Visual Psychophysics and Physiological Optics

Contrast Rivalry Paradigm Reveals Suppression of Monocular Input in Keratoconus

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Purpose. Keratoconus results in image quality loss in one or both eyes due to increased corneal distortion. This study quantified the depth of monocular suppression in keratoconus due to this image quality loss using a binocular contrast rivalry paradigm.

Methods. Contrast rivalry was induced in 50 keratoconic cases (11–31 years) and 12 age-matched controls by dichoptically viewing orthogonal Gabor patches of 5 cycles per degree (cpd) and 1.5 cpd spatial frequency for 120 seconds with their best-corrected spectacles and rigid gas permeable (RGP) contact lenses. The dwell time on each eye's percept was determined at baseline (100% contrast bilaterally) and at varying contrast levels (80–2.5%) in the stronger eye of keratoconus or dominant eye of controls. The contrast reduction needed in the stronger eye to balance dwell times on both eyes was considered a measure of suppression depth.

Results. At baseline with 5 cpd stimuli and spectacle correction, the rivalry switches were less frequent and biased toward the stronger eye of cases, all relative to controls ($P < 0.001$). The contrast balance point of cases (20.51% [10.7–61%]) was lower than the controls (99.80% [98.6–100%]; $P < 0.001$) and strongly associated with the overall and interocular difference in disease severity ($r = 0.83$, $P < 0.001$). The suppression depth reduced for 1.5 cpd (70.8% [21.7–94%]), relative to 5 cpd stimulus ($P < 0.001$) and with contact lenses (80.1% [49.5–91.7%]), relative to spectacles ($P < 0.001$).

Conclusions. The eye with lesser disease severity dominates binocular viewing in keratoconus. The suppression depth of the poorer eye depends on the extent of bilateral disease severity, optical correction modality, and the target spatial frequency.

Keywords: asymmetry, binocular rivalry, contrast sensitivity, D-index, keratoconus, optical quality, rigid gas permeable (RGP) contact lens, spatial frequency, wavefront aberrations

Deterioration of visual functions is well-documented in keratoconus (e.g. high contrast visual acuity[1]) and these are attributed to the underlying loss of the eye's optical quality arising from the increased corneal distortions.[1] This study is concerned with the status of binocular visual functions in bilateral and unilateral keratoconus. Stereoacuity, a token measure of binocularity, has been shown recently to be absent or severely impaired in patients with keratoconus corrected with spectacles and it may be partially recovered with rigid contact lens wear, vis-a-vis age-matched controls.[2–4] In general, binocularity is critically dependent on how efficiently information from the two eyes is processed by the visual system.[5] Suppression of input from one eye—typically the weaker of the two eyes—is one scenario in which the monocular inputs are not processed equally, leading to compromised binocularity.[6] Suppression of the eye with poorer image quality has been reported to occur iatrogenically following a treatment in only one eye (e.g. suppression of the operated eye in unilateral corneal transplants[7]) or when interocular differences in image quality are purposely induced for optimizing image clarity over a range of viewing distances (e.g. temporary suppression of blurred input in monovision correction for presbyopia[8]). In all these conditions, stereoacuity is severely compromised, relative to controls.[2–4,7,8] Following the same logic, might the eye with poorer image quality in keratoconus also be suppressed and could this contribute to the observed loss of stereoacuity in this disease condition? If so, would the depth of suppression scale with the magnitude of disease severity, with the refractive error correction modality, and with the spatial content of the object viewed?

This study systematically quantified the depth of suppression of monocular input in patients with keratoconus of different severities in the two eyes using a contrast rivalry

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paradigm.[9,10] Contrast rivalry is the alteration of the cyclopean percept between the two monocular inputs, when their image features are grossly dissimilar (e.g. orthogonally oriented gratings presented dichoptically).[11] The experience of perceptual bi-stability in the cyclopean percept is strongest, with nearly equal dwell time on each monocular input, when the two images are of equal salience (luminance contrast, in this case[12,13]). The cyclopean percept is increasing biased toward the more salient input with interocular differences in contrast, manifesting as increased dwell time on the more salient input, and lower number of perceptual switches between the two inputs within a given time frame.[12,13] Contrast rivalry has been used in the past to test for ocular dominance in healthy participants[10,14–16] and those with cataract[9] and to measure suppression in anisometropic and strabismic amblyopia.[17]

The present study tested five hypotheses related to suppression in keratoconus: (1) the contrast rivalry paradigm will reveal the presence of suppression in keratoconus. (2) The depth of suppression of the weaker eye will scale with keratoconus severity. (3) The weaker eye's suppression is deeper for targets with fine details than for coarse details because the latter is less affected by optical blur than the former. (4) Suppression of the weaker eye will be deeper when viewing through spectacles than rigid gas permeable (RGP) contact lenses, due to improved optical quality in the latter than the former. (5) The quantum of contrast loss in the retinal image due to distorted optics completely explains the depth of suppression of the weaker eye in keratoconus.

Methods

Fifty cases (age range = 11–31 years, 37 boys/men) with different severities of keratoconus and 12 age-matched controls (15–26 years, 6 boys/men) were recruited from among patients, students. and staff of the L V Prasad Eye Institute (LVPEI), Hyderabad, India. The study adhered to the tenets of the Declaration of Helsinki and it was approved by the Institutional Review Board of the LVPEI. All participants signed a written informed consent form. For participants < 18 years of age, assent was obtained wherein the consent form was signed by a parent or local guardian. The diagnosis of keratoconus was made by an experienced clinician on the basis of clinical (scissors reflex during retinoscopy, prominent corneal nerves, Vogt's striae, and corneal ectasia and thinning) and topographic findings (see below for details).[1] Cases with apical corneal scarring, superficial punctate keratitis, manifest strabismus, oculomotor deficiency of any form, and any other ocular comorbidity were excluded. Refractive errors of cases were corrected by an experienced optometrist using standard refraction techniques. Among the cases, some were experienced contact lens wearers, whereas others were fitted with these lenses as a part of their clinical management using standard operating protocols.[18,19] All subjects wore conventional tri-curve RGP contact lenses with an optimal fit on the eye, as judged using standard clinical protocols.[18,19] All experienced contact lens wearers discontinued wear of their existing lenses 2 weeks prior to the study visit to avoid any contact lens induced corneal reshaping, in accordance with the clinical practice at the institute.[20] All cases were recruited for the study either during their follow-up visit to the institute or during their contact lens collection visit. All controls had monocular best corrected visual acuity of 20/20 or better, < 1.00 diopter (D) anisometropia, binocular vision within normal limits, and no ocular pathology as determined by a comprehensive eye examination.

