ICare Pro: age dependent effect of central corneal thickness on intraocular pressure in glaucoma and ocular hypertension patients

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Abstract

Purpose: Measurement of the exact intraocular pressure (IOP) is essential in glaucoma diagnosis and follow-up, thus all therapeutic options affect IOP in order to win sighted lifetime. As it is known that corneal properties of glaucoma patients differ from normal subjects, the present study aimed to investigate the influence of CCT on rebound tonometry (ICT, ICare Pro) in glaucoma and ocular hypertension patients in dependency of age additionally considering different times of day.

Methods: Three hundred sixty-two eyes of 190 subjects were included: 339 open-angle glaucoma and 23 ocular hypertension. IOP was measured at 5 different times of day (6 a.m., 12 a.m., 4 p.m., 9 p.m., and 0 p.m.) by Goldmann applanation tonometry (GAT) and Icare Pro rebound tonometry in a sitting position. Central corneal thickness was measured by central ultrasonic pachymetry (Pachymeter SP-100). Δ ICT was calculated as the difference of GAT, corrected according to age and CCT, and ICT, respectively at each time point.

Results: All different GAT time points data correlated significantly ($p<0.05$) with ICT time points. An age effect was observed on overall ICT ($p=0.02$). A decrease of ICT was observed with increasing age. The within differences among ICT repeated measurements were significant as well. Additionally, repeated means of Δ ICT correlated significantly with age and CCT. Intercepts and coefficients were offered for each time point, respectively. GLM model yielded a relation between MD (dependent variable) and age together with CCT (age: $p<0.0001$) and (CCT: $p=0.043$).

Conclusions: IOP measurements with ICare Pro were shown to be dependent on age, CCT and time of day in glaucoma and ocular hypertension patients. Thus, aging, corneal biomechanical properties and circadian rhythms should be taken into consideration when adjusting IOP.

Keywords: intraocular pressure; glaucoma; ocular hypertension; rebound tonometry; central corneal thickness.

Introduction

Glaucoma is the second major cause of blindness in developing countries [1]. As ocular neurodegenerative disease, its diagnosis is based on an elevated intraocular pressure (IOP), visual field defects and corresponding alterations of the optic nerve head. The main risk factor of converting to glaucoma or its progression is a non regulated IOP, thus all conservative or surgical therapies are based on lowering IOP to an individual target level. Several techniques were developed to measure IOP (e. g. Goldmann applanation tonometry (GAT), rebound tonometry (e. g. ICare Pro, ICT) and Dynamic Contour Tonometry (DCT)). GAT yields highly reproducible and accurate measurements, therefore this technique is the gold standard in IOP measurements [2]. However, it has some disadvantages, for example, patients have to be in an upright position and the device is not portable. Also, measuring childrens` IOP is often a challenging topic. In these special clinical situations, alternative tools for measuring IOP might be useful. One of these devices is the rebound tonometry. These portable tonometers measure IOP without the demand of topical anesthesia and are well tolerated by kids. Additionally, some of them (i. e. ICare Pro) enable IOP measurements in a supine position.

Several tonometers are available for different approaches – 'normal' IOP measurements in a sitting body position (iCARE TA0li), self-tonometer for the patients at home (iCare Home, iCare ONE) or IOP measurements in sitting and supine positions (Icare Pro). Comparison of concordance of the different devices, iCare Pro (16.6±4.77 mmHg) yielded better results than iCare ONE (17.5±5.42 mmHg) compared to GAT (16.6±4.43 mmHg) [3]. Good correlations were found for iCare Pro with GAT as well as dynamic contour tonometry [4]. Additionally, iCare Pro was superior compared to Icare TA01 regarding consensus to GAT [5]. IOP data with good reliability can be measured using Icare Pro [6].

IOP measurements (e.g. GAT, ICT) were influenced by biomechanical properties of the cornea (e.g. central corneal thickness, CCT; corneal hysteresis)[7-10], thus several approaches were done to get the `real` unaffected IOP[11-14]. Additionally, biomechanical and viscoelastic properties of the cornea were known to differ between glaucoma or ocular hypertension patients and normal subjects [15,16] and vary significantly during day [17]. Thus, it was the aim of this study to investigate the influence of CCT and age on ICT in glaucoma and ocular hypertension patients, considering the time of day.

