Preclinical metrics to predict through-focus visual acuity for pseudophakic patients

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Abstract: This study compares the clinical through-focus visual acuity (VA) in patients implanted with different intraocular lens (IOL) to optical bench testing of the same IOLs to evaluate the suitability of optical metrics of predicting clinical VA. Modulation transfer function and phase transfer function for different spatial frequencies and US Air Force pictures were measured using an optical bench for two multifocal IOLs, three multifocal IOLs and an extended range of vision IOL. Four preclinical metrics were calculated and compared to the clinical through-focus VA collected in three different clinical studies (243 patients in total). All metrics were well correlated ($R^2 \geq 0.89$) with clinical data and may be suitable for predicting through-focus VA in pseudophakic eyes.

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1. Introduction

The preclinical optical performance of intraocular lenses (IOLs) is currently assessed using modulation transfer function (MTF) values at a single spatial frequency of 25, 50 or 100 cycles per mm (cpmm) (ISO standard 11979-2:2014). The MTF is commonly used to compare different IOL designs [1–3], evaluate the clinical outcomes [4–10] and to assess optical performance under different conditions, such as different pupil size [11,12] and rotation and tilt [13].

Figure 1(A) illustrates the differences between the through-focus MTF at 50 and 100 cpmm measured in an eye model that reflects the average corneal spherical aberration and chromatic aberration of the pseudophakic eye [14] in white light at 3mm pupil for a +4.0 D- add multifocal IOL (model ZM900, Abbott Medical Optics Inc, Santa Ana, California) while Fig. 1(B) shows binocular visual acuity (VA) measured clinically for the same IOL. As noted from Fig. 1, most through-focus MTF values at 100 cpmm are less than 0.09 which is considered to be the repeatability limit of the measurements according to the ISO standard (ISO 11979-2:2014-Annex C.5). In addition, the MTF values in the intermediate range are
very close to zero although the clinical VA for that defocus values is above 0.3 logMAR that can be considered functional intermediate vision.

![A. Modulation transfer function](image)

![B. Clinical VA](image)

**Fig. 1.** Comparison between the MTF measured at 50 and 100 cpmm measured in white light in the Average Corneal Model (A) and the logMAR VA (B) for a multifocal IOL from 0 to \( -3 \) D.

It is known that MTF at single spatial frequency is well correlated with contrast sensitivity measured clinically in pseudophakic patients [15,16]. However, visual acuity is clinically measured using optotypes that can be deconstructed into multiple spatial frequencies [17–20]. All these spatial frequencies contribute simultaneously to the interpretation of those optotypes. Accordingly, it may be advantageous to consider multiple spatial frequencies when evaluating the preclinical optical performance of an IOL design in order to predict the potential visual acuity achievable when an IOL design is implanted in the eye.

Different metrics have been previously proposed in order to predict visual acuity under different optical conditions [4–10]. Most of these metrics are based on wavefront measurements which also take into account the aberrations of the subject [4–8]. Moreover, in these experiments the visual acuity is usually measured under controlled conditions such as fixed pupil size and adaptive optics for total control of the optics [4–9].

In this study, we propose to define and evaluate different preclinical metrics based on optical-bench data in order to better predict the average binocular through-focus VA provided by different IOL designs when implanted in pseudophakic patients. For that purpose, we used an average model eye and a set of six different IOL designs that included refractive and diffractive designs, different IOL materials, different amounts of spherical aberration, and different add powers.

### 2. Methods

Through-focus modulation transfer function (MTF) and phase transfer function (PTF) were measured in the Average Corneal Model (ACE) model which reproduces the average spherical aberration and longitudinal chromatic aberration of the cornea [14]. MTF and PTF can be calculated by the modulus and phase, respectively, of the Fourier transform of the line spread function measured in the ACE model. Data were collected for six IOL designs (Table 1) of 20 D power in white light from 0 to \( -3 \) D. Additionally, the US Air Force (USAF) pictures were recorded under the same conditions. A pupil size of 3 mm was used to evaluate the optical performance based on the average age of cataract patients and the changes in pupil size related to age under photopic conditions [21,22].

