Report title: Report summarizing the effect of different parameters, including non-standard measurement conditions, on IOP measurements and uncertainties

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Abstract

The purpose of the report is to summarize the effect of different parameters on intraocular pressure (IOP). First, the effect of corneal parameters on IOP measurement, using rebound and non-contact tonometers, are described. Next, the influence of different short-term physiological stress factors on IOP is discussed. The report is focused especially on the factors, which can potentially influence IOP immediately before measurement and distort results such as aerobic exercise, hypoxia, body position and liquid intake.

Introduction

The measurement of intraocular pressure (IOP) is influenced by the mechanism of the used method and by the properties of the human eye, especially by the properties of the cornea. The most influential factors were defined in the previous report D4. The corneal properties which can affect the IOP measurement are corneal thickness, the geometrical parameters of the cornea (radius of the central corneal curvature, corneal astigmatism) and biomedical parameters as hysteresis or rigidity. If the values of some of these parameters exceed the normal range, the IOP reading can be falsely higher or lower.

It is also known that a number of physiological processes cause changes or fluctuations in IOP. Such changes can influence the IOP immediately before the measurement and thus the

measured IOP can differ from the ordinary IOP of the measured subject. Thus, the interpretation of the measured value can be complicated by short-time IOP changes associated with the various physiological processes. Moreover, changes as well as short-time fluctuations in IOP can be risk factors for development and progression of glaucoma (e.g. Goldberg 2003; Hasegawa et al. 2006; Krist et al. 2001). Factors with a relatively quick incidence are physical activities (for example, see Rowe et al. 1976; Krejci et al. 1981; Marcus et al. 1970; Price et al. 2003; Shapiro et al. 1978; Rowe et al. 1976; Najmanová et al. 2016; Najmanová et al. 2018; McArdle et al. 2014; Moura et al. 2002), hypoxia (Karadaq et al. 2008; Roach et al. 2006; Ersanli et al. 2006; Nebbioso et al. 2014; Cymermann et al. 2000; Bayer et al. 2004; Najmanová et al. 2019a), head or body position (e.g. Prata 2010; Fang et al. 2018; Najmanová et al. 2019b), hydration (e.g. Idu et al. 2015; Hunt et al. 2012; Read et al. 2010) and consumption of coffee or energy drinks (Avisar et al. 2002; Chandrasekaran et al. 2005; Ilechie & Tetteh 2011), pupil size (Rutkowski et al. 1972) and accommodation (Yan et al. 2014; Armaly & Rubin 1961). Another important factor is diurnal rhythm (Duke-Elder 1952; Wilensky et al. 1993).

The influence of the corneal factors was generally described in the report D4. One of the aims of this report is to provide the results of our study focused on the verification of the effect of corneal parameters on the IOP measurements by one selected rebound tonometer (ICARE PRO) and a non-contact tonometer with a measurement of corneal hysteresis (ORA G3). Another aim is to present the impact of short-time physical activity, short-time hypoxia and change in body position on IOP as these short-time effects can influence IOP immediately before measurement. The effects of hydration and consumption of energy drinks are also mentioned.

Influence of cornea on IOP measurement by rebound and noncontact tonometer

The most widespread type of rebound tonometers in Europe are in all probability ICARE tonometers (Vantaa, Finland). Only two modern tonometers enable the measurement of the biomechanical properties of cornea – such as ORA (Ocular Response Analyser, Reichert) or CorvisST (OCULUS). We therefore used the ICARE PRO and ORA G3 as representatives of rebound and non-contact tonometers to study the effect of corneal properties (corneal hysteresis *CH*, central corneal thickness *CCT*, mean central corneal radius *R*, corneal astigmatism *Ast*) and age on the IOP reading and its repeatability. We also compared both tonometers together and with the known properties of the Goldman applanation tonometer (GAT). The results were published in (Pluháček et al. 2019). ICARE provides one value of IOP (IOP_{IC}) from each measurement, which is the average of six subsequent measurements, whereas ORA provides two IOP values – IOP correlated with GAT (Goldmann-correlated IOP, IOP_G) and IOP with the calculated compensation of the influence of hysteresis (corneal-corrected IOP, IOP_{CC}).