Material and Methods

In a prospective study 362 eyes of 190 subjects (75 male, 115 female) of the Department of Ophthalmology, University of Erlangen-Nürnberg at the Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU) and from the Erlangen Glaucoma Registry (EGR; ClinicalTrials.gov Identifier: NCT00494923; ISSN 2191-5008, CS-2011 [18]) were recruited: 339 eyes of open-angle glaucoma patients (primary, POAG, and secondary, SOAG) and 23 eyes of ocular hypertension patients (OHT). Mean age was 67±12 years (range 22-88 years, figure 1). Demographic data of all probands can be seen in table 1. All patients underwent a complete ophthalmological examination including slit-lamp biomicroscopy, funduscopy, standard white-on-white full-field perimetry (Octopus 500, G1 protocol, Interzeag, Schlieren, Switzerland) and Spectralis Optical Coherence Tomography (Spectralis® OCT Version 1.9.10.0, Heidelberg Engineering, Heidelberg, Germany). Central corneal thickness was measured by central ultrasonic pachymetry (Pachymeter SP-100, Tomey, Aichi, Japan). Informed consent was received from all probands. The study was approved by the local ethics committee and performed according to the tenets of the Declaration of Helsinki.

Tonometry

IOP was measured by GAT (Haag Streit, Koeniz, Switzerland) and Icare Pro rebound tonometry (Tiolat, Oy, Helsinki, Finland), respectively. Before each measurement, the patients had to take a seat for at least 10-15 minutes. Afterwards, IOP was measured in the sitting position in the doctor's office or in the patient's room. Icare Pro measurements were done by the same person (C.S.). GAT measurements were done by ophthalmologists of the clinic, as GAT can only be performed by ophthalmologists in Germany. All observers worked independently of each other masking a clinical trial and choosing randomly the patients, based on that the observers did her/his measurements (20 minutes interval between the measurements). GAT measurements were done by using anaesthesia, thus ICT measurements consecutively after GAT were done under continuing anaesthesia. Yet, no additional anaesthesia was instilled for ICare Pro measurements. Tonometry was done at 5 different times of the day (6 a.m., 12 a.m., 4 p.m., 9 p.m., and 0 p.m.) in order to analyze a circadian rhythm of IOP.

Rebound tonometry - ICare Pro

ICare Pro tonometry is used as a hand-held device. Contrary to GAT, which measures the bounce to applanate a distinct part of the cornea (Imbert–Fick law), ICare Pro measures the deceleration of a small magnetized probe on the surface of the cornea at a distinct distance of 3-7 mm (according to the manufacturer's manual). Additionally, its rebound time was measured, calculating IOP of deceleration and rebound time. ICare Pro showed as final result the mean of all 6 measurements in a colored background corresponding to variance: red (>25% deviation of IOP), yellow (15-25% deviation of IOP), and green (<15% deviation of IOP).

Statistical analysis

The relations between age with GAT, and age with ICT data were tested with a generalized linear model (GLM) with repeated measures design. For each model, we examined if the test of sphericity was violated. Therefore, two p-values were calculated, one for the transformed variables (the linear, quadratic, and cubic time variables in this case) and the second on orthogonal components. The results for each model suggested that the assumptions were met. We tested the hypothesis if the within-subjects factors differ as a function of the between-subjects factors (the "GAT*age" and "ICT*age" effects). The univariate repeated measures ANOVA presents two different adjustments of the p levels for the F ratio. The first adjustment is given by the Greenhouse-Geisser epsilon (ε) and the second adjustment is the Huynh-Feldt episilon.

The relations between standard perimetric variables (mean defect, MD; loss variance, LV) and morphological parameters (global retinal nerve fibre layer, gRNFL) were done by a GLM model.

For the correction factors for ICT data, we started from the repeated GAC measures. A mixed model (with the intercept as a random effect) was built in order to calculate the age coefficient for the different GAC time points. All GAT data were corrected according to the estimated age coefficients and to the "CCT-equation" (ΔIOP = (-0.0423 x CCT) + 23.28), published by Kohlhaas et al.. We called the new fitted value 'corrected GAT', and this new parameter is supposed to be the 'real' IOP. Then, we proceeded to calculate the differences between 'corrected GAT' and ICT (i.e Δ ICT), which can be interpreted as the difference of 'real' IOP to ICT. For each time

points of Δ ICT we applied a new mixed model to estimate the intercepts, the age coefficients, and CCT. All the above elaborations were done using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

For the calculation of the Pearson correlations coefficients and their confidence intervals, between GAT and ICT repetitions, we used "*corrgram*" package from RStudio (Version 1.0.136 – 2009–2016 RStudio, Inc.).