Based on the optical bench data, the preclinical metrics were calculated for each defocus position for two monofocal IOLs, three multifocal IOLs with different add powers (\(+2.75, +3.25\) and \(+4\) D) and an extended-range-of-vision (ERV) IOL of 20 D power. These IOL models as well as a description of their base technology are listed in Table 1.
Table 1. Designs considered in the study. All the designs are from Abbott Medical Optics Inc (Santa Ana, California).

| IOL model | Design  | Optics material | Technology               | Spherical aberration\(^a\) (μm) | Add power at IOL plane (D) |
|-----------|---------|-----------------|--------------------------|----------------------------------|---------------------------|
| ZCB00     | Monofocal| Acrylic         | Refractive, aspheric     | −0.27                            | NA                        |
| 911A      | Monofocal| Silicone        | Refractive, spheric      | + 0.17\(^b\)                     | NA                        |
| ZM900     | Multifocal| Silicone       | Diffractive, aspheric   | −0.27                            | + 4.00                    |
| ZLB00     | Multifocal| Acrylic        | Diffractive, aspheric   | −0.27                            | + 3.25                    |
| ZKB00     | Multifocal| Acrylic        | Diffractive, aspheric   | −0.27                            | + 2.75                    |
| ZXR00     | ERV\(^c\) | Acrylic        | Diffractive, aspheric   | −0.27                            | NA                        |

\(^a\)Spherical aberration (Zernike coefficient Z12) for a pupil diameter of 6 mm

\(^b\)Spherical aberration provided for a 21.5 D lens and 6 mm pupil.

\(^c\)ERV = extended-range-of-vision IOL.

Four different preclinical metrics were evaluated to determine how well they estimate the clinically measured defocus curves and compared to the MTF at 50 and 100 cpmm.

- **MTF\(_d\)**: Area under the MTF from 0 to 50 cpmm Eq. (1) where \(d\) determines the sampling size of the spatial frequency (\(f\)). For this study, \(d\) was equal to 1 cpmm for the three metrics.

\[
MTF_d = \sum_{f=1}^{50/d} \frac{|d|}{50} MTF(fd)
\]  

(1)

- **wMTF**: The weighted MTF was calculated as the area under the product of the measured MTF and the threshold contrast sensitivity [23] \((CS_{th})\) from 0 to 150 cpmm Eq. (2).

\[
wMTF = \sum_{f=1}^{150/d} \frac{|d|}{150} MTF(fd) CS_{th}(fd)
\]  

(2)

- **wOTF**: The weighted optical transfer function was calculated as the area under the real part of the measured optical transfer function weighted by the \(CS_{th}\) from 0 to 150 cpmm Eq. (3).

\[
wOTF = \sum_{f=1}^{150/d} \frac{|d|}{150} MTF(fd) CS_{th}(fd) \cos(PTF(fd))
\]  

(3)

- **X-cor**: The cross correlation coefficient [7,24,25] was calculated using a custom-made MATLAB program (MATLAB R2013b; Mathworks, Inc) that compensates for differences in magnifications and decentrations of the collected images. The reference image used to compare the USAF pictures measured for the different IOLs and defocus positions was the USAF picture at the best focus using the ISO cornea (free of spherical aberration) for 3 mm pupil in green light in water without an IOL (ISO 11979-2:2014, clause C.3.1).

Spatial frequencies in the image plane of 50, 100 and 150 cpmm measured in the ACE model for 20 D IOLs correspond to approximately 15, 30 and 60 cycles per degree respectively in the object plane of a real eye [26].

To evaluate the performance at intermediate distances, the area under the through-focus VA (AU defocus) was used [27,28]. The AU defocus was defined as the area under the clinical VA (in decimal units) from −0.5 to −2 D in 0.5 D steps. The AU clinical defocus was
correlated with the area under the through-focus curves of the different metrics for the same defocus range (between \(-0.5\) and \(-2\) D).

