Effects of glaucoma surgery on visual field progression in open-angle glaucoma considering the floor effect

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ABSTRACT.

Purpose: **The aim of this retrospective analysis was to investigate whether trabeculectomy (TRAB) and XEN® Gel Stent implantation (XEN) – both filtrating surgery techniques – can slow down the deterioration of visual field (VF) parameters considering the floor effect, which could lead to a misestimation of pre- and postoperative VF rate of progression (ROP).**

Methods: **Included in this study were patients with open-angle glaucoma, who underwent either TRAB or XEN® gel stent implantation and who had at least three VF tests before and after surgery, over an observation period of 13 years. The annual ROP of the mean defect (MD) and the square root of loss variance (sLV) were calculated with two different censoring thresholds: by censored regression and by ordinary least squares regression (OLSR). In addition, the diagnostic range of sLV was calculated.**

Results: **48 eyes of 39 glaucoma patients were included in the study. The annual rate of MD progression was significantly reduced by filtering surgery when calculating the yearly ROP using OLSR ($p = 0.006$) and by censoring values exceeding a precalculated cut-off of 14.20 dB ($p = 0.041$) and a cut-off from the literature of 15.00 dB ($p = 0.028$). On average, the MD was impacted by a significant floor effect of 14.20 dB (95% CI: 12.83-15.56), corresponding to 17.7/59 absolute defects or 29.9% of the whole VF. When applying both OLSR and censored regression, the annual rate of sLV progression did not show a significant difference. The sLV showed a diagnostic boundary at a MD of 15.78 dB.**

Conclusion: **This study shows that filtering surgery can reduce the progression of VF in patients with open-angle glaucoma, especially those whose disease develops aggressively. This is valid even if the floor effect in advanced cases is compensated by censored regression. On average, the ROP of MD is affected by a significant floor effect at about 29.9% absolute loss of the whole VF.**

Key words: glaucoma surgery – visual field – trabeculectomy – XEN Gel Stent – floor effect – censored regression

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Introduction

Glaucoma is the second leading cause of blindness in the world. A systematic review of population-based studies reported that out of the European population aged 40 to 80 years old, 2.93% have glaucoma, the majority having open-angle glaucoma (prevalence of 2.51%) (Tham et al. 2014). Since glaucoma is a chronic progressive optic neuropathy resulting in visual field (VF) defects (European Glaucoma Society 2014), it is important to closely evaluate the progression of the VF in order to provide an adequate treatment strategy, resulting in a reduction of further spread and gravity of the disease.

With the use of the VF indices' mean defect (MD) and the square root of loss variance (sLV), an age-correlated, synoptic assessment of the patient's VF as well as a detection of the stage of the disease is made possible (De Moraes et al. 2017).

In addition to the correct performance of the investigation, there are sources of error in perimetric testing: a major one which can occur during the analysis of VF progression is the floor effect. Floor effects are common circumstances in measuring methods with a limitation of the measuring capacity. At an advanced stage of the disease, ganglion cells are not able to transduce a received signal, no matter how high the intensity of a presented light source is. Henceforth, no further progression of the disease can be detected, and the VF mistakenly appears to be stable given that no worsening is measurable. As the disease progresses, many different test locations reach their floor (i.e. absolute defect) and the overall floor effect accumulates consequently (De Moraes et al. 2017).

Glaucoma surgery is necessary when medical therapy cannot prevent further disease deterioration. Despite new developments towards minimally invasive glaucoma surgery, like XEN, trabeculectomy (TRAB) is still the most commonly performed filtrating glaucoma procedure and is considered the gold standard (Landers et al. 2012; Reitsamer et al. 2019).

The effects of TRAB and the ab interno gel implant XEN® Gel Stent (XEN® 45, Allergan Plc., Dublin, Ireland) are based on the same principle of pressure reduction: both TRAB and XEN create a permanent outflow pathway from the anterior chamber to the subconjunctival space. A frequently used antimetabolite in both surgical procedures is mitomycin C (Gregorio et al. 2018; Marcos Parra et al. 2019; Yuasa et al. 2020). The IOP-lowering effect of TRAB and XEN has been examined in several studies in the past (Gregorio et al. 2018; Reitsamer et al. 2019; Yuasa et al. 2020; Rauchegger et al. 2020), but only a few studies investigated the effect on VF deterioration (Folgar et al. 2010; Bertrand et al. 2014; Baril et al. 2017; Ratnarajan et al. 2018; Junoy Montolio et al. 2019; Liu et al. 2020).

This retrospective analysis aims to evaluate the effect of TRAB and XEN Gel Stent implantation on the ROP of VF parameters. The annual MD and sLV progression were calculated pre- and postoperatively using censored regression, taking the floor effect into consideration.