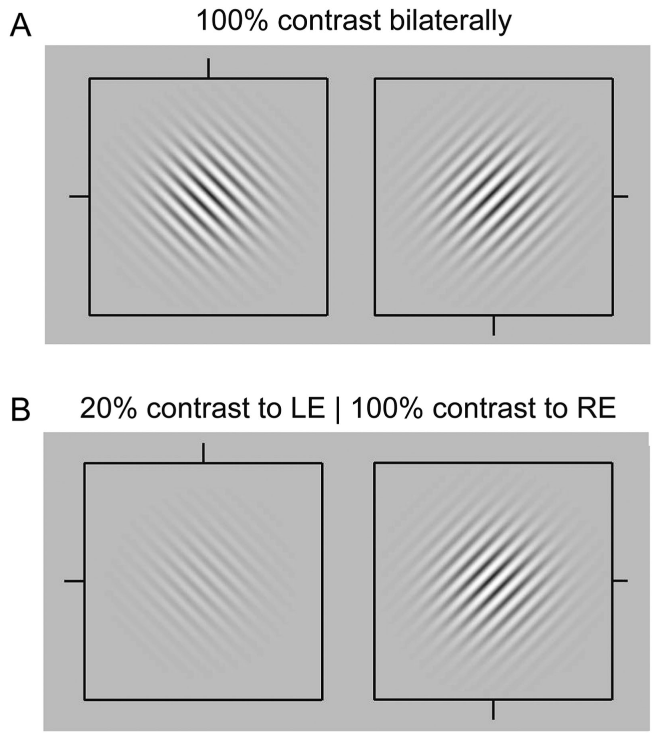

Figure 1. Example of orthogonally oriented Gabor patches used to induce binocular contrast rivalry in this study. Panel (**A**) shows image pair of equal contrast (100%) in both eyes (baseline) and panel (**B**) shows image pair with dissimilar contrasts in the two eyes. Each image pair can be cross-fused to experience binocular rivalry with equal and dissimilar contrasts in the two eyes.

Measurement of Balance Point Using Binocular Contrast Rivalry

Binocular contrast rivalry was stimulated using dichoptically presented, orthogonally oriented Gabor patches (135 degrees in the left eye and 45 degrees in the right eye, and 9 degrees angular subtense at the nodal point of the eye at 50 cm viewing distance) displayed and controlled using custom-written software in the Psychtoolbox interface of MATLAB (R2016a; The MathWorks, Natick, MA, USA) on a computer running Windows 10 operating system (Fig. 1).[21] Binocular fusion was aided by a bounding box and fusion crosses around each Gabor patch (see Fig. 1). Participants viewed the stimuli on a luminance and gamma-corrected LCD monitor (1680 × 1050 pixel resolution, 59 Hz refresh rate) from 50 cm with their best-corrected spectacles and with their accommodation and pupils in their respective natural states. Spectacle correction was incorporated into trial lenses and placed at 12 to 14 mm vertex distance for all the procedures. The participants' head was stabilized using a head and chin rest and they fused the image pair through a handheld stereo-viewer (Screen-Vu Stereoscope, Portland, OR, USA) into a single cyclopean percept. The stereo-viewer is essentially a miniaturized Wheatstone mirror stereoscope with movable periscopic mirrors to adjust for the participant's horizontal phoria and allow fusion of the two monocular percepts.[22] The stereo viewing had in-built +2D near

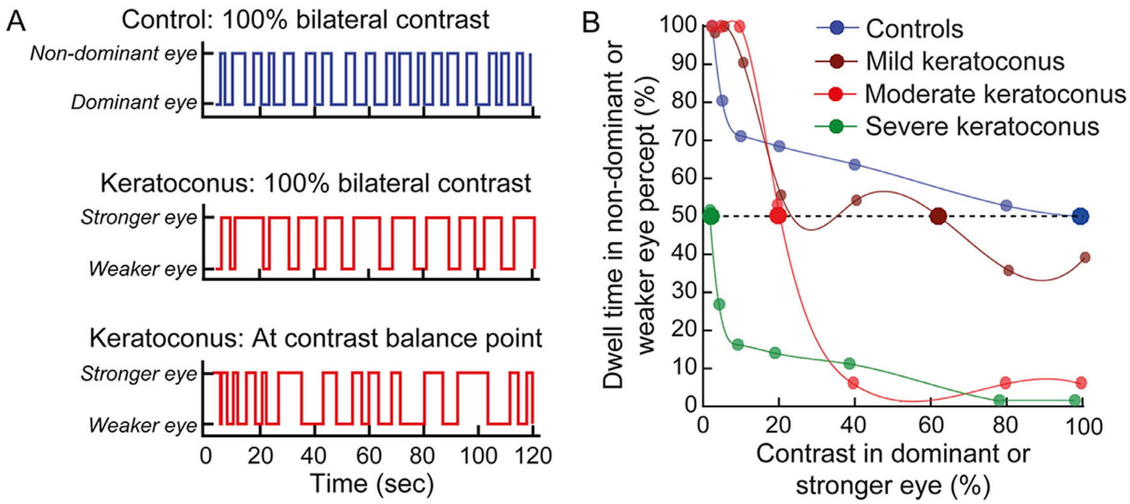

Figure 2. Panel (**A**) shows the contrast rivalry switches between the dominant and nondominant eye of a representative control subject plotted as a function of time at baseline (*top panel*). Similar rivalry switches between the stronger and weaker eye of a representative keratoconic case at baseline and at the contrast balance point (approximately 20% in the stronger eye and 100% in the weaker eye) is shown in the *middle* and *bottom panels*, respectively. Panel (**B**) shows the percentage of dwell time on the nondominant eye (in controls) or weaker eye (in patients with keratoconus) plotted as a function of the stimulus contrast in the dominant eye (in controls) or stronger eye (in patients with keratoconus). Data of one representative control and three cases with different severities of keratoconus in the weaker eye along with their respective balance points are shown here. The curves represent the spline interpolation functions that were fit to the individual data points to determine the balance point.

vision correcting lenses and therefore the accommodative state of the eye was in a relatively relaxed state during the experiment. These near-addition lenses are unlikely to create a disharmony between the accommodative and vergence demands of our subjects, because the lens power is within the negative relative accommodation of most subjects.