2.1 Clinical data

Clinical data were collected from three different studies (see Table 2 for the number of patients included in each study for each lens design). All the clinical studies followed the tenets of the Declaration of Helsinki. High contrast binocular through-focus VA was measured postoperatively using the 100% contrast ETDRS chart at 4.0 meters and trial lenses with the best distance correction in place under photopic conditions (85 cd/m\(^2\)). The image was defocused in \(-0.5\) D increments with spherical minus lenses [29]; at each defocus increment, one visual acuity measurement was obtained. To avoid learning effect, three distance VA charts were exchanged throughout the defocus testing, and alternating reading directions (left/right) were used. Defocus curves were adjusted to place the best VA at 0 D and the average of all patients was calculated. Patients performed the test under natural pupil sizes. Postoperative data were collected 3 months (clinical trial 3) and 6 month (clinical trials 1 and 2) after surgery.

All patients had bilateral cataract and were selected preoperatively to have otherwise healthy eyes. Patients with corneal abnormalities, previous refractive surgery or known pathologies that may affect vision were excluded from the trials.

Table 2. Sample size of the different clinical studies

| Clinical trial | IOL model implanted | Number of patients |
|----------------|---------------------|--------------------|
| #1             | ZM900               | 11                 |
|                | 911A                | 18                 |
| #2             | ZCB00               | 61                 |
|                | ZKB00               | 59                 |
|                | ZLB00               | 63                 |
| #3             | ZXR00               | 31                 |

2.2 Data analysis

For each IOL design, the clinical VA for the different defocus positions was compared to the preclinical metrics for the same defocus positions. The statistical analysis was performed using the MATLAB’s Statistical Tool box.

The function defined in Eq. (4) was used to fit the clinical VA and the preclinical metrics \(x\) by optimizing the \(R^2\) correlation coefficient. It has been previously found that through-focus VA has a linear correlation with the logarithm of different image quality metrics [30]. This is equivalent to the fitting to the exponential function described in Eq. (4). The parameters \(a\), \(b\) and \(c\) were optimized for each metric using the MATLAB’s Curve Fitting Tool box.

\[
VA(x) = ax^b + c
\] (4)

The ability of the different metrics to predict clinical VA is shown below using the \(R^2\) correlation coefficient of the fitted model and the absolute difference between the metrics and the clinical results. The \(R^2\) correlation coefficient illustrates the fidelity of the fitted model in Eq. (4) and indicates the percentage of variation in clinical VA that can be explained by the preclinical metric. The absolute difference between predicted VA and clinical VA was analyzed using ANOVA and multiple comparisons with Bonferroni correction (\(p<0.05\) was chosen as the significance level for evaluation). The absolute difference data are also depicted in Bland-Altman plots. The Bland-Altman plots indicate whether the 95% confidence interval...
of the prediction from the preclinical metric is within the confidence interval of clinical VA measurements, which is ± 0.1 logMAR [31–33].

3. Results

3.1 Prediction of the through-focus VA

Figure 2 shows the correlations between the clinical VA and the MTFa (A), wMTF (B), wOTF (C) and X-cor (D) between 0 D and −3 D of defocus. It is important to note that the x-axis represents the metric raised to the power b, as described in Eq. (4), and therefore, it depends on the metric. Figure 3 shows the correlation between the clinical VA and the MTF at 50 cpmm (A) and 100 cpmm (B).

Fig. 2. Correlations between the clinical VA and the preclinical metrics for different IOL models and for different defocus positions between 0 D and −3 D. Each point represents the clinical VA and the value of the metric for a specific IOL model and defocus position. The x-axis represents the preclinical metric raised to the power b (b = −1.0, −0.8, −0.4 and −1.4 for A, B, C and D respectively).

