Non-contact Tonometry Synchronized with Cardiac Rhythm and its Relationship with Blood Pressure

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Abbreviated title/running head: IOP with NT 4000 and Blood Pressure

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ABSTRACT

Purpose: The main objectives of this study were to determine the differences between non-synchronized intraocular pressure (IOP_N) and intraocular pressure readings synchronized with cardiac pulse and try to determine if these parameters are related to blood pressure values.

Methods: One-hundred sixty five right eyes from 165 volunteers (107 females, 58 males) aged from 19 to 73 years (mean $\pm$ SD, 29.93 $\pm$ 11.17) were examined with the Nidek NT-4000, a new non-contact tonometer that allows the measurement of IOP synchronized with the cardiac rhythm. IOP measurements in the four different modes of synchronization were taken in a randomized order. Three measures of each parameter were taken and then averaged. The blood pressure was determined three times with a portable manometer and mean values of systolic and diastolic pressure and the pulse rate were computed. Mean arterial pressure (MAP) was determined as being 1/3 of systolic + 2/3 of diastolic blood pressure.

Results: The mean $\pm$ SD values for the standard intraocular pressure (IOP_N: 14.76 $\pm$ 2.86), intraocular pressure in the systolic instant or peak (IOP_P: 14.99 $\pm$ 2.85), intraocular pressure in the middle instant between heart beats or middle (IOP_M: 14.68 $\pm$ 2.76), and intraocular pressure in the diastolic instant or bottom (IOP_B: 13.86 $\pm$ 2.61) were found. The IOP_P was higher than the remaining values. A significant difference in mean IOP existed between IOP_B and the remaining modes of measuring (p<0,05). Differences were statistically significant for all pair comparisons except between IOP_N and IOP_M (mean diff. 0.072 $\pm$ 1.49 mmHg, p=0.539). Arterial blood pressure values were systolic 125.5 $\pm$ 14.22, diastolic 77.7 $\pm$ 8.38 and MAP 93.64 $\pm$ 9.44 mmHg. The pulse rate was 77.3 $\pm$ 12.6 beats per minute. Except for the MAP (p=0.025) there was

no significant correlation between different IOP values and systolic or diastolic blood pressure, or pulse rate.

Conclusions: NT-4000 is able to differentiate IOP values when synchronized with the cardiac rhythm and those differences are expected to be within a range of ± 2.5 to ± 3.0 mmHg. IOP_B seems to be the parameter whose value differs from the non-synchronized and the remaining synchronized parameters in a significant way. Other than a weak association with MAP, no significant correlation between IOP and BP was found. The measurements of IOP readings for the three modes are consistent with timings during the cardiac cycle and IOP pulse cycle.

INTRODUCTION

An estimated 66.8 million people worldwide have glaucoma and nearly 6.7 million will be bilaterally blind as a result (Klein *et al.* 1992;Leske *et al.* 1994;Tielsch *et al.* 1991). Glaucoma is not a single disease but rather a heterogeneous group of disorders that share a distinct type of optic nerve damage that can lead to blindness caused by the death of retinal ganglion cells (Quigley 1999).

Elevated intraocular pressure (IOP) is frequently associated with glaucoma and explanations for how axons become damaged are usually based on the mechanical effects of elevated IOP. Currently, important known risk factors for glaucoma include elevated intraocular pressure, advanced age, optic disc abnormalities, and family history of primary open-angle glaucoma. However, the contribution of each of these factors to the progression of glaucoma is unknown.

Optic nerve damage can occur without abnormally high IOP and, conversely, elevated IOP does not necessarily lead to optic nerve damage. Nevertheless, enormous effort has been made in recent years to develop rapid and accurate methods to measure IOP by medical and non-medical staff. Non-contact tonometers have been at the forefront of these efforts, with the newest generation of these devices demonstrating a very good agreement with Goldmann tonometry, in both healthy (Jorge *et al.* 2002) and glaucoma patients (Jorge *et al.* 2003).