The rivalry stimulus was presented for 120 seconds during which time participants indicated every instance of a complete switch in perception (exclusive visibility) from one grating orientation to the orthogonal one using right (for 45 degrees grating) and left (for 135 degrees grating) arrow keys in the keyboard (Fig. 2A). Participants were explicitly instructed to ignore periods of piece-meal rivalry that appear in between periods of complete switch in grating orientation.[23] This task was performed with 100% contrast presented to each eye (baseline; see Fig. 1A) and for 6 levels of interocular contrast difference in the 2 eyes (see Fig. 1B). This difference was induced by maintaining the contrast at 100% in the weaker eye of cases and in the nondominant eye of controls, whereas the contrast to the fellow eye was attenuated to 80%, 40%, 20%, 10%, 5%, and 2.5% contrasts in each session, in randomized order. These produced interocular contrast differences of 20%, 60%, 80%, 90%, 95%, and 97.5%, respectively. The dwell time on each grating orientation was calculated for each interocular contrast combination from the sum total of the elapsed time between the key presses over the entire 120 second duration (see Fig. 2B). Accidental key presses indicating the same grating orientation sequentially were excluded from the calculations. A dwell time of 50% in one eye indicated that monocular percepts occupied equal durations of time over the entire task duration. A dwell time of 100% or 0% in one eye indicated that only one monocular percept dominated throughout the task duration, with no perceptual switches in grating orientation and, therefore, no binocular contrast rivalry. The percent dwell time on the weaker eye's percept for cases and on the nondominant eye's percept for controls was then plotted as a function of contrast and a spline interpolation function was fit to this data to determine the contrast at which 50% of dwell time was achieved (see Fig. 2B). This value was considered as the contrast "balance point" and represented the extent of contrast attenuation in the stronger eye required for both eyes to contribute equally to the rivalry percept (see Fig. 2B). Contrast balance points tending toward 0% indicated that the stronger eye's contrast needed to be attenuated extensively to achieve the balance point and, therefore, a deeper suppression of the weaker eye (see Fig. 2B). Contrast balance points closer to 100% indicated relatively shallow suppression of the weaker eye (see Fig. 2B). If the weaker eye's dwell time varied non-monotonically with a reduction in stronger eye's contrast such that the 50% mark was reached at multiple contrast values (see Fig. 2B; mild keratoconus), the highest of these contrasts were considered as the balance point. This effectively translated into a liberal criterion for suppression depth of the weaker eyes of cases and in the nondominant eyes of controls.

Experimental Sessions and Designation of Stronger/Weaker Eye in Keratoconus

The designation of stronger/weaker eye of keratoconus subjects was based on the D-index, a topographic measure of corneal distortions[24,25] and on high-contrast visual acuity, a functional measure of visual performance. In each case, the eye with higher D-index and poorer acuity was designated as the weaker eye, whereas the fellow eye was automatically designated as the stronger eye. There was never an instance in our cohort where the D-index and visual acuity values were exactly the same in both eyes, although the difference was small in cases with near-symmetric keratoconus in the two eyes. Eye dominance in controls was determined using the standard hole-in-the-card test.[26] All cases and controls performed the rivalry task using the 5 cycles per degree

Table. Demographic and Optical Details of Study Participants

		Cases of Keratoconus		Controls	
Age (Years)		**19.5 (13–31)**		**23 (15–26)**	
Gender, M/F		**37/13**		**6/6**	
		Stronger Eye	**Weaker Eye**	**Dominant Eye**	**Nondominant Eye**
Visual acuity (logMAR)		0.04 (0.0–0.14)	0.46 (0.3–0.70)	0.00 (0.0–0.0)	0.00 (0.0–0.0)
Keratometry (D)	**Max**	46 (44.6–49.5)	53.1 (51.2–56.7)	43.60 (43–44.7)	43.5 (42.9–44.7)
	Min	44.6 (43.1–45.7)	47.3 (45.5–50.9)	42.4 (41.9–43.6)	42.6 (41.7–43.2)
D-index (unitless)		4.7 (2.6–6.8)	9.7 (7.8–12.5)	1.4 (0.9–1.7)	1.5 (1.1–1.8)
Refractive error (D)	**M**	−1.3 (−4.4 to −0.5)	−4.2 (−6.5 to −1.9)	Plano (−0.3 to 0.0)	Plano (−0.3 to 0.0)
	J0	0 (−0.3 to 0.5)	−0.2 (−0.9 to 0.5)	± (0.0 to 0.0)	± (0.0 to 0.0)
	J45	0 (−0.2 to 0.4)	0 (−1.0 to 1.4)	± (0.0 to 0.0)	± (0.0 to 0.0)

All values (except gender distribution) represent median (25th–75th interquartile ranges). Sphero-cylindrical refractive errors are represented as M (spherical equivalent), J0 and J45 cross-cylinder power vectors.[30]

(cpd) grating, wearing their spectacle correction. A subset of cases also performed the task using the 1.5 cpd grating with spectacle correction ($n = 43$) and another subset performed the task using the 5 cpd grating with spectacles and with RGP contact lenses ($n = 21$). The order of measurement of the two spatial frequencies and the mode of correction was randomized across subjects. All subjects in the contact lens experiment were provided at least an hour of adaptation time with their lenses prior to participation. All subjects reported that they were comfortable wearing their contact lenses. To ensure optimal refractive correction, refraction was also performed over contact lenses to determine any residual refractive error, which was corrected with the help of trial lenses. The entire experiment took approximately 2 hours and participants took frequent breaks to overcome fatigue and boredom.

Measurement of Associated Parameters

In addition to the contrast rivalry measurements described above, the study also measured each participant's logMAR visual acuity, contrast sensitivity, stereoacuity, and corneal topography. Monocular high-contrast logMAR acuity was determined at 3 m using a computerized acuity measurement system (COMPlog; Medisoft Inc., Leeds, UK). Here, a series of 5 Sloan optotypes were displayed in random order on an LCD monitor (1366 × 768 pixels resolution) and their angular subtense decreased using a staircase thresholding algorithm until 3 of 5 optotypes were incorrectly identified. LogMAR acuity was recorded as the number of optotypes correctly identified at termination, with 0.02 logMAR units allotted per optotype.[27] Monocular contrast sensitivity function (CSF) was determined using a modified version of quick CSF program written in Matlab to verify that the 5 cpd and 1.5 cpd gratings presented in the rivalry task approximately corresponded to the peak CSFs of the stronger and weaker eyes, respectively, and their contrasts were always in the suprathreshold range.[28] Stereoacuity was measured using the clinical Randot stereoacuity test at 40 cm using the standard operating protocol. Corneal topography scans were obtained using the Wavelight Oculyzer II (Pentacam HR Technology, Oculus, Arlington, VA, USA). The severity of keratoconus (see Fig. 2B) was graded based on the Amsler-Krumeich classification (mild keratoconus: < 48 D; moderate keratoconus: 48–53 D; and severe keratoconus: > 53 D[29]).