Fig. 3. Correlations between the clinical VA and MTF at 50 and 100 cpmm for different IOL models and for different defocus positions between 0 D and −3 D. Each point represents the clinical VA and the value of the metric for a specific IOL model and defocus position. The x-axis represents the MTF at a single spatial frequency raised to the power b. Values under the repeatability limit of the measurements according to the ISO standard (0.09) are plotted in red while values above 0.09 are plotted in blue.
Figure 4(A) shows that MTFa, wMTF, wOTF and X-cor were better correlated with the clinical VA ($R^2 > 0.89$) than the MTF at a single spatial frequency ($R^2 = 0.80$ and 0.68 for 50 and 100 cpmm respectively). MTFa, wMTF and wOTF provided significantly better correlation with the clinical VA than the MTF at 50 and 100 cpmm (p-value was 0.0387 and 0.0003 for respectively for the MTFa 0.0129 and 0.0001 respectively for the wMTF and 0.0437 and 0.0004 respectively for the wOTF). X-cor and MTF at 50 and 100 cpmm were not statistically different (p>0.05). Figure 4 shows the root-mean-square error (RMSE) between the clinical VA and the simulated VA for the different metrics.

As it is shown in the Bland-Altman plots (Fig. 5), difference and average were not correlated ($R^2 < 0.11$) which indicates that there was no proportional bias. The 95% confidence levels were lower than 0.1 logMAR for the MTFa, wMTF, wOTF and larger than 0.15 logMAR for the MTF at 50 and 100 cpmm. The mean difference was close to zero for all cases.
Fig. 5. Bland-Altman plots. The dashed lines show the mean difference (in red) and the 95% limit of agreement (in black).

Figure 6 compares the clinical VA and the simulated VA calculated from the preclinical data for the six different IOL models. Due to their lower degree of correlation and for ease of reading, simulate VA using the MTF at 50 and 100 cpmm was excluded.
3.2 Evaluation of the intermediate performance

The AU defocus provides information about the average visual performance in the intermediate range. As an example, Fig. 7 shows the AU defocus calculated from clinical data for four IOL models representing four different classes of IOLs in terms of intermediate vision: monofocal (ZCB00), high add multifocal (ZM900), low add multifocal (ZKB00) and extended range of vision (ZXR00). The AU defocus metric showed that the monofocal and the multifocal IOLs with the highest add power (+4 D) had lower intermediate performance than the multifocal IOL with lower add power (+2.75 D). The extended-range-of-vision IOL (ZXR00) had the best visual performance in the intermediate range.
Figure 7. AU defocus from clinical data for the models ZCB00, ZM900, ZKB00 and ZXR00.

Figure 8 shows the correlations between the clinical AU defocus and the MTFa, wMTF, wOTF and X-corr for the six IOL designs. There were no statistically significant differences between wMTF and wOTF (p>0.05). wOTF and X-corr provided significantly higher correlation than MTFa (the p-value for wOTF was 0.0008 and for X-corr 0.0067). The RMSE between the clinical AU defocus and the simulated AU defocus based on the MTFa, wMTF, wOTF and X-corr is shown in Fig. 9.

![Graph showing correlations between clinical AU defocus and different metrics](image1.png)

**Fig. 8.** Correlations between the clinical AU defocus and the area under the different metrics from −0.5 to −2 D for the six IOL designs.

![Graph showing RMSE for different metrics](image2.png)

**Fig. 9.** RMSE between the clinical and predicted AU defocus for the different metrics and all IOL designs.
4. Discussion

This study compares the binocular visual acuity measured clinically in pseudophakic patients to that provided by different metrics based on optical bench testing. The MTFa, wMTF, wOTF and X-cor metrics were defined in order to consider the effect of the different spatial frequencies on the through-focus visual acuity. We have found that the MTFa, wMTF and wOTF were significantly better correlated with the average clinical VA than the MTF at a single spatial frequency. As the confidence interval for MTF at 50 cpmm and 100 cpmm is larger than 0.15 logMAR, these metric are practically inadequate for predicting clinical defocus curves.

Based on this study, we conclude that the use of multiple spatial frequencies is required to reliably predict clinical visual acuity. We found that the RMSE when predicting clinical VA using MTF at 100 cpmm was twice as high as the RMSE provided by any of the metrics that incorporate multiple spatial frequencies. The differences increase for more complex IOL designs like, for example, the extended-range-of-vision IOL (model ZXR00). For the model ZXR00 (Fig. 6(F)), the RMSE when predicting the clinical VA using the MTF at 100 cpmm was 2.4 times higher than the RMSE provided by the same metric for the rest of IOL designs and 3.4 times higher than the RMSE provided by the MTFa for the same model.