IOP is not a fixed constant value but rather has pulsatile components (Evans *et al.* 2002). While elevated IOP remains the most prevalent risk factor for glaucomatous neural damage, evidence now suggests that abnormal ocular blood flow may contribute to the pathogenesis of glaucoma in some patients. Furthermore, systemic vascular anomalies seem to play a role in modern theories to explain elevation of IOP in patients with glaucoma (Emre *et al.* 2003;Grieshaber and Flammer 2005). Another association

between systemic and ocular pressure, although indirect, arises from the proposed impact of nocturnal systemic hypotension in the pathogenesis of glaucomatous damage in the form of anterior ischemic optic neuropathy and glaucomatous optic neuropathy which has been supported by different authors.(Hayreh *et al.* 1994;Yazici *et al.* 2003)

The small variation in IOP associated with each heart-beat seems to be a manifestation of the intraocular vasculature pulsating wave during the cardiac cycle. Several studies have documented the direct and significant association between IOP and systemic blood pressure (BP) in cross-sectional and longitudinal studies (Chen and Lai 2005;Klein *et al.* 2005;Wu and Leske 1997).

The NT4000 is a new non-contact tonometer with the ability to synchronize IOP measurements with the cardiac rhythm. Lam et al. compared NT-4000 in its different modes against Goldmann applanation tonometry (Lam *et al.* 2004). However the relationships and consistency of differences among measurements in the different modes have not yet been fully characterised.

The goals of this study were to determine the differences between standard IOP measurements and IOP readings synchronized with the cardiac pulse; their variability from 3 repeated measures; and whether those parameters are related to blood pressure values.

MATERIAL AND METHODS

One-hundred sixty five right eyes from 165 volunteers (58 males, 107 females) aged from 19 to 73 years (mean ± SD, 29.93 ± 11.17) were examined with the Nidek non-contact tonometer (Nidek Co. Ltd., Gamagori, Japan).

Inclusion criteria required that the subjects did not suffer from any current eye disease or injury, except ocular hypertension or glaucoma. However, despite some subjects presenting with IOP higher than 20 mmHg, there were no clinical signs of glaucoma on preliminary examination or in response to questions directed to the patient about his/her medical, pharmacological and ophthalmic history. So none of the patients in the sample population presented here had been previously or at the time of the study diagnosed with glaucoma. No subject was taking any medication for systemic hypertension that could artificially alter blood pressure parameters. Additionally, none of the subjects exhibited corneal pathology, recent corneal scarring or corneal surgery, nor were taking any ocular or systemic medication likely to induce corneal changes. All procedures followed the rules stated in the Declaration of Helsinki and were approved by the Scientific Committee of the School of Sciences at University of Minho (Portugal).

After the nature of the experimental procedures had been explained, informed consent was obtained from each subject prior to data acquisition. After the patient arrived at the clinic, they were allowed to rest for at least 10 minutes. After slit lamp examination and indirect ophthalmoscopy were performed, BP was measured three times with a portable manometer Braun Precision Sensor 2550 upgrade (Braun BP 2550 (UG) (Gillette Gruppe Deutschland GmbH & Co) for self-blood pressure measurement in the left arm following the instructions given by the manufacturer. This instrument has demonstrated to be accurate for home measures of BP, passing the European Society of Hypertension (ESH) protocol (Nolly *et al.* 2004). All measures were taken by the same

practitioner. Mean values of systolic and diastolic pressure (SBP and DBP, respectively) and pulse rate were registered with the portable manometer. The mean value of three repeated readings was computed for subsequent analysis.

The Nidek Model NT-4000 non-contact tonometer optically detects the momentary state of the cornea (applanated by air pressure) and measures intraocular pressure without touching the cornea. The instrument operates at a working distance of 11 mm and is able to detect IOP within the range from 1 to 60 mmHg. By means of the auto-alignment facility the instrument automatically performs alignment in the up, down, left, and right directions, and focuses in the back and forth directions when the measuring unit approaches the center of the pupil. The measurement procedure then starts automatically.