Patients and Methods

Study population

Our study included 1531 glaucoma surgeries, which were performed at our department from 1 January 2005 to 31 December 2017, which were reviewed retrospectively. Patients with OAG who underwent TRAB or XEN with no previous performed incisional glaucoma surgery were included in a raw data set, if they had at least 6 valid VF tests using the standard G pattern white-on-white applying the normal or dynamic strategy (1000 and 4000 apostilbs, respectively) of the Octopus 600/900 perimeter (Haag-Streit International, Koeniz, Switzerland) during the follow-up period. Both strategies present standard stimulus size III. The inclusion pathway is shown in Figure 1.

The VF data were obtained in the time span between 1 January 2005 and 1 April 2020. VF tests that had a reliability factor (RF) larger than 20.0 were excluded in order to guarantee reliable VF data. RF is defined as the ratio of both false-positive and false-negative answers to the sum of positive and negative catch trials presented. Only eyes that had at least 3 VF tests before surgery and at least 3 VF tests after surgery were transferred from the raw data set to the final data set. If a XEN implantation after primary TRAB/XEN or a second TRAB was performed, no additional VF data were obtained from this time-point on.

Breaking Point Calculation

First, we investigated the limiting effect of MD on sLV. Data were obtained from a raw data set in order to receive a larger sample size and consequently more reliable results. The breaking point of MD dependent on the associated sLV was estimated using the 'segmented' package of the open-source programming language R Statistics (Muggeo 2003, 2008).

A pseudoscore test and a Davies test were performed in advance, in order to test for a non-constant regression parameter in the linear predictor. The aim of this test was not to determine the exact breaking point, but to test the assumed null hypothesis 'no difference between the slope parameters' (null hypothesis: left slope = right slope) of a segmented relationship (Davies 1977; Muggeo 2016).

In a next step, the application allowed for an estimation of a new model considering an existing broken-line relationship. Consequently, the slope parameters for two connected slopes (intercept + slope) and their most probable breaking point could be calculated. This approach was used to determine a precise MD value at which the local defect (sLV) began to decrease again relating to the extent of the diffuse defect (MD).

Concerning the MD cut-off, we counted the number of absolute defects of each VF test of the censored regression data and calculated the breaking point, which corresponded to the number of absolute defects, wherefrom the MD progression deviated. The calculation was performed in the same way as for the sLV cut-off using segmented regression. Then, we performed censored regression with two different cut-offs: the calculated corresponding mean MD value (14.20 dB) and a cut-off from literature (15.00 dB), as previously recommended by De Moraes et al. (De Moraes et al. 2017). In 2 approaches, MD values exceeding 14.20 dB and 15.00 dB, respectively, were censored using censored regression via the R statistics package censReg (see below). In order to properly calculate censored progression slopes, all respective eyes with measured VF tests (preoperatively or postoperatively) that exceeded the censoring threshold were excluded from censored regression data. This is due to the fact that no suggestive calculation of the ROP was possible. To avoid overestimation of the OLSR method, these VF were included in the OLSR calculation.

The censoring threshold for sLV was calculated as follows: since the local defect, that is the sLV, is limited by the diffuse defect, that is the MD, it was not possible to set a generalized censoring threshold. Above a certain breaking point, the sLV starts to decrease again. Therefore, we calculated the censoring threshold for every distinct eye using the average ratio of sLV to the corresponding MD value and calculated the proportional sLV of an assumed MD of 15.78 dB.

Censored regression models

Censored regression models are special modifications of the standard Tobit regression model, an econometrical approach by James Tobin (Tobin 1958). In contrast to the classic Tobit approach, which is naturally left-censored, a censored regression model can also be right – or right and left-censored. The estimation is carried out by using the maximum-likelihood (ML) method, assuming that the disturbance term ε follows a normal distribution. For better illustration, see Equation 1.

Equation 1: Censored regression model as published by Henningsen (Henningsen 2010). i = measured value, y_i^* = unobserved ('latent') variable, x_i = vector of explanatory variables, β = vector of unknown parameters, ε_i = disturbance term, a = lower limit, b = upper limit.