Data Analyses

Data analyses were performed using Matlab R2016a and IBM SPSS Statistics 20.0 (SPSS, Chicago, IL, USA). The first hypothesis was evaluated by analyzing the number of perceptual switches in grating orientation between eyes and their dwell times at baseline and at the balance point. The second hypothesis was evaluated by plotting the balance point of each subject against the respective interocular difference in acuity and D-index. Acuity and D-index represented the primary functional and structural measure of disease severity used routinely in the clinic for grading keratoconus, respectively.[24,25] The third and fourth hypotheses were evaluated by directly comparing the balance points obtained with low and high-spatial frequency gratings and with spectacles and RGP contact lenses. The Shapiro-Wilk test indicated that the outcome variables were not normally distributed, the data were therefore analyzed using nonparametric statistics. The data of all outcome variables are reported as median and 25th to 75th interquartile ranges (IQR). Statistical significance was set to $P \leq 0.05$.

Results

Data were successfully collected in all participants. The demographics details of the participants are shown in the Table. The keratoconus cohort contained cases with all grades of disease severity that were similar or dissimilar in the two eyes. According to the Amsler-Krumeich classification of keratoconus severity,[29] across the 100 eyes of 50 cases that participated in this study, 4 eyes were normal, 6 eyes had forme-fruste keratoconus, 40 eyes had mild keratoconus, 34 eyes had moderate keratoconus, and 16 eyes had severe keratoconus. Some of the combinations of keratoconus in the two eyes of the 50 cases included, 2 with moderate keratoconus in one eye and no disease in the fellow eye, 5 with forme-fruste keratoconus in one eye and moderate keratoconus in the fellow eye, and 4 with severe keratoconus in both eyes. There were no subjects with forme-fruste keratoconus in both eyes. The smallest interocular difference in average keratometry was 0.1 D, whereas the largest difference was 20.9 D. Eyes that were classified as normal or forme-fruste keratoconus were usually designated as the stronger eye, whereas the weaker eye had mild, moderate, or severe keratoconus.

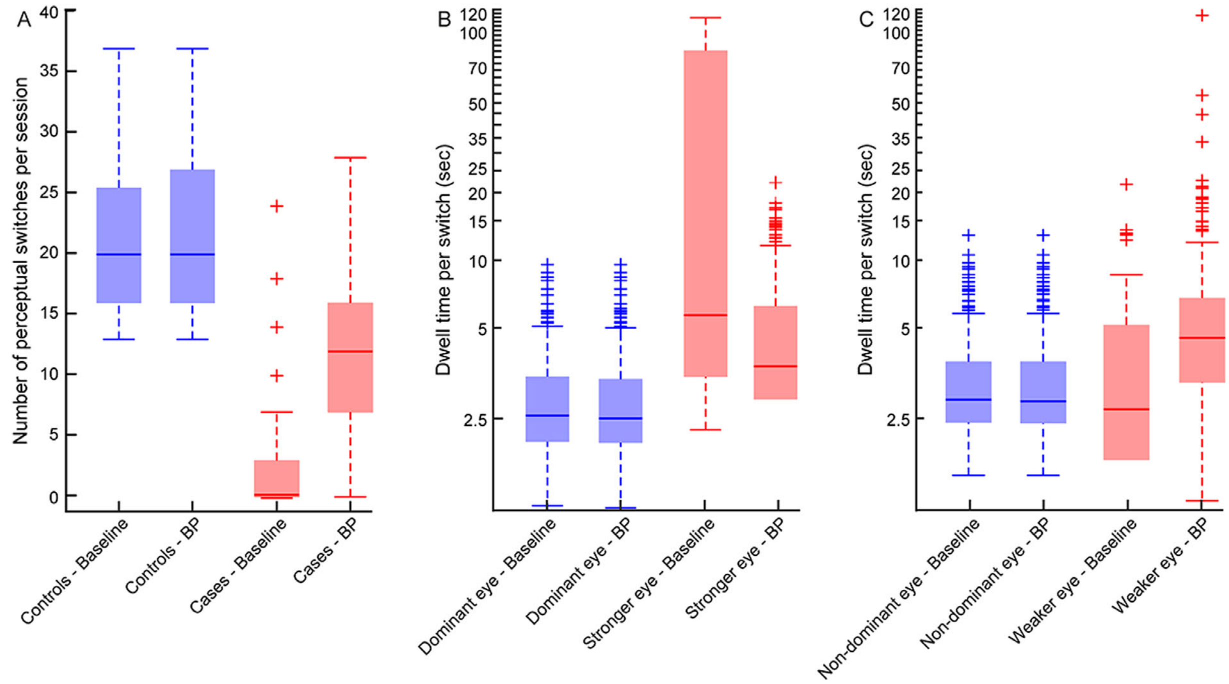

Figure 3. Box and whisker plots of the number of perceptual rivalry switches per session panel (**A**), the dwell time on the dominant eye of controls and stronger eye of cases panel (**B**) and the dwell time on the nondominant eye of controls and weaker eye of cases panel (**C**) at baseline and at the balance point (BP). In all three panels, the *blue* plots indicate data from controls and the red plots indicate data from cases. In each panel, the *solid horizontal line* within the box indicates the group median, lower and upper edges of the box indicate the 25th and 75th interquartile range, lower and upper whiskers indicate the 1st and 99th quartiles and the plus symbols indicate outliers.

Hypothesis 1: Patterns of Rivalry and the Balance Point in Controls and Cases

At baseline, the rivalry pattern of controls showed more frequent perceptual switches between eyes and approximately equal dwell times on the two eyes (see Fig. 2A). In contrast, the rivalry pattern of cases at baseline showed lesser number of perceptual switches and longer dwell time on the stronger eye's percept, relative to the weaker eye (see Fig. 2A). The percent dwell time on the weaker eye of cases at baseline decreased with an increase in that eye's disease severity (compare the 100% data point along the abscissa in the 4 curves in Fig. 2B). Overall, the cyclopean percept appeared biased toward the stronger eye in keratoconus at baseline, with this bias growing stronger with increasing disease severity in the weaker eye. The balance points progressively moved from close to 100% contrast in the stronger eye in mild keratoconus toward 0% contrast in the stronger eye in severe keratoconus (see Fig. 2B). In controls, the nondominant eye's contribution to cyclopean percept was approximately 50% at baseline and this progressively shifted toward 100% when the dominant eye's contrast was purposely reduced (see Fig. 2B). The contribution of the weaker eye in mild and moderate keratoconus also reached approximately 100% with the lowest stimulus contrast in the stronger eye, indicating that, similar to controls, their weaker eye dominates cyclopean perception when the stronger eye receives very weak input. In patients with keratoconus with severe disease in the weaker eye, such a reversal of bias in the cyclopean percept was not apparent as the curves do not extend beyond the balance point even at the lowest contrast to the stronger eye (see Fig. 2B).

