties as well as optics (including enhancing astigmatic and presbyopic corrections). Currently, the increasing

use of modern-day scleral lenses and associated hypoxic complications has again highlighted the importance of understanding the COT.

Recent scientific work has led us to consider, however, that the COT cannot be a precise value, either in individual humans or in human beings in general – and we therefore propose that the COT is more likely a range around 80-100 mmHg for normal human corneas. There will undoubtedly be variability from individual-to-individual and from time-to-time in the same individual, with additional methodology variability, and perhaps under different physiological conditions, as well. Corneas that are not normal, such as those diagnosed with Fuch's corneal dystrophy, or secondary to corneal transplants etc, may also behave differently.

This should come as no surprise. Polse & Mandell [1970] originally reported a range in COT. Efron & Brennan [1987] showed how varied were the results of previous research. Moreover, both Larke et al [1981] and Takatori et al [2012] showed that both human anterior corneal oxygen flux and consumption varied widely from individual-to-individual. We suspect COT may also vary from time-to-time within the same individual – as does "normal" corneal thickness [Doughty & Zaman 2000].

Moreover, consider: the measured COT is most likely a reflection of several physiological changes, primarily increased anaerobic metabolism (already considerable at "normally" perhaps 85% in the human cornea [Riley 1969; Maurice & Riley 1970; Freeman 1972]) and the secondary increase in lactate production when the cornea's cells (primarily basal epithelium) become more hypoxic [Klyce 1981]. But this is a very complex topic. Both Bonanno & Polse [1987a, 1987b] and Giasson & Bonnano [1994, 1995] observed that soft hydrogel contact lens hypoxia induces stromal acidosis. Harvitt & Bonanno [1999] found that such acidosis increases corneal oxygen consumption up to 1.8 times that of normal pH through activation of pH-regulatory mechanisms. Accordingly, increasing oxygen consumption increases energy demand to produce additional ATP molecules via oxidative phosphorylation. Alternately, oxygen consumption declines with glucose concentration decrease when oxygen partial pressure is low. Frahm et al [2003] explained that only excess glucose is independent of glucose concentration during respiration. Compañ et al [2016] recently observed that the Monod kinetics model for oxygen consumption reaction with glucose describes a maximum as a transition from aerobic to anaerobic metabolism. Oxygen consumption initially increases as oxygen tension decreases, depending on the intensity of the change in pressure (with variation in pH). Oxygen

consumption then decreases, however, with greater reductions in pressure, possibly due to changes in the concentration of glucose related to anaerobic respiration.

Weissman and Ye [2006] plotted several models of calculated contact lens related tear layer oxygen tension vs contact lens oxygen transmissibility (Dk/t) (without considering tear exchange such as would be the case for soft contact lenses) for both open and closed eye situations. Several of the earlier proposed COT values were plotted on the same graph. Both sets of curves begin to asymptote at about 60-100 mmHg. There is no evidence of alignment, however, with any of the previously proposed fixed COT values.

Compañ et al [2017] used Monad equations, and the most current boundary conditions, to calculate the corneal stroma location where oxygen tension is minimal with different anterior corneal surface oxygen tensions. Maximum corneal hypoxic stress deepens, advances from near the endothelium towards the epithelium, and broadens, as corneal surface oxygen tension declines from 155 to 20 mmHg. Both calculated oxygen consumption and flux in the corneal epithelium and stroma are supported down to a corneal surface oxygen tension of about 60-100 mmHg, where changes are seen in the graphs. But again, there is no clear boundary; rather a slow shift in the curves is seen, consistent with the concept that the COT is a reflection of physiological changes such as described above.

Of interest, corneal neovascularization (probably in response to a hypoxic induced change in cytokine like VEGF release, not lactate buildup) was also found recently to have a “critical” oxygen value about 80 mmHg, and also with a large variability [Yeung et al 2017].

Finally we need to mention another source of variability. As noted above, Polse & Mandell [1970] originally suggested a COT around 2% oxygen or 11-19 mmHg. This brings up the question of reporting in percent oxygen or mmHg oxygen tension.

Oxygen is responsible for 21% of atmospheric pressure on this planet: 21% of a normal barometric pressure of 760 mmHg. This suggests each 1% of pressure is worth 7.6 mmHg - but this quantification is only true at sea-level, so sea-level oxygen tension is about 160 mmHg. When considering elevations above sea-level, however, oxygen percent maintains at 21 but barometric pressure declines. At an elevation of 10,000 feet (3,000 meters), for example, barometric pressure declines to about 520 mmHg and so oxygen partial pressure declines to

about 110 mmHg. When authors report COT values in oxygen percentage, the reader must assume, unless otherwise stated, that the evaluation is set at sea-level and will be different at other elevations.

In summary, low Dk/t contact lenses produce low oxygen tension in the post-lens tear film and then secondarily depress corneal oxygen consumption. We suggest that the COT in the anterior corneal surface tears (whether due to contact lens wear or otherwise) should no longer be considered a hard or fixed value, but thought of as a range for normal human corneas - perhaps about 80-100 mmHg. This is proposed both for clinicians considering care of their patients and for the contact lens industry as it develops new contact lens materials and designs.

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