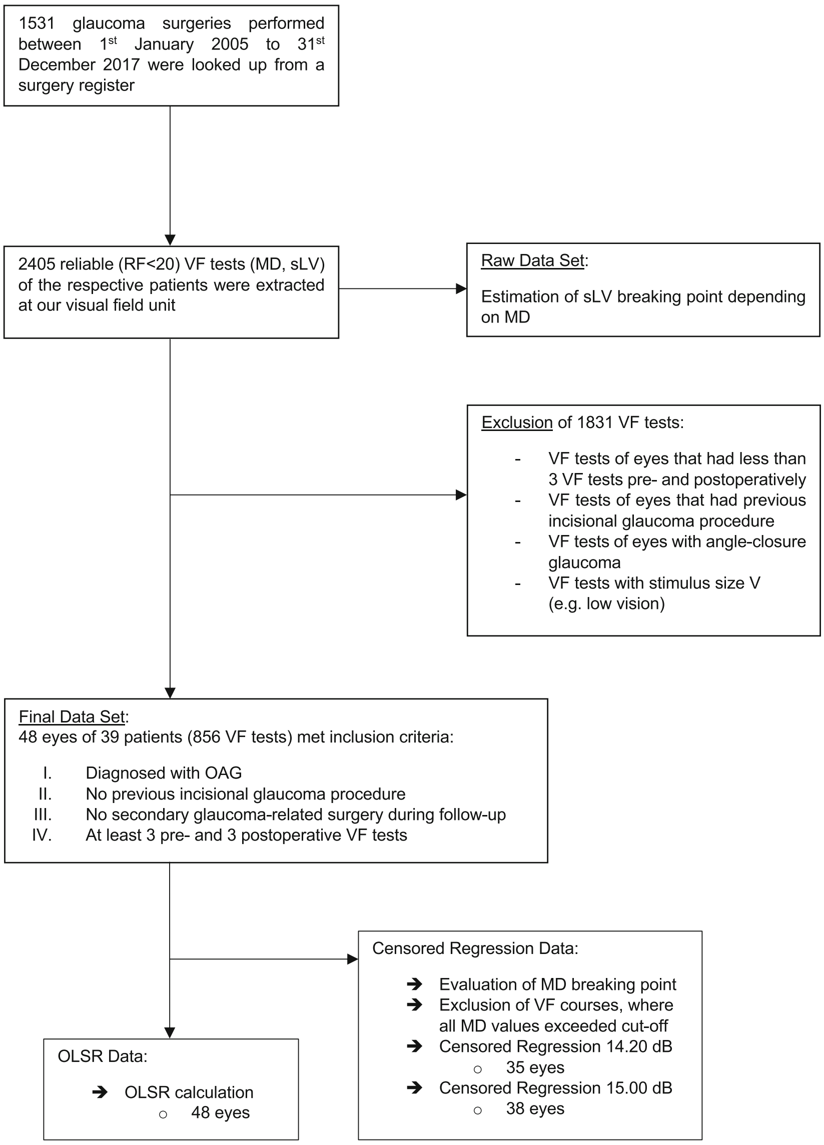

Fig. 1. Inclusion criteria and elaboration of the raw data set and the final data set, respectively. MD = Mean Defect; OAG = open-angle glaucoma; OLSR = ordinary least squares regression; sLV = square root of Loss Variance; VF = visual field; RF = reliability factor

$$y_i^* = x_i'\beta + \varepsilon_i$$
$$\begin{cases} a & \text{if } y_i^* \le a \\ y_i^* & \text{if } a < y_i^* < b \\ b & \text{if } y_i^* \ge b \end{cases} \quad (1)$$

Evaluation of VF indices

Equation 2: Calculation of MD. N = total number of test locations, d_i = sensitivity loss at test location i, MD = mean defect.

$$\text{MD} = \frac{1}{N}\sum_{i=1}^{N}(d_i) \quad (2)$$

The MD mirrors the arithmetic mean of the difference between measured values and normal age-depending values at the different test locations. A MD of 0 displays a normal VF and positive numbers directly express the extent of the damage (Flammer 1986).

In contrast, the sLV expresses the localized dissimilarity of a VF defect. If it is large, the VF damage is not homogenously distributed and indicates a glaucoma-related VF defect (Liao et al. 1988).

Equation 3: Calculation of sLV. N = total number of test locations, di = sensitivity loss at test location i, sLV = square root of Loss Variance, MD = mean defect.

$$\text{sLV} = \sqrt{\frac{1}{N-1}\sum_{i=1}^{N}(d_i - \text{MD})^2} \quad (3)$$

In eyes in which no measured MD or sLV exceeded the censoring threshold, the annual slope for MD and sLV was calculated using OLSR. If one or more measured values exceeded the respective censoring threshold, censored regression was used for the calculation of the annual VF slope as described above.

Additionally, the number of VFs that showed significant deterioration before and after surgery was calculated using a t-test for linear regression coefficients.

Statistical analysis

Descriptive data are shown as mean and standard deviation (SD). The level of significance was set to ≤0.05. Statistical evaluation was performed using the statistical analysis program SPSS, version 26 (IBM SPSS Statistics, Armonk, US) and the open-source programming language RStudio, version 1.2.5019 (RStudio, Inc., Boston, US). Diagrams were generated using R statistics. Wilcoxon signed-rank tests were used for significance testing between pre- and postoperative VF data. The Chi-squared test was used for significance testing in categorical variables. The Hodges-Lehmann estimator was used for the estimation of confidence intervals.