As expected, the number of perceptual switches between the two eyes and the dwell times on each percept was similar at baseline and at the balance point in controls ($Z < 0.4$, $P > 0.7$, for all; Fig. 3). The median number of perceptual switches between the 2 eyes in cases increased from zero at baseline to 12 at the balance point ($Z = 5.1$, $P < 0.001$; see Fig. 3A). Cases also showed a significant decrease in dwell time on the stronger eye from baseline to balance point ($Z = 3.9$, $P < 0.001$) and a corresponding increase in dwell time on the weaker eye from baseline to balance point ($Z = 2.4$, $P = 0.02$; Figs. 3B, 3C).

Hypothesis 2: Contrast Balance Point and Interocular Difference in Acuity and D-Index

Figure 4 plots the balance point of controls and cases against their corresponding interocular difference in decimal acuity (panel A) and D-index (panel B). The asymmetry in disease severity was considered as a continuous variable in this analysis. Visual acuities were converted from logMAR to decimal values for ease of interocular difference calculations in this analysis. As expected, the data of controls showed little or no interocular difference in acuity or D-index and their balance points were also close to 100% (see Fig. 4). Cases had a wide range of interocular differences in acuity and D-index, reflecting the varying severities of disease presentation in the two eyes (see Fig. 4). The balance points of all cases and controls combined were strongly negatively correlated with the interocular difference in acuity ($r = 0.85$, $P < 0.001$) and D-index ($r = 0.74$, $P < 0.001$) and were well explained by a two-parameter

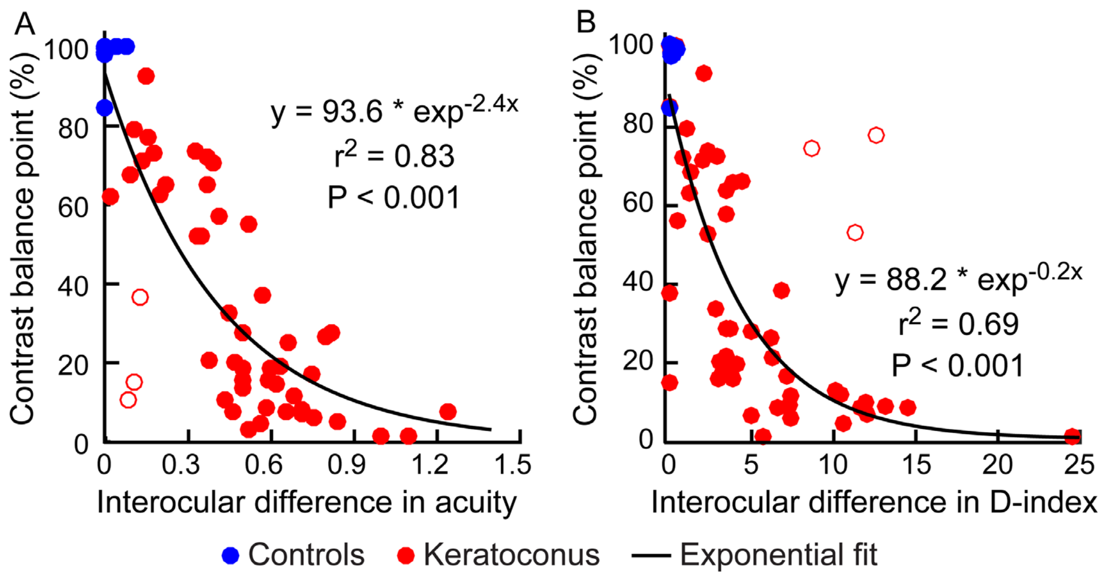

Figure 4. Scatter diagram of the contrast balance point of cases and controls plotted against their respective interocular differences in decimal acuity panel (**A**) and D-index panel (**B**). The open red symbols indicate outlier data points (see discussion for details).

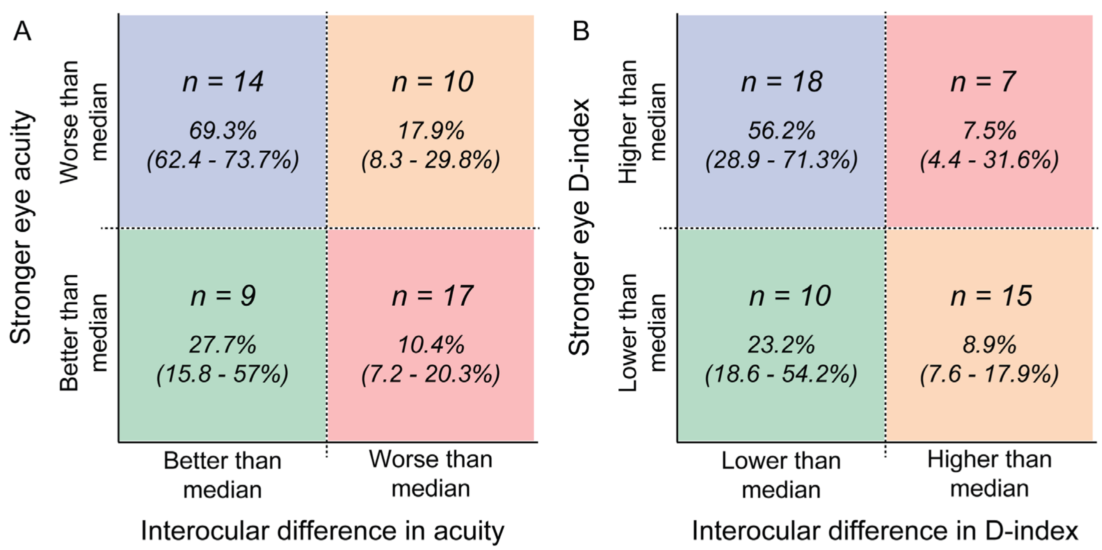

Figure 5. Median (25th–75th interquartile range) balance points for cases divided into four groups depending on the acuity in stronger eye and interocular difference in acuity panel (**A**) and the D-index in stronger eye and interocular difference in D-index panel (**B**). Each cell in this contingency table is color coded, with the *red cell* indicating the worst median balance point (closest to 0%), the *blue cell* representing the best median balance point (closest to 100%) and the *orange* and *green cells* representing the intermediate balance points, across groups.

exponential fit to the data (see Fig. 4). As expected, the y-intercepts of the exponential fits were close to 100% of the balance points (coefficients [with 95% confidence interval] for acuity: 93.6% [83.7–100%] and D-index: 88.2% [75.8–100%]) indicating negligible to no suppression of monocular input in the absence of an interocular difference in acuity or D-index (see Fig. 4). The balance points then dropped at the rate of 2.4% (1.9–2.9%) per unit increase in interocular difference in acuity and 0.2% (0.15–0.29%) per unit increase in interocular difference in D-index (see Fig. 4).