Results

Icare Pro rebound tonometry (ICT) and Goldmann applanation tonometry (GAT)

Icare Pro rebound tonometry measured a mean of 15.35±4 mmHg (range 6-34 mmHg) at 6 a.m., 15.78±4 mmHg (range 7-36 mmHg) at 12 a.m., 16.0±5 mmHg (range 3-43 mmHg) at 4 p.m., 14.61±4 mmHg (range 6-33 mmHg) at 9 p.m. and 14.53±4 mmHg (range 6-33 mmHg) at 0 p.m.. Consecutively GAT measurements yielded mean IOP of 13.83±4 mmHg (range 5-32 mmHg) after ICT measurement at 6 a.m., 14.27±4 mmHg (range 3-35 mmHg) after ICT measurement at 12 a.m., 14.91±4 mmHg (range 4-39 mmHg) after ICT measurement at 4 p.m., 13.91±4 mmHg (range 5-36 mmHg) after ICT measurement at 9 p.m. and 13.77±4 mmHg (range 4-35 mmHg) after ICT measurement at 0 p.m.. Mean CCT was 533±37.0 µm (range, 429-640 µm, figure 2). Correlations between GAT and ICT (with the relative intervals of confidences) were presented in figure 3. All the Pearson correlations between GAT and ICT were significant ($p<0.05$).

Relations between ICT and GAT variables with age and CCT

General linear model with repeated measures revealed that age has an effect on ICT (figure 4). With increasing age, ICT showed a decrease. Furthermore, the results suggested significant differences in the ICT means at the five-time points taking in consideration the variable age (except for ICT at 0 p.m., table 2). Moreover, there was a significant dependency between the ICT repeated measurements and age together with CCT (interaction ICT*age p=0.02).

However, the relation between age and the repeated measurements GAT at 5 different time points was not significant.

Correction factors for ICT data

Corrected GAT, corrected according to age and to Kohlhaas et al., is supposed to be the `real`IOP, unaffected by CCT. Thus, the difference of this 'CCT-corrected GAT' and ICT (i.e Δ ICT) is the difference of 'real' IOP to ICT. The univariate tests of hypotheses for within subject effects was significant for all ICT data at different time points ($p<0.0001$, table 3). As repeated means of Δ ICT correlated significantly with age and CCT, intercepts and coefficients were calculated for age and CCT, respectively at each time point:

$$\Delta ICT_{0\ p.m.} = 0.03*age - 0.05*CCT + 25.5$$

$$\Delta ICT_{6\ a.m.} = 0.06*age - 0.05*CCT + 22.9$$

$$\Delta ICT_{12\ a.m.} = 0.03*age - 0.05*CCT + 24.6$$

$$\Delta ICT_{4\ p.m.} = 0.03*age - 0.05*CCT + 25.5$$

$$\Delta ICT_{9\ p.m.} = 0.004*age - 0.06*CCT + 33.8$$

Relations between ICT variable and clinical parameters

The last GLM model was built in order to investigate the relation between MD (dependent variable) and age together with CCT (age: $p<0.0001$) and (CCT: $p=0.043$). In the Contour Fit plot (figure 5) we could observe that with an increase of age, we have an increase of MD and a decrease of CCT. Other significant relationships were not detected with the other variables (gRNFL, LV).

Discussion

Measurement of IOP is essential in glaucoma diagnosis and follow-up. Each single millimeter of mercury can increase glaucoma progression rate about 12-13% [19]. All therapeutic options try to lower IOP in order to win sighted lifetime. Thus, it is the aim to get exact data of each patient, considering the patients' individual parameters (e.g. CCT, corneal hysteresis). GAT data yielded a good correlation with ICT at each time point. The general linear model presented a significant relationship between ICT repeated measurements and age together with CCT, being one biomechanical factor of the cornea. However, this observation was not done for GAT. Mean defect, a standard functional parameter, correlated with age and CCT. Yet, global retinal nerve fibre layer and loss variance did not show this dependency. IOP, measured with ICare Pro, showed an age-, CCT- and time of day-dependency in glaucoma and ocular hypertension patients.