Results

In the end, forty-eight eyes of 39 patients were included in the final data set of this retrospective analysis. Thirty-seven eyes underwent TRAB, and 11 eyes underwent XEN stent implantation. At the time of the surgery, the mean age of the patients was 67.6 ± 10.3 years. The mean MD before and after surgery was 9.7 dB and 10.1 dB, respectively. The mean MD at the time-point of surgery was therefore 9.9 dB. The mean sLV before and after surgery was 6.0 dB and 5.8 dB, respectively. The mean total follow-up time was 10.0 ± 3.7 years, which was divided into 4.7 ± 3.3 preoperative years and 5.2 ± 3.6 postoperative years.

On average, every eye had 17.7 ± 7.9 VF tests performed during the follow-up period. A mean number of 9.0 ± 6.5 preoperative VF tests and 8.9 ± 6.4 postoperative VF tests have been performed. At the time of the patients' inclusion in the study, the mean MD was 7.0 ± 5.7 dB and the mean sLV was 4.92 ± 2.60 dB.

Patient demographics and baseline characteristics are shown in Table 1.

Breaking Point Estimation

2405 VF tests of 186 eyes out of the raw data set were used to estimate the breaking point at which the MD began to decline the sLV. Pseudoscore and Davies tests, which were performed beforehand, indicated a significant change in the slope (both $p < 0.0001$). The limiting effect of the MD on the sLV started to emerge when hitting a breaking point of 15.78 dB (95% CI: 15.48–16.09, $p < 0.0001$) (Fig. 2).

Out of the final censored regression data set, 690 VF tests were used to estimate the breaking point at which the amount of the absolute defect began to decline the MD. Pseudoscore and Davies tests performed beforehand indicated a significant change in the slope (both: $p < 0.0001$). MD was limited at 14.2 dB (95% CI: 12.83-15.56), corresponding to 17.68 absolute defects (95% CI: 15.42–19.95) of 59 test locations (29.9%) (Fig. 3).

Mean Defect

When comparing pre- and postoperative VF data of both surgery techniques combined, the mean annual MD ROP significantly decreased from 1.00 dB/year to 0.19 dB/year using OLSR (−0.81 dB/year, 95% CI: −1.26 – −0.17, $p = 0.006$), from 1.06 dB/year to 0.31 dB/year using a censoring cut-off of 14.20 dB (−0.75 dB/year, 95% CI: −1.270 – −0.012, $p = 0.041$), and from 1.10 dB/year to 0.25 dB/year using a censoring cut-off of 15.00 dB (−0.85 dB/year, 95% CI: −1.345 – −0.027, $p = 0.028$) (Fig. 3).

When performing only the TRAB analysis, the mean MD ROP significantly decreased from 1.14 dB/year to 0.24 dB/year using OLSR (−0.90 dB/year, 95% CI: −1.37 – −0.013, $p = 0.015$). In contrast, when the TRAB analysis was performed with censored regression (with the cut-offs of 14.20 and 15.00 dB) the mean annual rate of MD progression calculated was not significant. Regarding the XEN group, there were no significant differences regarding the annual MD ROP when using all calculation methods. Comparison of annual MD/sLV ROP with all calculation methods (OLSR, censored regression from 14.20 dB, and censored regression from 15.00 dB) is shown in Table 2.

Square root of Loss Variance

The annual sLV ROP changed from 0.33 dB/year to 0.19 dB/year when including both surgery groups in the analysis, using the OLSR calculation (−0.14 dB/year, 95% CI: −0.36–0.05, $p = 0.119$) and from 0.31 dB/year to 0.18 dB/year applying a censored regression (−0.13, 95% CI: −0.368-0.097, $p = 0.207$), showing no significant difference.

When only considering TRAB, there were no significant differences in pre- and postoperative annual sLV ROP detectable. Regarding XEN, sLV decreased significantly when calculated with both OLSR and censored regression ($p = 0.003$ and $p = 0.006$, respectively).

An overview of annual sLV ROP calculations is shown in Table 2.

In total, out of 48 eyes 20 showed significant progression ($p < 0.05$) of MD before surgery. In contrast, only 12 eyes showed a significant progression of MD after surgery ($p = 0.08$, Chi-squared test).

Table 1. Baseline characteristics and patient characteristics

	Mean	±SD	Median	Min	Max
Gender M/F	20/28				
Right Eye (%)	22 (45.83)				
Age	67.58	10.29	72.00	48.00	84.00
FU pre (years)	4.75	3.30	4.46	0.54	12.89
FU post (years)	5.21	3.61	4.19	0.61	14.05
FU total (years)	9.95	3.65	10.10	2.40	15.13
No. of VF pre	8.94	6.50	7	3.00	30.00
No. of VF post	8.90	6.38	7	3.00	30.00
No. of VF total	17.83	7.68	16.5	6.00	35.00
Baseline MD	7.04	5.74	5.60	-0.90	22.90
Baseline sLV	4.92	2.60	4.55	1.70	11.70
Trabeculectomy	37				
XEN	11				
Secondary Surgery	64				
Bleb Needling	43				
TRAB Revision	14				
Re-XEN	6				
Re-TRAB	1				

F = female; FU = follow-up; M = male; MD = Mean Defect; SD = standard deviation; sLV = square root of Loss Variance; VF = visual field test; XEN = XEN® stent implantation; TRAB = trabeculectomy.