The severity of disease in the stronger eye reflects the best possible visual performance of cases and this may also have an influence on the suppression depth of the weaker eye, in addition to the interocular difference described earlier (see Fig. 4). To address this issue, an additional analysis was undertaken wherein the cases were divided into four categories depending on whether the severity of keratoconus in the stronger eye and the interocular difference in disease severity was higher or lower than the respective median values of the cohort (Fig. 5). The asymmetry in disease severity was considered as a binary variable in this analysis. If the contrast balance points were determined only by the interocular difference in acuity (see Fig. 5A) or D-index (see Fig. 5B), the values will differ only along the columns but not along the rows in the contingency table (see Fig. 5). Contrarily, if the contrast balance points were determined only by

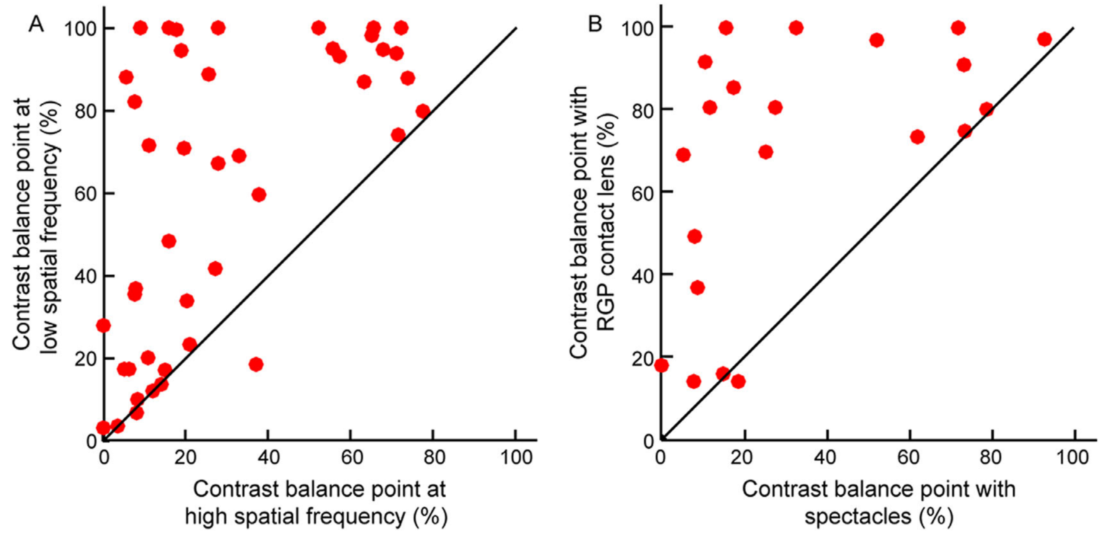

Figure 6. Scatter diagrams of contrast balance point of cases obtained using low and high-spatial frequency stimuli panel (**A**) and with spectacle and RGP contact lens correction panel (**B**). The diagonal line in both panels indicate the 1:1 line of equality.

the acuity or D-index of the stronger eye, the values will differ only along the rows but not along the columns in the contingency table (see Fig. 5). If both parameters determine the balance points, the values will be different in each cell of the contingency table (see Fig. 5).

As expected from the categorization based on median values, the number of participants were roughly equally distributed across each cell in the contingency table (see Fig. 5). The balance points were significantly different in each cell of the table, indicating both interocular difference and stronger eye value had an influence on the balance point ($\chi^2 > 17.9$, $P < 0.001$ for both; see Fig. 5). The balance points were in general lower for larger than median interocular difference in acuity and D-index, relative to smaller than median interocular difference (Z > 2.2, $P < 0.03$; see Fig. 5). For acuity, the balance points were also lower when the stronger eye value was better than the median, relative to when they were worse than the median (Z = 2.2, P = 0.03; see Fig. 5). This effect was, however, not statistically significant for D-index (Z < 1.7, $P > 0.58$; see Fig. 5B). Overall, these trends indicated the suppression of the monocular input was deeper for larger interocular differences in acuity or D-index and for better than median acuity or D-index in the stronger eye, relative to their fellow counterparts.

Hypotheses 3 and 4: Balance Point Changes with Spatial Frequency and Refractive Correction

The balance point in cases improved approximately 3.5-fold when the target spatial frequency decreased from 5 cpd (19.4% [8.6–53.7%]) to 1.5 cpd (70.8% [21.7–94%]; Z = 5.4, $P < 0.001$; Fig. 6A) and by approximately 4-fold with RGP contact lenses (80.1% [49.5–91.7%]), relative to spectacles (18.7% [10.7–62.3%]; Z = 3.8, $P < 0.001$; see Fig. 6B). The spatial frequency content did not appear to significantly impact suppression depth for cases with relatively deep suppression (balance points approximately <20%) and for two participants with relatively weak suppression (balance points approximately 75–80%; see Fig. 6A). One subject had worse suppression for the low spatial frequency target, relative to the high frequency target (see Fig. 6A). The optical correction modality too did not have an influence on the suppression depth for two participants with relative deep (balance points approximately 15–20%) and for three participants with relatively weak (balance points approximately >70%) suppression. The balance point, and therefore, the suppression depth, thus appeared dependent on the spatial frequency of the stimulus and the eye's optical quality.

Hypothesis 5: Contrast Loss and Depth of Suppression in Keratoconus

The contrast balance point obtained by attenuating the stimulus contrast in the stronger eye, vis-à-vis, the weaker eye that was always retained at 100% contrast, is a surrogate measure for suppression depth in keratoconus (see Figs. 4, 5). Does the level of contrast attenuation in the stronger eye (in other words, the interocular contrast loss experienced at baseline; 1–contrast balance point) completely explain the contribution of the weaker eye of keratoconus in the binocular rivalry task at baseline? If so, this pattern of data in cases should match the data obtained by purposefully reducing the contrast to the dominant eye of controls in the same rivalry task. Figure 7 shows the percentage contribution of the dominant eye of controls (n = 12) for different levels of induced interocular difference in contrast. As expected, the percentage contribution of the dominant eye was close to 50% when there was no interocular difference in contrast (see Fig. 7). The percentage contribution reduced with an increase in the interocular difference in contrast, with the contribution steeply dropping for interocular contrast differences > 80% (Z > 2.35, $P < 0.02$ between adjacent contrast values) Figure 7 also plots the data of the percentage contribution of the weaker eye of cases against their corresponding contrast loss experienced at baseline (1 − contrast balance point) for spectacle and RGP contact lens viewing. With spectacle viewing, the data of all cases (except 4 subjects) fell below the 95% confidence interval range of controls, indicating that the percentage contribution of their weaker eye at baseline was lower