Previous studies report good correlations between the clinical VA measured in pseudophakic patients and metrics that contain multiple spatial frequencies [10,15,34]. Felipe et al. found a correlation coefficient of $R^2 = 0.91$ between the VA measured in patients implanted with three multifocal IOLs and the average MTF [10]. Plaza-Puche et al. found an $R^2 = 0.85$ when comparing the clinical VA of patients implanted with three different IOLs (one monofocal and two multifocal IOLs) and an image quality metric based on the cross-correlation coefficient [34]. In this study, we used a larger number of IOL designs which included refractive and diffractive designs, different IOL materials, different amounts of spherical aberration, and different add powers. Although all the IOLs are from Abbott Medical Optics (Santa Ana, California), the models herein included cover a wide range of designs that are currently on the market. Consequently, the correlations found in this study may be applicable for a wide range of IOL technologies and designs.

Despite the effect that the phase can have on the quality of the image [35], no differences were found between the wOTF (that contains information about the phase shift) and the metrics based on MTF (MTFa and wMTF). Similar results were reported by Legras et al. when comparing the visual performance of subjects wearing multifocal contact lenses and different metrics based on MTF and PTF measurements [4].

It is important to note that the MTFa was calculated for spatial frequencies up to 50 cpmm. This value was chosen because the correlation coefficient between the clinical VA and the MTFa reaches a plateau (Fig. 10). Therefore, adding higher spatial frequencies into the calculation of the MTFa does not increase the accuracy of the metric, only the noise due to potential measurement errors. This is consistent with the fact that, when one single spatial frequency is used, MTF at 50 cpmm better predicts clinical performance than at 100 cpmm. Ginsburg showed that Snellen letters are not identified by the width of their bar segments but from its general shape [36]. Therefore letters with the same size could be differently identified, depending on the number of spatial frequencies they contain. For example, the identification of a 20/20 letter depends on the contrast sensitivity over the range of 18 to 24 cycles per degree [36], that roughly corresponds to a range of 60 to 80 cpmm, considering that 1 degree corresponds to approximately 0.3 mm on the retina. Therefore, 50 cpmm is closer to the relevant range of spatial frequencies to identify a 20/20 letter than 100 cpmm. Several studies have shown that letter recognition of the smaller letters is mediated by the low frequency channel of spatial vision [19,20], with the dominating stroke frequency for Sloan letters being 1.6 cycles per letter [17]. These studies show that the dominant spatial frequency for letter recognition is considerably smaller than the commonly used 2.5 cycles per letter. While 50 cpmm is often taken to be the spatial frequency equivalent to 0.3 logMAR, it is actually 25 cpmm that is equivalent to 0.3 logMAR. The selection of a cutoff spatial
frequency was not required for the wMTF and wOTF because the contribution of the different spatial frequencies is accounted for the neural sensitivity function.

Although pupil size was not controlled during clinical testing, preclinical measurements were performed for a 3 mm pupil. The selection of this pupil size was based on the average age of pseudophakic patients and the changes in pupil size related to age [21,22]. However, it should be noticed that IOL designs that provide a visual performance that depends strongly on the pupil size may result in larger variation between the VA predicted by the metrics and the clinical results. Moreover, although the metrics provided a good prediction of the average through-focus VA, they may not predict individual performance.

This study utilised the AU defocus as a way to evaluate the average visual performance in the intermediate range. Buckhurst et al. found that the area under the defocus curves for the intermediate, near and distance ranges were well correlated with the subjective performance provided by three different IOLs [27]. Moreover, this metric provides a single value to estimate the average visual performance over a range of defocus positions and can be used to rank the intermediate vision provided by different IOL designs. By means of the correlations found in this study, it is possible to predict the AU defocus of new IOL designs from preclinical data when implanted binocularly in a patient.

5. Conclusion

This study shows the correlation between preclinical metrics based on optical-bench data and clinical VA. We have found that metrics with multiple spatial frequency content were highly correlated with the clinical VA and therefore, can be used to better predict the visual performance of pseudophakic patients implanted with new diffractive or refractive IOL designs.