In addition to the non-synchronized IOP measurement mode, this instrument monitors heart pulse by a special device placed in the forehead rest of the chin-rest allowing the detection of IOP fluctuations synchronized with the cardiac rhythm. (Yaoeda *et al.* 2005) When the signals of the pulse and the completion of the alignment are detected simultaneously, the pulse synchronized IOP measurement is executed. With this instrument three different modes of synchronization with cardiac pulse are available. These include IOP measurement simultaneously with the systolic phase of systemic blood circulation (IOP_P); when the IOP is measured simultaneously with the diastolic phase of the systemic circulation (IOP_B); at an instant in the middle of these phases, this is, after systolic phase and before diastolic phase (IOP_M). IOP_N is the value which is currently measured by non-contact tonometers, that is not synchronized with heart rate. An automatic puff control protects the patient's eye from excessive air pressure, in order to improve patient's comfort and so allowing continuous measurements in the different modes to be performed smoothly.

Different IOP parameters (synchronized, non synchronized) were taken with the NT-4000 in a randomized to minimize potential effects of the consecutive measurements on IOP as a consequence of aqueous outflow by corneal compression after each air-puff. Three measures of each of the four values of IOP were taken and then averaged. Focusing to take readings was achieved in the manual mode of the instrument.

In order to estimate the potential association between BP and IOP, we correlated systolic, diastolic and mean arterial pressure (MAP) with each one of the IOP parameters. MAP was computed as being 1/3 of systolic + 2/3 of diastolic BP, as used by previous authors (Franklin 1999).

In this study, data were analyzed using the statistical package SPSS version 13.0. Variability associated to each IOP measurement mode was assessed by comparing the standard error of mean (SEM) associated to each IOP value by ANOVA, with Bonferroni post-hoc correction of p-values. SEM was computed as the standard deviation of each set of three measures divided by the square root of the number of measures.

The bias was assessed statistically as the mean of the differences compared with zero. The hypothesis of zero bias was examined by ANOVA with Bonferroni post-hoc correction of p-values. The level of significance was established at $\alpha=0.05$. The 95% limits of agreement (LoA = mean of the difference ± 1.96 x S.D. of the differences) were also calculated (Bland and Altman 1986).

RESULTS

Table 1 presents the mean values of IOP registered in the four different modes allowed by the NT-4000 non-contact tonometer along with the BP and pulse rate values. As expected, IOP_P was higher than the remaining values. Figure 1 graphically illustrates the boxplot of different IOP parameters. From this picture we can conclude that IOP_B presents the narrower interquartile range and the lower median value. Conversely, IOP_P displays the greater interquartile range and the larger distance between maximum and minimum values. Also, we can see that minimum values are similar for the four parameters while the maximum values in each boxplot seem to better reflect the nature of each parameter, this is, highest for IOP_P, lower for IOPN and IOP_M and the least for IOP_B.

Table 2 shows the pair comparisons among different IOP parameters. The highest difference was present between IOP_P and IOP_B (mean diff. 1.13 ± 1.37 mmHg, t = 7.47, p<0.001). The relationship with mean difference closest to zero was between IOP_N and IOP_M. Differences were statistically significant for all pair comparisons involving IOP_B (p<0.05).

Plots in figure 2 show the interrelationships between different modes of measuring IOP with the NT-4000. Figure 1d shows the narrowest confidence interval with LoA of ± 2.07 corresponding to the relationship between IOP_P vs IOP_M. Conversely, Figure 1c presents the widest 95% confidence interval with LoA of ± 3.00 corresponding to the relationship between IOP_N vs IOP_B. A fixed bias around 1 mmHg (0.82 to 1.13 in the present study) could be expected when comparing IOP_B with the remaining IOP parameters. Those differences were statistically significant (p<0.001). Another feature to note from this figure is the higher spread of differences between IOP_B and the remaining synchronized parameters (IOP_N, IOP_P and

IOP_M) as the measured IOP increases, while differences are closer to zero for lower values. This trend is evident in Figures 2-c, 2-e and 2-f that is not present for the remaining comparisons.

There was no significant correlation of the different IOP parameters with SBP, DBP or pulse rate. However, when comparing IOP for patients with MAP above and below 95 mmHg, we found statistically significant differences in mean IOP values. These results are shown in table 3. Mean differences in IOP values between the two MAP groups differ from almost 0.8 mmHg for IOP_P to almost 1 mmHg for IOP_M. Differences of IOP between MAP groupings are only statistically significant for IOP_M (p=0.025). We also note that standard deviation of IOP parameters are higher in the group with greater MAP, suggesting a wider distribution of IOP values within this group as compared with those presenting with lower MAP values.