Investigative Ophthalmology & Visual Science

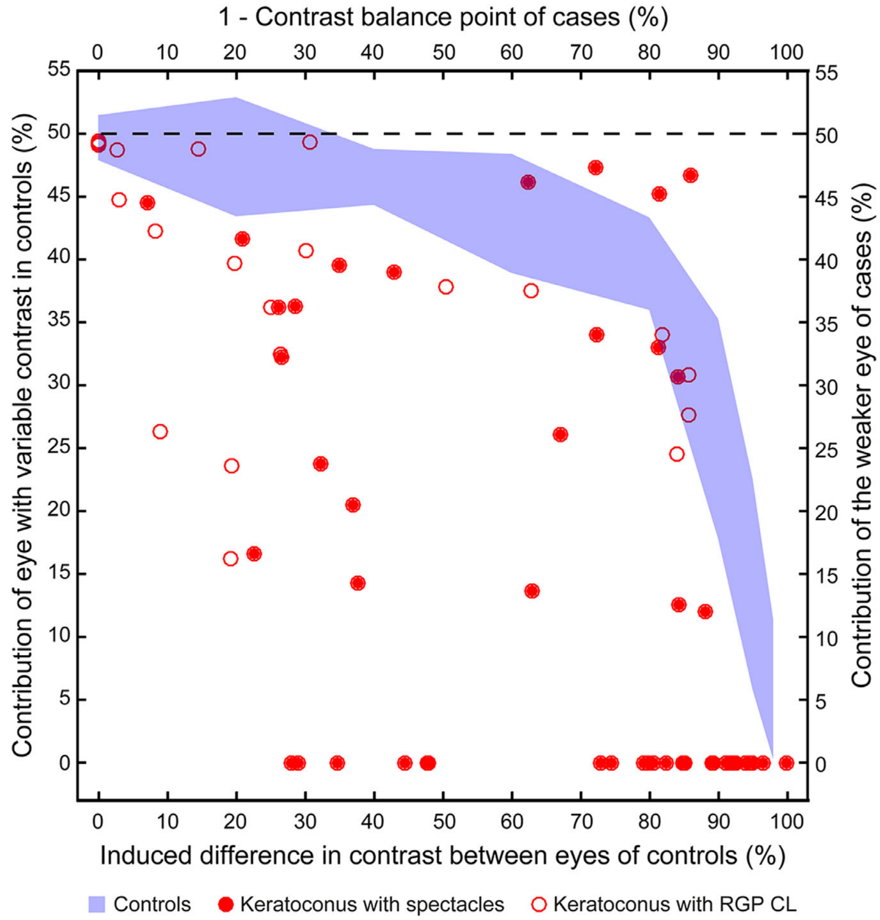

Figure 7. Percentage contribution of the dominant eye of controls to the binocular rivalry task for varying levels of induced interocular difference in contrast (*blue band*; bottom abscissa and left ordinate). The blue band shows the ±95% confidence intervals of controls. The actual data points are not shown to avoid clutter. Percentage contribution of the weaker eye of patients with keratoconus to the binocular rivalry task plotted against the corresponding contrast loss experienced at baseline (i.e. 1 – contrast balance point; top abscissa and right ordinate). Data from spectacles and RGP contact lenses are shown as *closed* and *open red circles*, respectively. The *dashed horizontal line* along the 50% ordinate mark indicates equal contribution between the dominant and nondominant eyes of controls and between the stronger and weaker eyes of cases.

than what was predicted simply from a contrast loss in that eye (see Fig. 7). The data with RGP contact lens wear moved toward lower interocular contrast difference values and toward the data of controls, both as per the predictions from the improvements in balance point of subjects shown earlier (see Fig. 7). However, these data were still lower than those of controls, reflecting the residual suppression that continues to exist in these subjects with RGP contact lens wear. These results indicated that the contrast loss experienced by the weaker eye of keratoconus only partially explains its depth of suppression and its reduced contribution to binocular viewing at baseline.

Discussion

The impact of optical quality loss due to higher-order wavefront aberrations on binocular vision is the focus of the present study. Although the population average higher-order aberrations in normal eyes are very small[30–32] to impact binocularity,[33,34] disease conditions,[2–4] or iatrogeny[7,35–37] where they are exaggerated (approximately 4 to 5-fold compared with healthy controls[2,38]) could be used as models to address this question. Stereoacuity loss,[2,7] poor binocular summation,[33,35] near-complete suppression of the highly aberrated eye,[3,7] and binocular high contrast acuity being largely determined by the monocular acuity of the stronger eye[2,7,39] are all indications of how optical quality losses affect the way inputs from the two eyes are combined by the visual system to create a cyclopean percept. The results of the present study provide further insights into the nature of this combination using keratoconus as a disease model. The study clearly demonstrated that naturalistic binocular viewing in these cases is dominated by the eye with lesser disease severity (i.e. with relatively stronger optics[24,25]), whereas the fellow eye with poorer optics may be suppressed and contribute only a limited extent to binocular viewing. The depth of suppression of the weaker eye depended on its own severity (see Figs. 2, 3) and optical quality (see Fig. 6B), the extent of its difference in severity from the fellow eye (see Figs. 4, 5) and the spatial content of the scene viewed (see Fig. 6A). This suppression along with impaired correspondence matching due to interocular differences in image quality,[40] may explain the stereoacuity losses demonstrated previously in keratoconus.[41] Stereoacuities measured in this study using the clinical Randot test do not provide enough resolution to compare against the psychophysical measures of suppression recorded here. The exact relation between suppression depth and stereoacuity thus remains unknown in keratoconus and needs further investigation.