Our results indicated that the IOP readings from both tested tonometers are significantly correlated with the *CH* (increasing *CH* leads to a decrease in the IOP readings) and *CCT* (a higher *CCT* leads to higher IOP readings). The stronger influence of both parameters was observed in the case of ORA. The effect of *CH* is in agreement with other studies (Chui et al., 2008; Shin et al., 2015). In the case of *CCT*, the present studies, which did not include biomechanical parameters, found a positive correlation with IOP readings for both ICARE (Brusini et al. 2006; Illiev et al. 2006; Jorge et al. 2008; Malini et al. 2014; Martinez de-la-Casa et al. 2005; Nakamura et al. 2006; Shin et al. 2015) and ORA (Jorge et al. 2008; Martinez de-la-Casa 2006; Shin et al. 2015). If the biomechanical parameters were included in the analysis, however, the effect of corneal rigidity was observed instead of the effect of *CCT* (Chui et al. 2008; Shin et al. 2015). Since *CCT* is positively correlated with corneal rigidity (e. g. Çevik et al. 2016; Shin et al. 2015), it is possible to consider the influence of CCT observed in our (Pluháček et al. 2019) and other studies to be a reflection of the influence of corneal rigidity. Other

observed parameters (*R*, *Ast* and age) did not significantly affect the IOP reading. This result corresponds to other studies (Hagishima et al. 2010; Martinez de-la-Casa 2006; Shin et al. 2015). The values of the multiple regression analysis, found in our study (Pluháček at al. 2019), is presented in table 1.

A mutual comparison of both instruments has shown that ICARE readings and Goldmann-correlated IOP did not differ significantly, whereas corneal-correlated IOP was significantly higher in comparison with the mean of the ICARE reading by approximately 1.1 mmHg ± 3.6 mmHg. In both cases, however, a relatively high variability of differences between instruments was found in individual eyes (see Fig. 1, left panels). Due to this variability, the mutual interchangeability of the results from both equipment is impossible. The mean differences between equipment were significantly influenced by intraocular pressure and *CH* (see Fig. 1, right panels), whereas *CCT*, *R*, *Ast* and age did not show any significant effect. A similar dependence on *CH* is reported (Shin et al. 2015). Recent studies also reported an agreement between ICARE readings and Goldmann-correlated ORA readings. In contrast, published comparisons of ICARE and corneal-correlated ORA readings differ (Gillan 2015; Jorge et al. 2008) depending on the presence of glaucoma. The cause of this dissimilarity can be the proved dependence on *CH* and IOP, because glaucoma patients present different *CH* and higher IOP compared to normal subjects.

Table 1 Partial correlation coefficients of all the considered parameters (corneal hysteresis coefficient *CH*, central corneal thickness *CCT*, average central corneal radius *R*, corneal astigmatism *Ast* and age) with intraocular pressure (IOP_{IC} represents data from ICARE PRO and IOP_G and IOP_{CC} data from ORA). Significant correlations are marked by an asterisk.

	IOP_{IC}	IOP_G	IOP_{CC}
CH	-0.316*	-0.510*	-0.701*
CCT	0.433*	0.521*	0.512*
R	-0.065	-0.035	-0.046
Ast	-0.151	-0.147	-0.148
age	-0.142	-0.199	-0.197

Our study also proved the better repeatability in the case of ICARE, which is comparable with GAT (Sullivan-Mee et al. 2009; Wang et al. 2013). ORA has shown worse results, with the worst repeatability established for corneal-corrected IOP. Both ORA readings presented a small, statistically significant, but clinically insignificant decrease in the case of the repeated measurement. The reason may be the practical familiarity of the tested person with the measurement and therefore less stress upon a repeated measurement. The repeatability of studied IOP readings was represented by the coefficient of repeatability, which is the half-width of 95% confidence interval of differences between two IOP measurements (test and retest). The uncertainty of the measurement on the real subjects is proportional to this coefficient. The coefficient of the repeatability was 3.0 mmHg for IOP_{IC}, 3.8 mmHg for IOP_{G} and 4.8 mmHg for IOP_{CC}.