The best and 'real' IOP measurement yield an invasive technique, which is not common in clinical all day life [7]. Measuring IOP with GAT after adjustment of IOP at a fixed defined level invasively, Kohlhaas et al. were able to offer an equation for GAT measurements considering CCT, yet no other biomechanical properties of the cornea (e.g. corneal hysteresis). It is certainly not possible to correct IOP adequately only considering CCT. Further intrinsic (e.g. ocular factors) and extrinsic factors (e.g. time of day) as well as aging should be taken into consideration when correcting IOP. Up to date, GAT is the gold standard in IOP measurements. It is a well-known effect that GAT measurements are dependent on central corneal thickness. CCT decreased with increasing age in the present study group, going along with the data of Ocular Hypertension Treatment Study (OHTS) [20]. Considering CCT dependency on GAT, correction factors were offered in literature, varying from 0.12 – 0.4 mmHg per 10 µm CCT [7,21-23]. One explanation for these differences may be in the investigated patients' groups itself - the different ages of the cohorts [14]: mean ages of 35 years (21-62 years) [21], 48 years (13-87 years) [24], 60 years (40-80 years) [25] or 73 years (18-91) [7] were described in the studies, thus Spoerl et al. hypothesized that age may affect each single correction factor and has to be considered in addition to CCT [14]. Like GAT, rebound tonometry was observed to be affected by CCT in the present study. This finding went along with previous studies, presenting correlation coefficients 'r' for the relationship of CCT and ICT varying between +0.167 (50.38±23.58 years) [26] and +0.385 (46.1±16.8 years) [27]. Only one negative correlation was found with a correlation coefficient of -0.243 (mean age 70.1±13.9 years) [4], and one study

presented no correlation of ICT with CCT at all (mean age 22.3±3.3 years).[28] These recent studies were done in diverse study populations with different age groups (e. g. mean age: 9.8±3.1 years [29], 59.3±19.9 years [30], 63.8±15.6 years [31]), thus consecutive different correlation coefficients of CCT and ICT were observed. The data of the present study confirmed this finding that ICT repeated measurements were dependent on CCT, yet additionally on age. However, only few correction factors are offered in literature up to now, considering the relationship of CCT on ICT – none of them additionally considering the factor 'age': a correction factor of 4 mmHg (mean age of the study group 33.0±11.8 years) [32], 2.7 mmHg (50.38±23.58 years) [26] and 5.3 mmHg (53 years) [33] per 100 µm CCT. Plotting these factors against age, a trend for increasing correction factors with increasing age can be seen (figure 6). These recent studies substantiate an additional age- and CCT-dependent effect on ICT. These two dependencies might be seen as two separate influencing factors or potentially with a common basis. Biomechanical properties of the cornea change with increasing age. Corneal hysteresis and corneal resistance factor decreased with increasing age,[34,35] thus, these additional corneal properties should be taken into consideration when adjusting IOP. The present data of a general linear model with the repeated design provided that ICT repeated measures were dependent of age, with ICT showing a decrease with increasing age. Additionally, ICT data presented an additional time-dependent effect on ICT. Thus, circadian rhythms should be taken into consideration when adjusting ICT. Rebound tonometers are easy to handle, quick and can be used by all health care personal. Especially, children benefit from this non-contact IOP measurement, which does not uses air puffs or anesthetic eye drops.

Our study is not without limitation. Several other intrinsic and extrinsic factors might affect IOP like corneal curvature or biomechanical properties (e.g. corneal hysteresis), which we did not control in the present study. Thus, further studies are necessary to investigate an additional effect of these corneal properties on ICT measurements. Further on, the correction factor for ICT in younger persons, especially children, might be of further interest.

Conclusion

Intraocular pressure measurements of iCare Pro were observed to be dependent on age, CCT and time of day in glaucoma and ocular hypertension patients. Intrinsic (e.g. corneal

characteristics) and extrinsic factors (e.g. circadian rhythm) influence IOP in a multifactorial way and should be taken into consideration when adjusting IOP.

Legends

Table 1: Demographic data of all patients (mean±standard deviation).

Table 2: Age dependency: ICare Rebound tonometry at 5 time points (0 p.m, 6 a.m., 12 a.m., 4 p.m., and 9 p.m.).

Table 3: Partial correlation coefficients and p-values of pairways comparison of ICare Rebound tonometry at 5 time points (0 p.m, 6 a.m., 12 a.m., 4 p.m., and 9 p.m.).