Discussion

The current study proves that glaucoma surgery slows down the progression of VF in a real-life setting. Especially in advanced glaucoma, variability and floor effects play an important role in perimetric progression analysis (Lindgren 1999). By applying a censored regression model, an attempt was made to prevent the influence of the floor effect on VF progression in advanced disease stages.

In this study, the annual MD ROP was significantly reduced from 1.00 dB/year preoperatively to 0.19 dB/year postoperatively (−0.81 dB/year, $p = 0.006$) using the conventional OLSR method. When applying censored regression with two different cut-offs, first using 14.20 dB which we calculated by segmented regression, and second 15.00 dB, a value that is recommend in literature, we could still detect a significant deceleration of MD deterioration (censReg 14.20: −0.75 dB/year, $p = 0.041$; censReg 15.00: −0.850 dB/year, $p = 0.028$) in OAG patients. This observation supports the positive effect of filtering surgery despite the floor effect in advanced disease stages with severe VF defects.

At present, only a few papers report on the influence of surgery on MD progression (Bhardwaj et al. 2013; Bertrand et al. 2014; Mataki et al. 2014; Iverson et al. 2016; Baril et al. 2017). Comparing our results with other studies, it is noteworthy that many studies use 'mean deviation' of the Humphrey field analyzer (HFA, Humphrey Instruments, San Leandro,

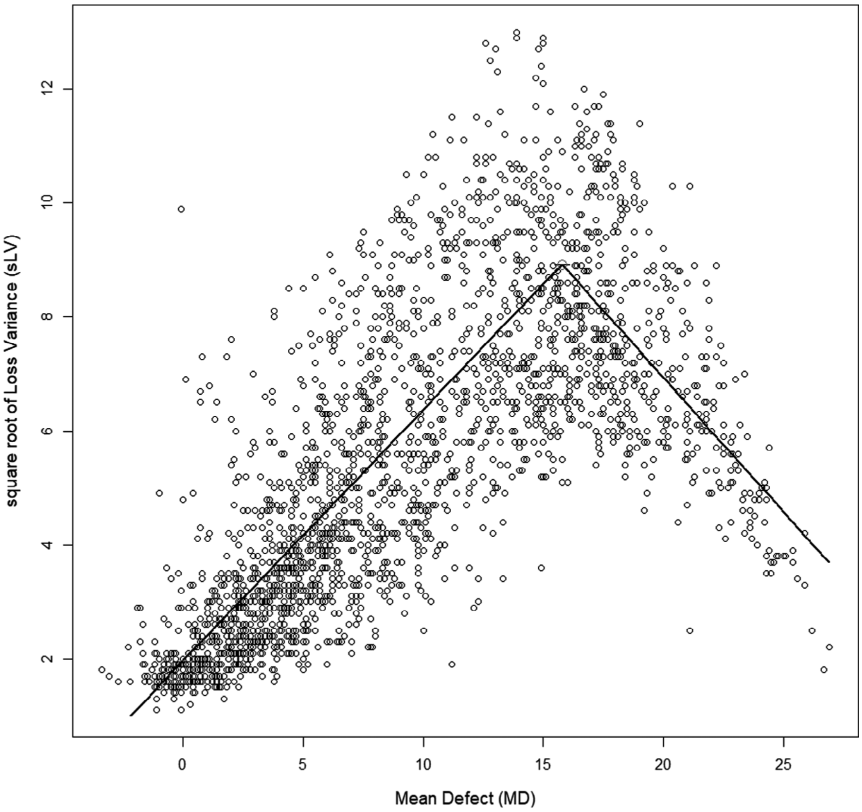

Fig. 2. Evaluating the limiting effect of MD on sLV (both expressed in dB). Breaking point (15.78 dB) is circled in grey and indicated by a vertical line. The decrease of the sLV (y-axis) in dependence of the MD (x-axis) is clearly visible starting from the estimated breaking point

California, USA). However, given that the differences between 'mean deviation' and 'mean defect' are negligible, they can be used interchangeably (Monsalve et al. 2017; Funkhouser & Fankhauser 1990). Nevertheless, it should be kept in mind that with increasing loss in the VF, the MD increases (becomes more positive) while the mean deviation decreases (becomes more negative).