Three interesting trends related to suppression emerged from this study. First, the dwell time on each monocular input in the rivalry task – a surrogate for the relative dominance of the two eyes – depended on which of the two percepts had higher contrast (see Fig. 2B). At baseline, the cyclopean percept was dominated by the stronger eye, wherein, even though the stimulus contrast was equal bilaterally (100%), the retinal image contrast of the stronger eye was higher due to lesser optical degradation, relative to the weaker eye (see Fig. 2B). The pattern reversed to reflect the dominance of the weaker eye when the stimulus contrast to the stronger eye was purposely reduced to appear less salient (see Fig. 2B). In between these two ends was the contrast balance point, where both eyes contributed equally to the cyclopean percept (see Fig. 2B). This pattern indicates that the visual system may be weighting the monocular inputs depending on their relative salience (contrast, in this case) while forming the cyclopean percept, with the higher salience input given more weight than the fellow eye's input. This strategy may also explain the reduced depth of suppression with improved optical quality through contact lens wear (see Fig. 6A)[2,42] and with lower spatial frequency targets that are relatively more immune to blur than high spatial frequencies (see Fig. 6B).[43] The same strategy may also explain previous observations of binocular visual acuity following the stronger eye's acuity in the presence of interocular differences in image quality[2,7,39] – stronger acuity reflects relatively superior spatial resolution and hence more weight is attached to that eye's input during binocular viewing. Similar patterns of suppression have been demonstrated in anisometropic amblyopia,[44,45] suggesting that the visual system may adopt generalized strategies to optimize binocular viewing in the presence of image quality degradation, irrespective of the source of the problem. Any further comparison between amblyopia and keratoconus must be avoided as these entities entail very different disease pathophysiologies.

Second, suppression depth depended both on the disease severity of the stronger eye and on the interocular difference in disease severity (see Figs. 4, 5). The suppression was deepest when the interocular difference was higher than the median value and the stronger eye's disease severity were lower than the median value (see Fig. 5). On the other end, the suppression was least when the interocular difference was lower than the median value and the stronger eye's disease severity was higher than the median value (see Fig. 5). This pattern almost resembles a Weber's law behavior where the discrimination threshold of a given variable is proportional to the baseline quantum of that variable.[46] Individuals with keratoconus and a given magnitude of interocular difference in disease severity are more likely to suppress their weaker eye if the disease manifestation is less severe. As a nuance, the y-intercepts in both panels of Figure 4 did not quite reach the 100% balance point mark where the data of controls lie. This was found to be because of three outlier data points indicated by open symbols in Figure 4. Removal of these data points increased the y-intercepts of the exponential fits to 99.9% and 90.7% for acuity and D-index, respectively, without influencing the rate of change coefficient and the goodness of fit. Similar dependence of stereoacuity on the overall and interocular loss of image quality has been demonstrated previously for induced lower-order aberrations.[47–49] Similar Weber's law type behavior is also observed for acuity discriminations in keratoconus wherein the suboptimal acuity worsens their ability to discriminate different patterns of optical blur relative to controls, more so with spectacles than with RGP contact lenses.[2,7]

Third, the percentage contribution of the weaker eye of keratoconus at baseline was poorer than what was predicted from the data of controls with varying levels of induced interocular difference in contrast (see Fig. 7). This suggested that the depth of suppression of monocular input in keratoconus is only partially attributable to the contrast loss experienced by the weaker eye due to the distorted optics. Other factors, such as phase shifts in the retinal image induced by the optical blur[50,51] or neural insensitivity due to prolonged exposure to blur,[52] may also contribute to this suppression of monocular input and need further exploration. Metlapally et al.[40] did observe that the stereoacuity loss in keratoconus was attributable to both contrast loss and phase shifts induced by higher-order aberrations of these eyes. Additionally, the depth of suppression of the weaker eye may also depend on several other covariates, such as the location and type of the cone in keratoconus, age of onset and stability of the disease, other differences in the biometric parameters of the two eyes, duration of contact lens wear, and the associated reshaping of the cornea.[1,4] The sample size in the present data set is too small to determine the individual or combined impact of these parameters on the subjects' binocularity. Addressing these points will be the subject matter of a future study.

This study has several important clinical implications. First, even though keratoconus is a bilateral disease with potentially different severities in the two eyes,[1,53] its impact on visual functions are almost always assessed only monocularly (e.g. monocular visual acuity[1,54,55] or contrast sensitivity[4,55]). The present and previous results[2,4,40] strongly suggest binocularity measures (e.g. stereoacuity) should also be included as part of the comprehensive assessment protocol in keratoconus. Second, the severity of keratoconus was quantified in this study using high contrast visual acuity (see Fig. 4A) and D-index (see Fig. 4B). These are correlated parameters in that both will increase commensurately with an increase in disease severity ($r = 0.73, P < 0.001$) and it is therefore expected that their relation with suppression depth will be similar (see Figs. 4, 5). Clinically, therefore, either of these entities can point to a probable suppression of the poorer eye in keratoconus. The depth of suppression can then be quantified, if required, using psychophysical measures, such as the rivalry paradigm used in this study. Third, clinicians need to watch out for suppression of the poorer eye in keratoconus, especially for asymmetric disease manifestation in the two eyes. This suppression appears like a dynamic strategy adopted by the visual system to optimize binocular viewing depending on the optical quality of each eye and the target characteristics (see Fig. 6). Whether this dynamically varying suppression will give way to a more permanent one with disease progression and/or with prolonged exposure to blur remains unknown.[52] Fourth, management strategies for keratoconus using contact lenses should aspire not only to improve the monocular visual quality but also to make it as equal as possible in both eyes in order to reduce suppression (see Fig. 6B) and improve stereoacuity in these patients with contact lens wear.[2,4] Similar relation between the reduced interocular difference in image quality and improved stereoacuity has also been recently reported in patients undergoing laser refractive surgery.[37]

Suppression is typically measured as a binary entity (present or absent) in the clinic using the Worth's four dot test or Bagolini lenses, and its efficacy has been shown in cases with gross suppression of one eye's input.[56,57] However, as shown here in keratoconus and previously in amblyopia,[58] suppression may be graded in depth depending on the disease severity. Toward this end, measures of contrast balance point have become the mainstay parameter in laboratory-based studies to quantify the depth of suppression.[58,59] Several different psychophysical measures of this balance point are now available in the literature, including those using dichoptic motion coherence,[44] phase combination,[58] letter acuity,[59] and binocular rivalry (see Fig. 1). Although these paradigms all tap into different mechanisms of visual information processing, they follow a common logic of manipulating the stronger eye's contrast while retaining the weaker eye's contrast at 100% to reach a balance in performance of the two eyes (see Fig. 2B).[58] This study chose the contrast rivalry paradigm simply because of task simplicity and the readiness of rivalry perception. Future studies have to determine the diagnostic accuracy of these techniques and translate them to the clinic.

In conclusion, the contrast rivalry paradigm demonstrated suppression of the weaker eye in unilateral and bilateral keratoconus. The depth of suppression depends on the eyes' disease severity, difference in severity from the stronger eye, its optical quality, and the spatial frequency of the target viewed. It is therefore recommended that clinicians watch out for signs of suppression in keratoconus and they aspire to achieve good and equal quality of vision in both eyes of these patients to optimize binocularity.

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