Figure 1: Distribution of age in 190 patients.

Figure 2: Distribution of central corneal thickness in 362 eyes.

Figure 3: Correlation between ICare Pro rebound tonometry and Goldmann applanation tonometry at 5 time points (relative intervals of confidences; 6 a.m., 12 a.m., 4 p.m., 9 p.m., and 0 p.m.). All the correlations values have a p-values <0.05.

Figure 4: Age dependency of ICare Pro rebound tonometry at 5 time points (95% confidence interval; 6 a.m., 12 a.m., 4 p.m., 9 p.m., and 0 p.m.).

Figure 5: Contour Fit plot of age with the mean defect (MD) and central corneal thickness (CCT): an increase of MD, as well as a decrease of CCT, was observed with increasing age.

Figure 6: Previously published IOP correction factors [mm Hg/100 µm] in dependency of the mean age of the study group [years].

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Table 1: Demographic data of all patients (mean±standard deviation).

	OAG	**OHT**
Number of eyes [n]	339	23
Gender [m/w]	72/107	3/9
Age [y]	68,4 ± 11,3 SD	57,1 ± 17 SD
MD [dB]	9,5 ± 6,8 SD	1,2 ± 2,3 SD
LV [dB^2]	33,4 ± 25 SD	9,1 ± 6,6 SD
gRNFL [µm]	67,8 ± 20 SD	85 ± 14,7 SD
CCT [µm]	531,8 ± 36 SD	548,2 ± 41,8 SD

Abbreviation: OAG (open-angle glaucoma), OHT (ocular hypertension),
MD (mean defect), LV (loss variance), gRNFL (global retinal nerve fiber layer),
CCT (central corneal thickness);
The two eyes of one female patient were separated into different groups
(right eye OHT; left eye OWG).

Table 2: ICT dependency on age: ICare Rebound tonometry at 5 time points (0 p.m, 6 a.m., 12 a.m., 4 p.m., and 9 p.m.).

ICT repetitions	DF	Type I SS	Mean Square	F Value	Pr > F
age at ICT 0 p.m.	1	34.34	34.34	2.4	0.123
age at ICT at 6 a.m.	1	180.33	180.33	12.31	0.001
age at ICT at 12 a.m.	1	350.05	350.05	20.92	<.0001
age at ICT at 4 p.m.	1	223.06	223.06	9.55	0.002
age at ICT at 9 p.m.	1	130.75	130.75	8.28	0.004

Table 3: Partial correlation coefficients and p-values of pairways comparison of ICare Rebound tonometry at 5 time points (0 p.m, 6 a.m., 12 a.m., 4 p.m., and 9 p.m.).

	ICT 0.00 p.m.	**ICT 6.00 a.m.**	**ICT 12.00 a.m.**	**ICT 4.00 p.m.**	**ICT 9.00 p.m.**
ICT 0.00 p.m.	1	0.65 <.0001	0.56 <.0001	0.59 <.0001	0.69 <.0001
ICT 6.00 a.m.	0.65 <.0001	1	0.55 <.0001	0.51 <.0001	0.62 <.0001
ICT 12.00 a.m.	0.56 <.0001	0.55 <.0001	1	0.66 <.0001	0.63 <.0001
ICT 4.00 p.m.	0.59 <.0001	0.51 <.0001	0.66 <.0001	1	0.64 <.0001
ICT 9.00 p.m.	0.69 <.0001	0.62 <.0001	0.63 <.0001	0.64 <.0001	1