In accordance with our results, Junoy Montolio *et al* published a meta-analysis based on eight studies highlighting an overall surgery-induced change in ROP of mean deviation of 0.44 (95% CI 0.25-0.64; $p < 0.0001$) dB/year. However, looking at each study individually, it is noteworthy to comment that most of them showed no significant effect on mean deviation progression and also, no censoring method was used (Junoy Montolio et al. 2019). The fact that this analysis includes eight studies with different levels of mean MD progression might also have an impact on the significance of Junoy Montolio's results. It is therefore evident that different hospitals follow different MD progression rates when assessing on the indication for surgery. For instance, in a study which compared VF parameters of 52 patients with different types of glaucoma, Bertrand *et al.* reported a preoperative annual progression rate of mean deviation of −0.36 dB/year (compared to the observed preoperative MD ROP of 1.0 dB/year in our study) (Bertrand et al. 2014). In their study, surgery induced a non-significant difference of ROP of mean deviation of 0.20 dB/year ($p = 0.15$). This observation indicates that the capacity of TRAB to slow down the MD progression applies to patients with aggressive disease courses. Additionally, we observed that the number of significant progressive VF courses before surgery could be reduced by surgery (20 vs. 12, $p = 0.08$), indicating also the beneficial effects of surgery in the case of rapid progressors.

In accordance with our results, Junoy Montolio *et al* demonstrated that the mean postoperative progression was close to −0.2 dB/year in most of the studies included in the meta-analysis and they also hypothesize that glaucoma surgery can bring rapid progressor glaucoma patients back to the normal progression range of glaucoma patients (Junoy Montolio et al. 2019). In our study, the postoperative MD progression was 0.19 dB/year.

More data will be needed to evaluate a positive effect of XEN to show a significant reduction of these measures on its own, as we could not find a significant difference in the analysis of this surgery technique. In patients undergoing TRAB, the annual rate of MD progression as calculated by OLSR was significantly lower (−0.90 dB/year, $p = 0.015$).

To our best knowledge, there are no data available on when the MD is influenced by absolute defects on average. By applying a segmented regression model, we found that a 29.9% absolute loss in the VF does affect the MD, therefore representing a significant floor effect. This corresponds to a mean MD of 14.2 dB (95% CI: 12.83 – 15.56), which is similar to the cut-off proposed by De Moraes et al of 15 dB (De Moraes et al. 2017). For clinical practice, this means that the MD values exceeding 14.2 dB should be treated with caution due to the fact that the progression analysis could be misestimated.

The comparison between OLSR and censored regression is illustrated in Figure 4 by showing the mean pre- and postoperative MD ROP per year. The mean ROP calculated by OLSR falls both preoperatively and postoperatively less steeply than the mean rates calculated by censored regression, supporting the hypothesis that OLSR underestimates the extent of progression in far-advanced disease cases. Comparing to this, the censored regression rates of progression (ROP) with cut-offs of 14.20 dB and 15.00 dB are both pre- and postoperatively steeper than the ROP calculated by OLSR. Applying censored regression to all VF courses with values exceeding 14.20 dB and 15.00 dB, respectively, we were able to demonstrate the positive effects of the surgical intervention despite the elimination of the deceptive positive effects of the floor effect.

Besides MD as an index for the general status of the VF, we decided to include sLV as a VF parameter to investigate the effect of surgery on localized defects, which are considered characteristic for early glaucomatous

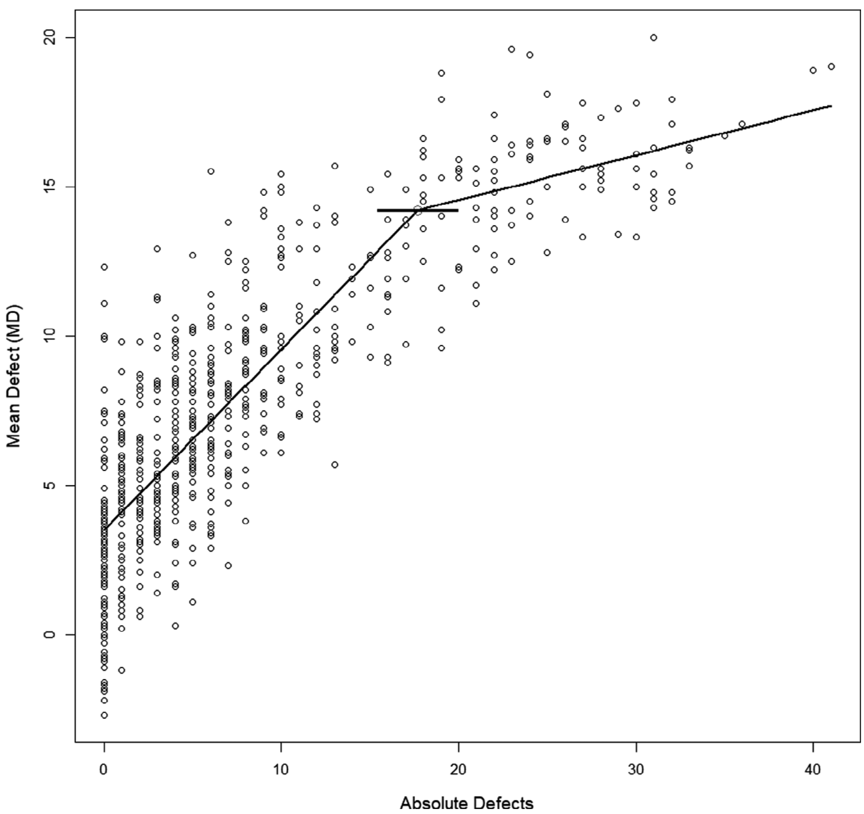

Fig. 3. Evaluating the beginning of significant floor effect of MD expressed in dB using segmented regression. Each MD (y-axis) is plotted versus the number of absolute defects per VF (x-axis). Breaking point is circled in grey, horizontal line displays 95% CI (12.83 – 15.56)