Table 4 presents the values of SEM along with their range of variation for the four different modes of IOP measurement. This table shows that IOP_B displays the lower mean values of SEM while non-synchronized IOP (IOP_N) shows the higher variability. **Table 5** presents statistical details of the ANOVA test used to compare SEM values between IOP parameters. This table shows that the SEM from three repeated measures of IOP_B is significantly lower than non-synchronized IOP (p<0.001) as well as compared to the remaining synchronized measurements of IOP_P and IOP_M (p=0.003).

DISCUSSION

The relationship between IOP and systemic circulation is well established (Chen and Lai 2005;Klein *et al.* 2005;Nomura *et al.* 1999;Wu and Leske 1997). As tonometers indirectly measure pressure inside the ocular globe, it seems reasonable to think that as the choroidal circulation fills the vessels after a heart pump, the pressure inside this cavity will increase, thus affecting IOP readings.

The studies of Jorge et al (2002,2003) demonstrated good agreement between Goldmann applanation tonometry and a new NCT in healthy subjects (12.30±2.20 against 12.42±2.08 mmHg; limits of agreement 0.12±2.17 mmHg) and glaucomatous patients (18.98±2.77 against 19.08±3.02 mmHg; limits of agreement –0.09±3.30 mmHg) Despite the good agreement found in these and other studies, the ocular reflex of the pulsatile systemic circulation has been quoted as a potential source of variability during repeated IOP readings with non-contact tonometers (McCaghrey and Matthews 2001). Now with the NT-4000 non-contact tonometer is possible to measure different IOP parameters with or without synchronization with the cardiac rhythm. Lam et al. (2004) compared NT-4000 in its different modes against Goldmann applanation tonometry. Limits of agreement (LoA) obtained by those authors were within a range of approximately ± 4 mmHg for the four parameters when compared against Goldmann applanation tonometry in 31 young patients. They reported that the differences between IOP among NT-4000 measuring conditions were in the range of 0.6 to 0.8 mmHg(Lam *et al.* 2004). Our values show mean values approximately 0.5 to 1 mmHg lower than those reported by Lam et al. for IOP_P (14.99 vs 16.1 mmHg), IOP_M (14.68 vs 15.3 mmHg) and IOP_B (13.86 vs 14.7 mmHg) with similar standard deviation. Although we do not know the range of values from which Lam et al. calculated their mean values, we can assume that this difference could be due to IOP readings higher than ours as Yaoeda

et al. obtained mean values very similar to those of Lam et al. averaging values between 6 and 34 mmHg. Interestingly, our mean value with no synchronization is similar to that of Yaoeda et al (2005).

In the present study, the NT-4000 non-contact tonometer has shown good consistency among the different measures provided. The LoA between ±2.07 to ±3.00 mmHg support this assumption. This instrument has previously demonstrated a very good agreement with Goldmann applanation tonometry (Lam *et al.* 2004;Yaoeda *et al.* 2005) Our results for different modes of measuring (IOP_P, IOP_M and IOP_B) are slightly lower than those found by previous authors. Differences in sample size, age distribution, IOP range and ethnicity among the samples could account for such differences. As reported by Yaoeda et al., (2005) our results demonstrate that synchronization is associated with a better agreement between a set of three repeated measures taken within the same session. Our results also support this assumption, particularly for IOP_B.

BP parameters in our population are comparable to those presented by Nomura et al. (1999). Those authors found a positive correlation between IOP, SBP and body mass index (BMI). Although we did not find significant relationships between different parameters of IOP and SBP or DBP, we observed a trend towards an increase in IOP as BP raises. Klein et al (2005) found both SBP and DBP to be associated with higher values of IOP as obtained with Goldmann applanation tonometry. Their cross-sectional results, revealed that an increase of 10 mmHg in SBP and DBP will be associated with an increase in IOP of 0.3 and 0.6 mmHg respectively. Similar results were found in a retrospective study with a change in IOP of 0.24 mmHg corresponding to a change in SBP of 10 mmHg. (Chen and Lai 2005) The Barbados Eye Study demonstrated a direct

association between systemic hypertension (defined as increased SBP) and increased IOP. (Wu and Leske 1997)

We did find a more obvious and significant relationship regarding mean arterial pressure MAP by splitting our sample into two subgroups, those with MAP ≤ 95 mmHg and those whose MAP was higher than 95 mmHg. This cut-off value was chosen because it represents the nearest ±5 mmHg interval to the average MAP we found in our population (93.64 mmHg).