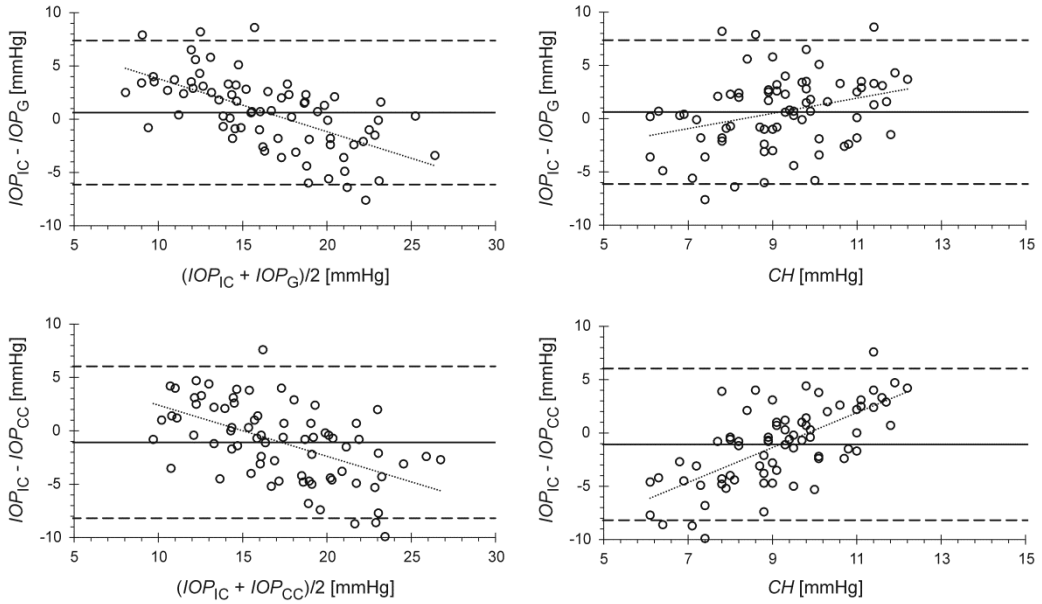

Fig. 1 Bland-Altman plots depicting the difference in intraocular pressure readings from ICARE PRO (IOP_{IC}) and ORA in the case of Goldmann-correlated values (IOP_{G}; top panels) and corneal-corrected values (IOP_{CC}; bottom panels) against their average (left) and the corneal hysteresis (*CH*) (right). Circles represent the values of the individual eyes, the dashed lines represent the 95% confidence interval and the solid line is the mean difference. Dependence is approximated by a regression (dotted) line.

Recent studies, including our results, indicate that the measurement of intraocular pressure using rebound (ICARE) and non-contact (ORA) tonometers is influenced by corneal hysteresis and corneal thickness. The observed influence of the corneal thickness may indirectly reflect the effect of corneal rigidity. Thus, if some of these parameters are markedly out of the normal range, the IOP reading can be distorted. The values obtained by different equipment (rebound x non-contact) are not interchangeable. Therefore, e.g. upon observation of IOP changes over time, it is always necessary to use the same type of tonometer. In this case, the repeatability is also an important parameter. The best repeatability (for the same operator), comparable with GAT, is presented by ICARE. For Goldmann-correlated ORA IOP, the repeatability is slightly worse than for GAT and the worst is for cornea-correlated IOP. However, if different operators use the equipment, the repeatability for ICARE may worsen more than for ORA, which is less influenced by operator skills.

Effect of short-term physical activity on IOP

Physical activity is an inseparable part of recreational and professional activities. It is well documented that physical activity can have positive effects on health conditions particularly with patients who suffer from cardiovascular and metabolic diseases such as hypertension (Tsai et al., 2004) or diabetes mellitus (Short et al., 2003). The effects of physical activity on IOP are still under examination and the underlying mechanism of this response is still poorly understood.

Previous studies have shown that short-time moderate aerobic exercise (such as walking upstairs, running, cycling, etc.) cause an IOP decrease during (Rowe et al. 1976; Krejci et al. 1981) and immediately after the activity (e.g. Marcus et al. 1970; Price et al. 2003; Shapiro et al. 1978; Rowe et al. 1976). Our previous findings, obtained under well-defined and controlled conditions (Najmanová et al. 2016), proved this decrease. The maximal reduction in IOP was 2.7 mmHg ± 2.0 mmHg and was obtained immediately after the exercise. This clinically significant decrease (i.e. > 2 mmHg (Qian et al. 2012)) was followed by a gradual increase to the baseline in