changes (Iverson et al. 2016). Due to its natural behaviour of declining at a certain stage of the diffuse VF defect, we also applied censored regression to calculate the annual rate of change. The difference between the pre- and the postoperative sLV progression was not statistically significant. This observation can be explained by the sLV's characteristics of being an indicator of early-stage glaucoma. Since we included all stages of disease severity in our study, the effect of the surgery on early-stage disease remains unknown.

When analysing the raw data set, we found a limiting effect of MD on sLV starting from 15.78 dB. Pearson *et al* conducted a similar approach analysing 17 eyes with 'pure glaucomatous loss' (Pearson et al. 1990). They showed a covariance of MD and sLV reaching up to 18 dB. Sousa *et* al and Heo *et al* found similar results. Given that we used the Octopus perimeter, instead of the Humphrey field analyzer, we assume that this to be the reason for our calculated breaking point (15.78 dB) to be slightly lower. To the best of our knowledge, no data investigating the relationship between sLV and MD in Octopus perimeters are available. Therefore, our results consolidate the conventional opinion of sLV as an early-stage glaucoma VF index. The dependency of sLV from MD is illustrated in Figure 2.

It has to be noted that our study has some limitations. While our study accurately reflects glaucoma surgeries in real-life conditions, it is – as a retrospective study – prone to selection and information biases. It is suspected that glaucoma patients enrolled in prospective clinical trials show lower ROP due to increased adherence to the therapy plan (Chauhan et al. 2014). In our study, its retrospective design could be regarded as a strength.

Regarding the effects of censored regression, it should be noted that censored regression is susceptible to the so-called expansion bias, possibly leading to an overestimation of the calculated ROP (Rigobon & Stoker 2009). However, this rather speaks for the effect of the surgery since most of

Table 2. Pre- and postoperative rates of progression (ROP) as calculated for MD using censored regression with two different cut-offs (14.20 and 15.00) and ordinary least squares regression (OLSR). For sLV, an individual cut-off proportional to a MD of 15.78 dB was calculated for each patient

	VF Index	Method	N	Mean preop (dB/y)	Mean postop (dB/y)	Difference	95%CI	p
Overall	*MD*	OLSR	48	0.998	0.187	−0.811	−1.259 – −0.172	0.006
		CensReg 14.20	35	1.059	0.309	−0.750	−1.270 – −0.012	0.041
		CensReg 15.00	38	1.103	0.254	−0.849	−1.345 – −0.027	0.028
	sLV	OLSR	48	0.333	0.191	−0.142	−0.360 – 0.053	0.119
		CensReg 15.78	48	0.311	0.178	−0.133	−0.368 – 0.097	0.207
TRAB	*MD*	OLSR	37	1.139	0.237	−0.902	−1.372 – −0.127	0.015
		CensReg 14.20	29	1.059	0.434	−0.625	−1.158 – 0.139	0.206
		CensReg 15.00	30	1.186	0.364	−0.822	−1.371 – 0.076	0.086
	sLV	OLSR	37	0.306	0.319	+0.013	−0.246 – 0.280	0.898
		CensReg 15.78	37	0.296	0.312	+0.016	−0.396 – 0.167	0.944
XEN	*MD*	OLSR	11	0.523	0.021	0.502	−1.783 – 0.517	0.248
		CensReg 14.20	6	1.061	-0.300	−1.361	−3.251 – −0.057	0.075
		CensReg 15.00	8	0.789	-0.156	−0.945	−2.184 – 0.353	0.161
	sLV	OLSR	11	0.423	-0.239	−0.662	−1.164 – −0.298	0.003
		CensReg 15.78	11	0.362	-0.269	−0.631	−1.231 – −0.221	0.006

CensReg = censored regression; MD = Mean Defect; OLSR = ordinary least square regression; sLV = square root of Loss Variance; TRAB = trabeculectomy; XEN = XEN® stent implantation.