For the group with MAP higher than 95 mmHg all IOP parameters are higher, with mean differences of approximately 1 mmHg. We speculate that one possible explanation for this finding could be that patients within the group presenting MAP above 95 mmHg are significantly older than those in the lower MAP group. However this finding warrants further investigation.

The clinical implications of the present study focus on the application of the non-contact tonometer NT-4000 to measure synchronized IOP values. Clinicians should expect a better repeatability when using the synchronization facility than with non-synchronized measurements. This could also be of interest when designing research protocols as this value has a lower variability and correlates significantly with IOP_P and IOP_N.

Summary

The present study has shown that the NT-4000 non-contact tonometer is able to differentiate IOP values when synchronized with the cardiac rhythm and those differences are expected to be within a range of ± 2.5 to ± 3.0 mmHg. As expected, IOP_P was higher than the remaining synchronized and non-synchronized values. IOP_N as measured without synchronization should not be significantly different from

IOP_M value with a maximum difference of ± 2.0 mmHg (95% LoA). This study also

demonstrates that measures of the diastolic IOP (IOP_B) with the NT4000 would be

expected to be significantly different and will present higher repeatability than the

remaining parameter. Compared to non-synchronized IOP values (IOP_N), the higher

repeatability of IOP_B could bring advantages in statistical terms (i.e. estimating sample

size) when planning to use IOP parameters in clinical studies. Regarding the

relationships between IOP and BP, only mean arterial pressure (MAP) showed a

relationship, demonstrating a rise in all IOP values with higher values of MAP, except

for IOP_P. The potential of NT-4000 to differentiate normal from glaucomatous eyes is

still to be explored.

Table 1. Descriptive statistics regarding IOP and BP values

	Minimum	Maximum	Mean	Std. Deviation
IOP_N	7.7	23.7	14.76	2.86
IOP_P	8.0	24.0	14.99	2.85
IOP_M	8.0	25.0	14.68	2.76
IOP_B	7.0	22.3	13.86	2.61
Systolic Blood Pressure (SBP)	94	186	125.5	14.22
Diastolic Blood Pressure (DBP)	60	107	77.7	8.38
Mean Arterial Pressure **MAP = (1/3 SBP +2/3 DBP)**	71.67	133.67	93.64	9.44
Pulse Rate (bpm) [*]	47	118	77.3	12.6

[*]All measures in mmHg except "pulse rate" in beats per minute (bpm)

IOP_N: standard IOP; IOP_P: peak IOP; IOP_M: middle IOP; IOP_B: bottom IOP

Table 2. Paired comparisons among IOP values.

Pair	Mean difference	95% Confidence interval of the difference		Significance*
		Lower	**Upper**	
IOP_N vs IOP_P	-0.24	-1.05	0,57	1
IOP_N vs IOP_M	0.072	-0.74	0.88	1
IOP_N vs IOP_B	0.90	0.08	1.70	0.022
IOP_P vs IOP_M	0.31	-0.50	1.12	1
IOP_P vs IOP_B	1.13	0.32	1.94	0.001
IOP_M vs IOP_B	0.82	0.01	1.63	0.044

*ANOVA, post-hoc Bonferroni corrected p-values
  IOP_N: standard IOP; IOP_P: peak IOP; IOP_M: middle IOP; IOP_B: bottom IOP

Table 3. IOP values for two separated groups of patients with (MAP) below 95 mmHg

(n=96) and above 95 mmHg (n=69).