Figure 1

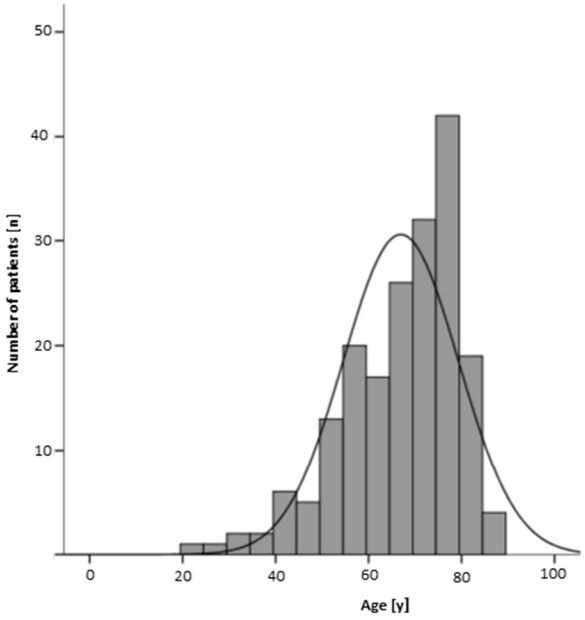


Figure 2

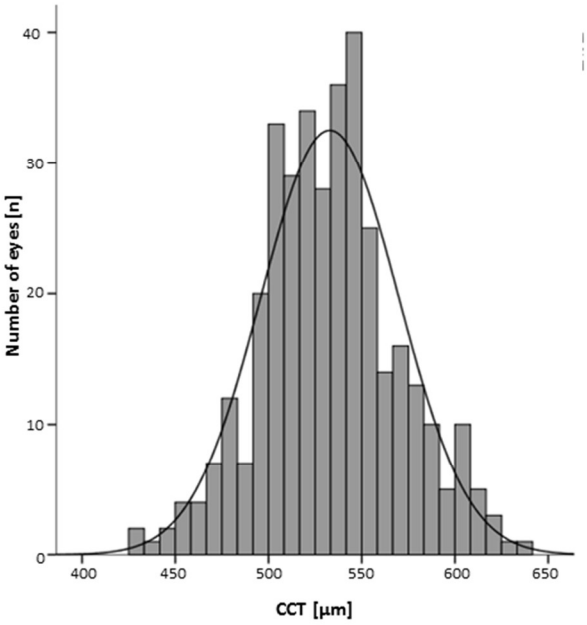


Figure 3

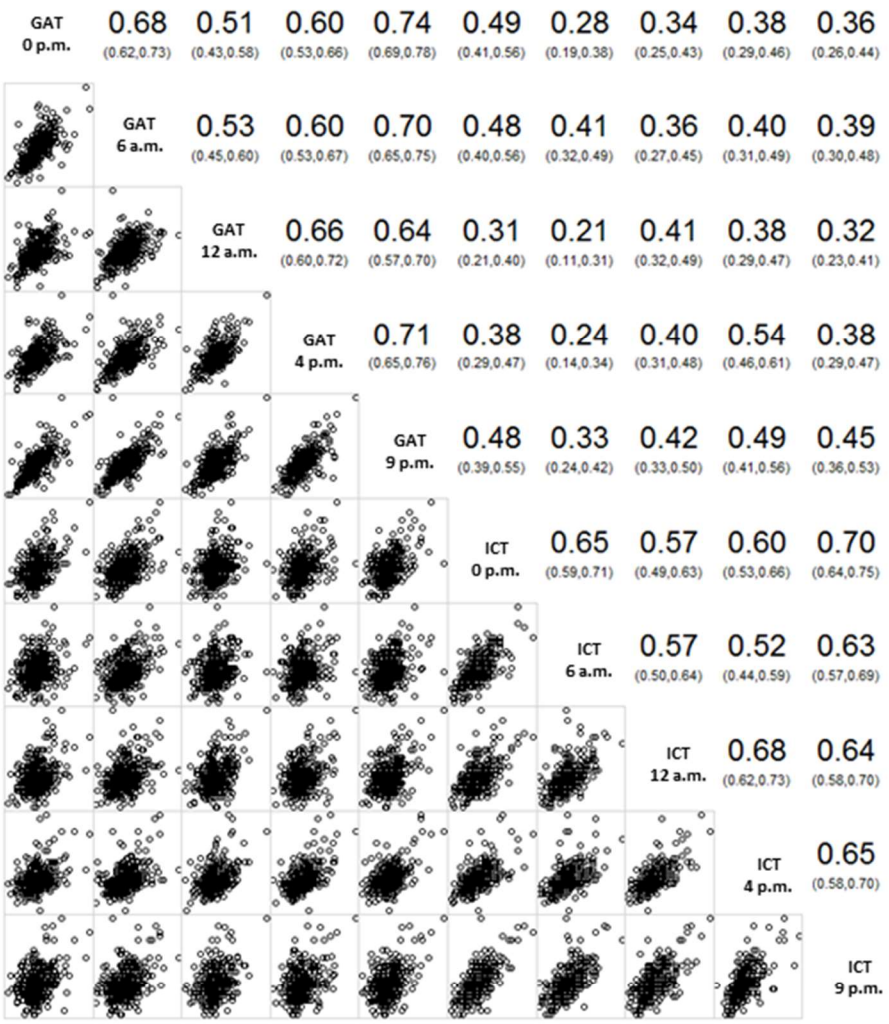

GAT 0 p.m.
0.68 (0.62,0.73)
0.51 (0.43,0.58)
0.60 (0.53,0.66)
0.74 (0.69,0.78)
0.49 (0.41,0.56)
0.28 (0.19,0.38)
0.34 (0.25,0.43)
0.38 (0.29,0.46)
0.36 (0.26,0.44)
GAT 6 a.m.
0.53 (0.45,0.60)
0.60 (0.53,0.67)
0.70 (0.65,0.75)
0.48 (0.40,0.56)
0.41 (0.32,0.49)
0.36 (0.27,0.45)
0.40 (0.31,0.49)
0.39 (0.30,0.48)
GAT 12 a.m.
0.66 (0.60,0.72)
0.64 (0.57,0.70)
0.31 (0.21,0.40)
0.21 (0.11,0.31)
0.41 (0.32,0.49)
0.38 (0.29,0.47)
0.32 (0.23,0.41)
GAT 4 p.m.
0.71 (0.65,0.76)
0.38 (0.29,0.47)
0.24 (0.14,0.34)
0.40 (0.31,0.48)
0.54 (0.46,0.61)
0.38 (0.29,0.47)
GAT 9 p.m.
0.48 (0.39,0.55)
0.33 (0.24,0.42)
0.42 (0.33,0.50)
0.49 (0.41,0.56)
0.45 (0.36,0.53)
ICT 0 p.m.
0.65 (0.59,0.71)
0.57 (0.49,0.63)
0.60 (0.53,0.66)
0.70 (0.64,0.75)
ICT 6 a.m.
0.57 (0.50,0.64)
0.52 (0.44,0.59)
0.63 (0.57,0.69)
ICT 12 a.m.
0.68 (0.62,0.73)
0.64 (0.58,0.70)
ICT 4 p.m.
0.65 (0.58,0.70)
ICT 9 p.m.