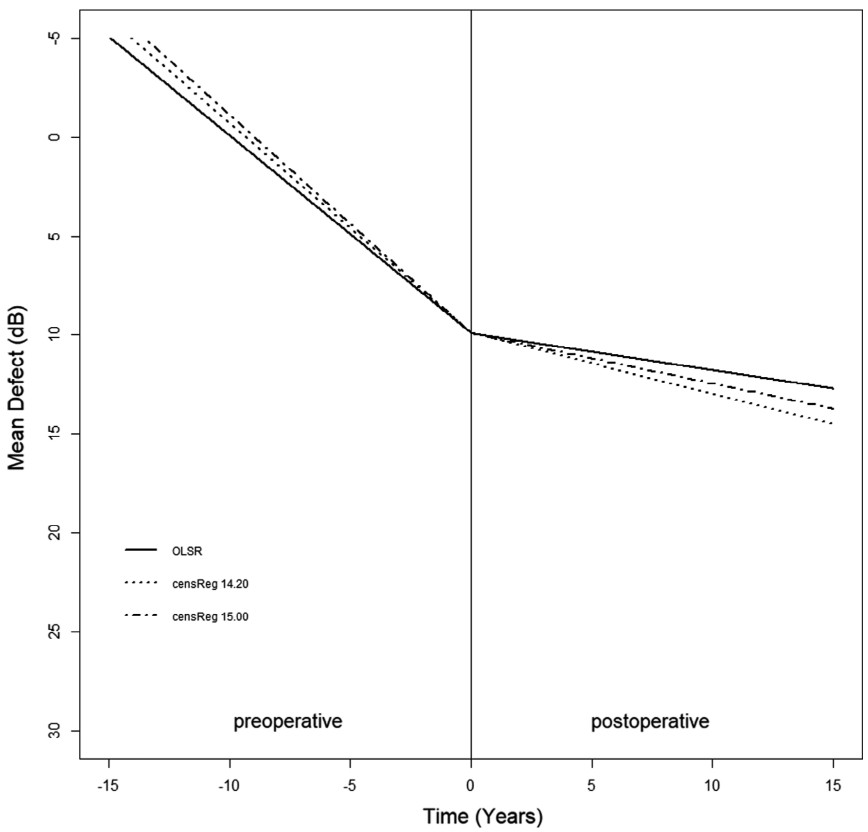

Fig. 4. Comparison of ordinary least squares regression (OSLR) and censored regression (CensReg) for mean pre- and postoperative MD ROP in filtering surgery. Horizontal line displays the time-point of surgery is displayed at year 0. Mean of each last and first MD before and after surgery is used as intercept. OLSR: ordinary least squares regression; censReg: censored regression

the MD courses are censored in ascending manner, and thus, despite potential overestimation, the ROP could be slowed down.

Although we counted the number of absolute defects per VF test, it cannot be ruled out that there are VF tests with over 15 dB at every distinct location without any absolute defect. One option to combat this could be to censor sensitivities at individual test locations before the MD calculation. This approach would add further information on the individual status of every individual test location. In contrast, MD as a 'whole field index' mirrors the mean damage to the field.

However, when analysing Figure 3, the relationship between MD and absolute defects seems to be linear and VFs with MD values above 15 dB without absolute defects in glaucoma seem rather unlikely.

Since cataract surgeries were not recorded, our results may include either positive effects of cataract surgery on the VF or may indicate a deterioration due to cataract progression. Several studies have investigated the effect of cataract development on VF parameters (Guthauser & Flammer 1988; Lam et al. 1991; Yao & Flammer 1993; Smith et al. 1997; Carrillo et al. 2005; Novak-Laus et al. 2007). Although most show an influence of cataract presence on the MD, it is expected that the effect of a mild to moderate cataract on the VF is immaterial (Guthauser & Flammer 1988; Lam et al. 1991; Yao & Flammer 1993; Stewart et al. 1995; Smith et al. 1997; Carrillo et al. 2005; Novak-Laus et al. 2007). On the other hand, a large-scale cohort study has investigated the effect of TRAB on the development of cataracts and showed a 78% higher risk of cataract development after TRAB (AGIS Investigators 2001). Despite these possible reinforcing effects of cataract development on VF progression, we were able to demonstrate a significant reduction of MD progression after surgery. Because previous studies indicated a discrepancy between IOP and VF course, we did not include IOP in our study (Chauhan et al. 2014; Baril et al. 2017).

Furthermore, we decided to relinquish implementing a control group. As MD progression indicates surgery, non-operated patients present with a less severe deterioration and therefore cannot be compared to operated patients.

In conclusion, this study was able to demonstrate that glaucoma surgery can reduce the progression of VF in patients with open-angle glaucoma significantly. If 29.9% of VF thresholds have reached their floor, the MD is affected by a significant floor effect. Therefore, censored regression implements an objective setting, which compensates the floor effect of advanced disease courses.

Ethical approval

The statutes of the ethics committee of the Medical University of Innsbruck, Austria, approve retrospective data collection as part of an observational study in a general statement. Retrospective studies are not required to be presented to the ethics committee if the data collection was carried out before 8 July 2020. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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