	MAP (mmHg)	Mean	SD	Mean Difference	Significance*
IOP_N	≤95	14.39	2.45	-0.87	0.067
	>95	15.26	3.29		
IOP_P	≤95	14.67	2.45	-0.78	0.100
	>95	15.45	3.30		
IOP_M	≤95	14.28	2.42	-0.97	0.025
	>95	15.25	3.09		
IOP_B	≤95	13.51	2.11	-0.85	0.053
	>95	14.36	3.12		

*Paired sample T-test

IOP_N: standard IOP; IOP_P: peak IOP; IOP_M: middle IOP; IOP_B: bottom IOP

Table 4. Mean values, SD and range of SEM for the different IOP parameters resulting

from the three repeated measures

|	Standard Error of Mean			
	Mean	**Min**	**Max**	**SD**
IOP_N	0.57	0.00	1.53	0.35
IOP_P	0.51	0.00	1.53	0.32
IOP_M	0.51	0.00	1.67	0.35
IOP_B	0.42	0.00	1.53	0.26

[*]All measures in mmHg
IOP_N: standard IOP; IOP_P: peak IOP; IOP_M: middle IOP; IOP_B: bottom IOP

Table 5. Paired comparisons among standard error of mean for IOP parameters.

| Pair	Mean difference	95% Confidence interval of the difference		Significance*
		Lower	Upper	
SEMIOP_N - SEMIOP_P	0.06	-0.04	0.15	0.612
SEMIOP_N - SEMIOP_M	0.05	-0.04	0.15	0.845
SEMIOP_N - SEMIOP_B	0.15	0.05	0.24	<0.001
SEMIOP_P - SEMIOP_M	-0.006	-0.1	0.09	1
SEMIOP_P - SEMIOP_B	0.09	-0.005	0.18	0.073
SEMIOP_M - SEMIOP_B	0.1	-0.1	0.19	0.045

*ANOVA, post-hoc Bonferroni corrected p-value

Figure 1. Box plots illustrating median, quartiles, and extreme values for the different

IOP parameters measured with the NT-4000.
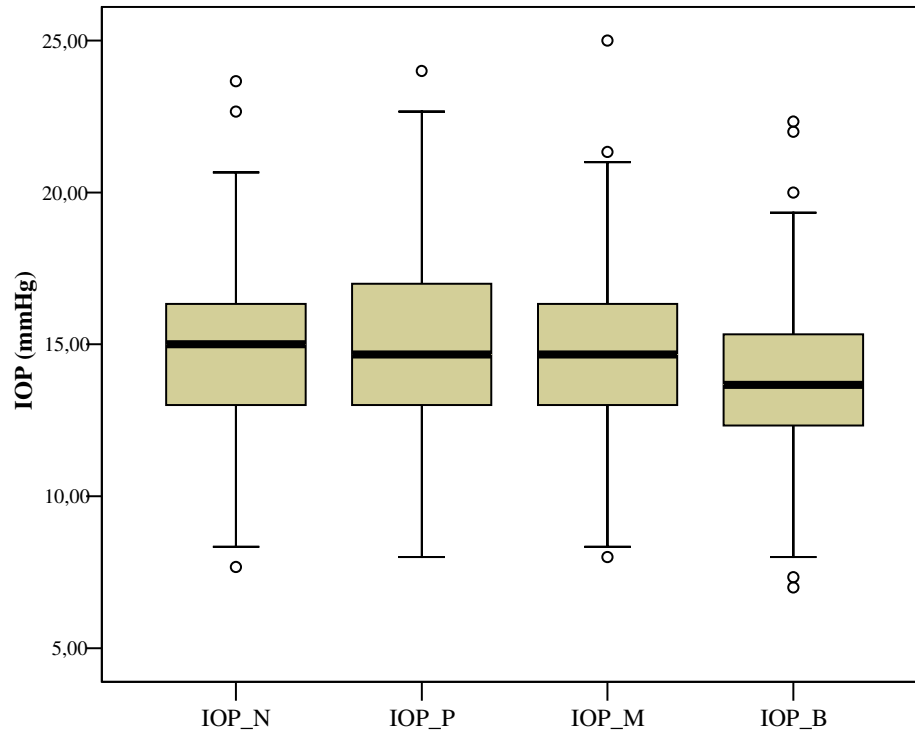
IOP_N: standard IOP; IOP_P: peak IOP; IOP_M: middle IOP; IOP_B: bottom IOP