Figure 4

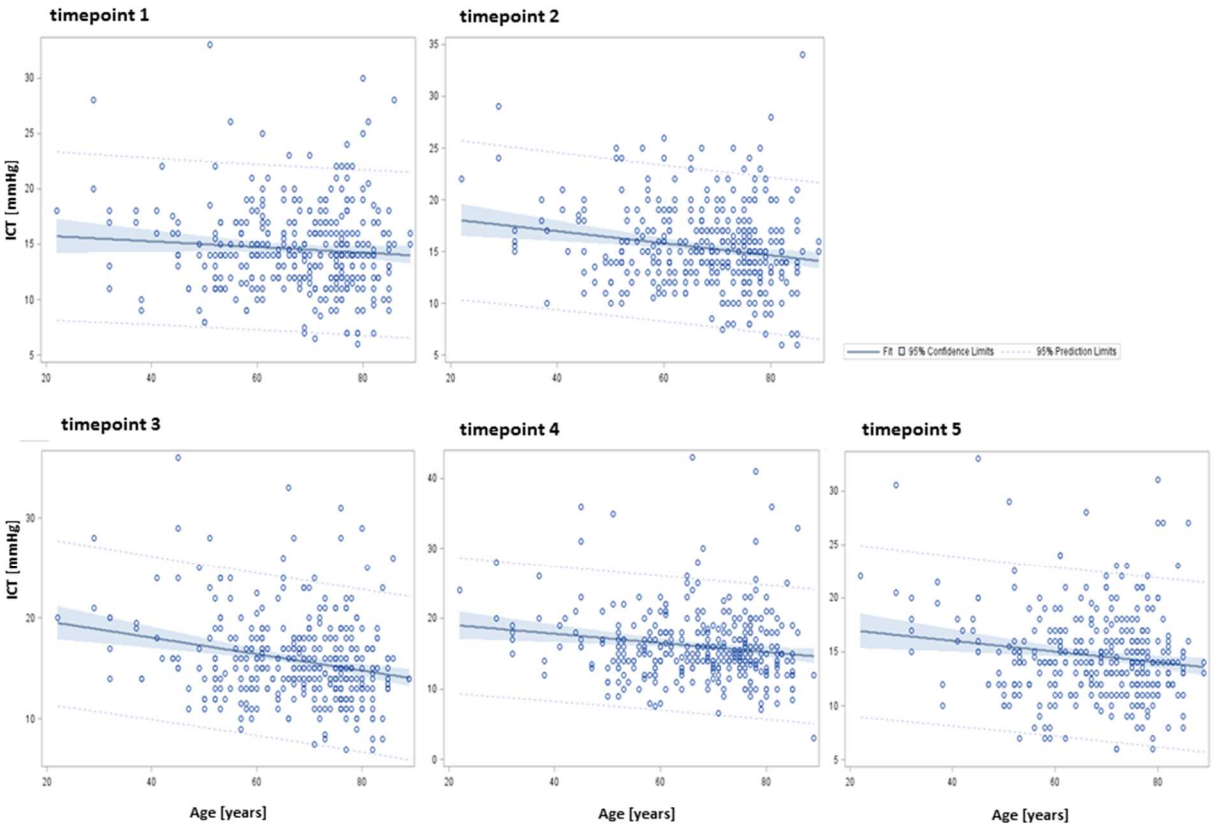

timepoint 1
timepoint 2
timepoint 3
timepoint 4
timepoint 5
ICT [mmHg]
Age [years]
Fit
95% Confidence Limits
95% Prediction Limits

Figure 5

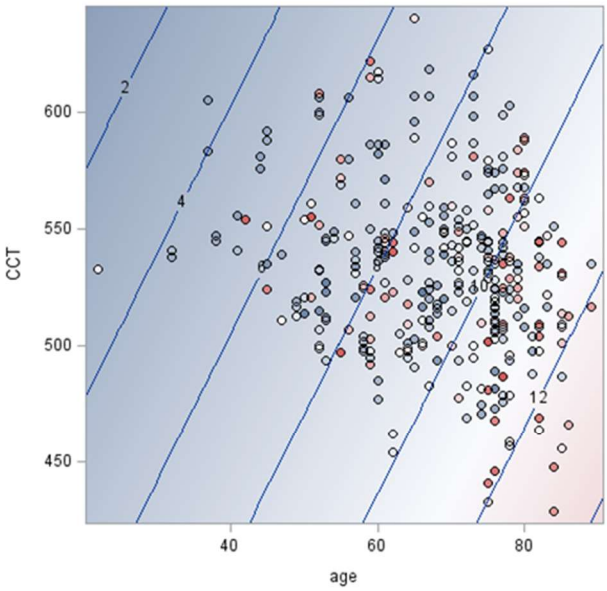
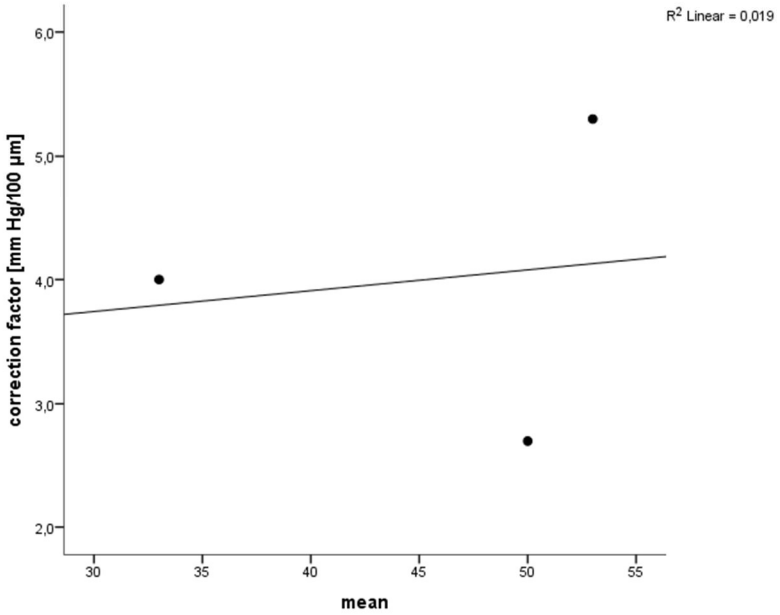


Figure 6


R2 Linear = 0,019
6,0
5,0
4,0
3,0
2,0
correction factor [mm Hg/100 µm]
30
35
40
45
50
55
mean