Figure 2. Bland and Altman plots of difference vs mean of IOP values for (a) IOP_N vs IOP_P, (b) IOP_N vs IOP_M, (c) IOP_N vs IOP_B, (d) IOP_P vs IOP_M, (e) IOP_P vs IOP_B, (f) IOP_M vs IOP_B. The mean of the difference and the 95% confidence interval limits (solid lines) between techniques are indicated. Values of mean differences are listed in table 2.
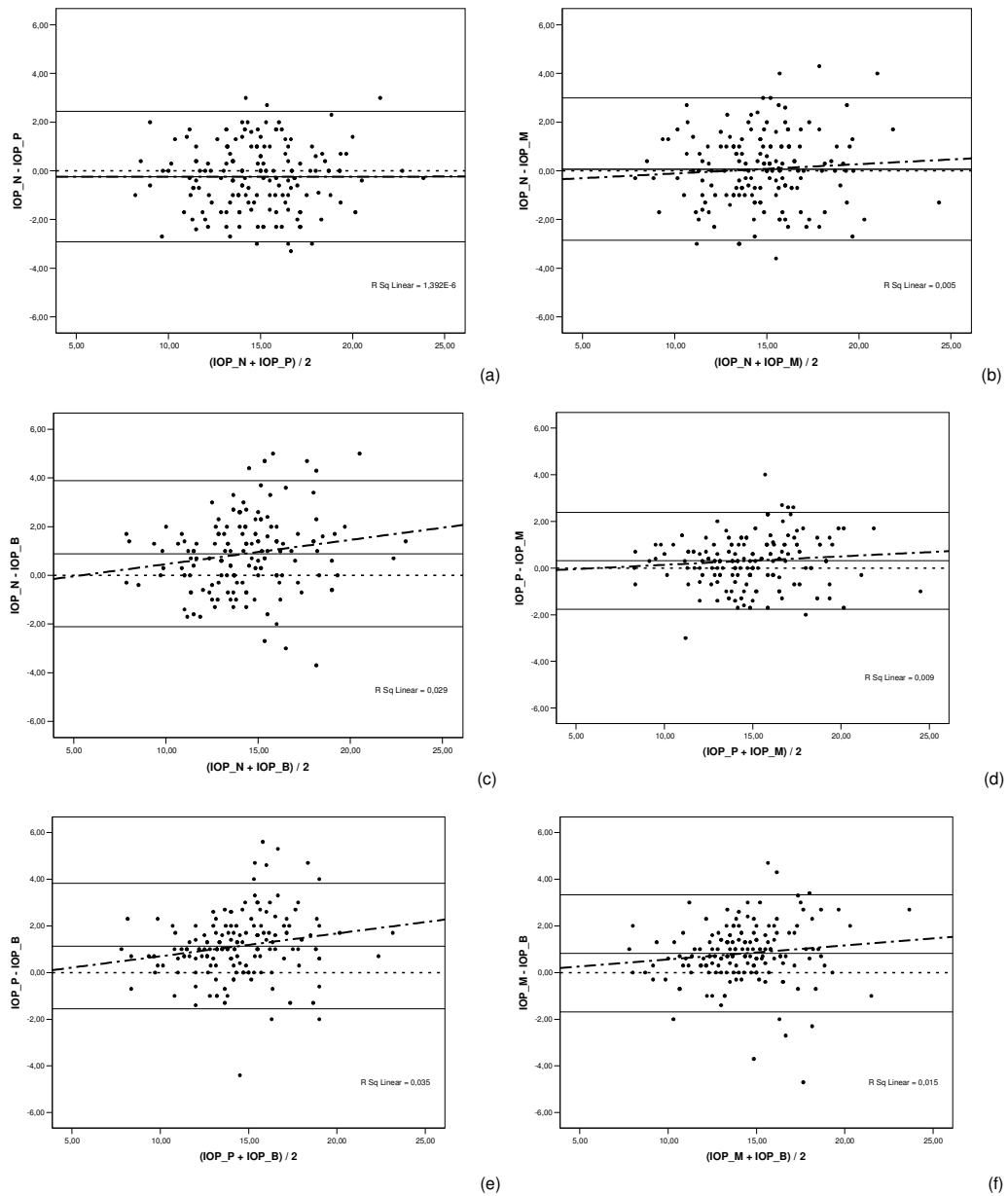
IOP_N: standard IOP; IOP_P: peak IOP; IOP_M: middle IOP; IOP_B: bottom IOP

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