minute 20 after the completion of the exercise. The immediate decrease correlated with the initial IOP (baseline). The correlation was confirmed by most of the other studies (e.g. Leighton et al. 1970; Becker et al. 1955; Stewart et al. 1970; for an exception see Price et al. 2003). The magnitude of the IOP reduction increases with exercise intensity (Kiuchi et al. 1994; Kielar et al. 1975; Kypke et al. 1973; Leighton & Philips 1970; Marcus et al. 1970). E.g. Marcus et al. (1970) presented the IOP reduction 5.9 mmHg for a similar baseline, but for a higher workload. Najmanová at al. (2016) also observed a correlation between the magnitude of the decrease and the initial (resting) heart rate. As the resting heart rate is influenced by the fitness level, the IOP changes after the aerobic activity should be affected by the fitness level as well.

While short-time moderate aerobic exercise leads to a decrease in IOP, the effect of resistance exercise is ambiguous. Some studies presented a decrease (Lanigan et al. 1989), while others showed an increase (Dickerman et al. 1999; Movaffaghy et al. 1998; Bakke et al. 2009) or no significant change in IOP (Marcus et al. 1974; Wimpissinger et al. 2003). We studied the effect of resistance exercise in combination with drinking of water. The results are included in the thesis (Kadlčíková 2019). Pure water and hydrogen water were used. Hydrogen water is simply pure water with dissolved molecules of hydrogen and is considered to have positive effects on the human organism (Ohta 2014). It is also used as support for body regeneration during exercise (Oshawa et al. 2007; Ostojic 2015). The results show that IOP changed during resistance exercise and that its time course was influenced differently by the type of water (for details see Kadlčíková 2019). The IOP changes seem, however, to be unspecific.

As mentioned above, the magnitude of the IOP decline, induced by aerobic physical activity, increases with a rising workload. The maximal workload, leading to exhaustion, did not show, however, the exactly defined IOP changes (Najmanová et al. 2018). The main effect is high interindividual variability of IOP represented by an increase in the IOP standard deviation up to 1.7-fold of baseline in the observed group of subjects – the maximal exercise influences differently different subjects. The high variability persisted up to minute 10 after exercise completion and in minute 20 returned to the initial value.

The effect of hypoxia on IOP

Active vacations at high altitudes such as skiing, heli-skiing, hiking, and mountain climbing have become increasingly popular for people all around the world. Due, however, to rapid modern transportation patterns (lifts, cars, helicopters, airplanes), it is currently easy to passively reach an altitude over 2,500 m, and people without appropriate acclimatization to hypobaric hypoxia may start experiencing symptoms related to acute mountain sickness for instance with headache, fatigue, nausea, or gastrointestinal issues, and in severe phases also by pulmonary oedema and/or high-altitude cerebral oedema (Sutherland et al. 2017). Moreover, various altitude or hypoxic activities are included in the training strategies of elite athletes (Wilber 2011). Such activities should have consequences for their health status including ocular health. Based on previous studies, it seems that hypoxia affects the IOP. The results are, however, ambiguous.

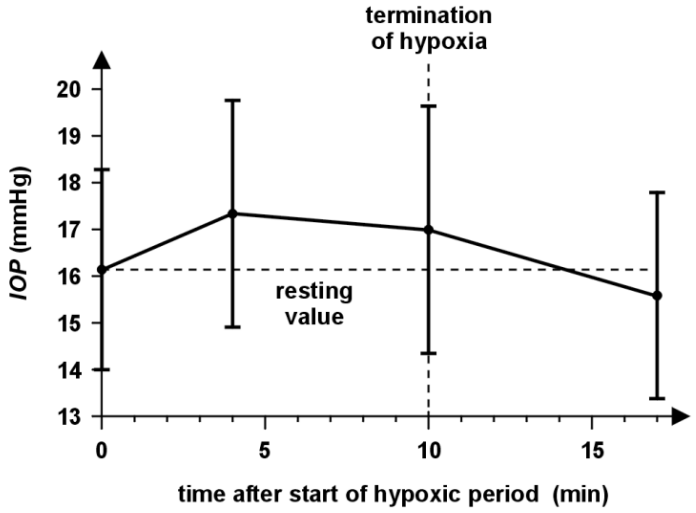

Fig. 2 The time course of IOP during the experiment for all the subjects. The circles represent the mean IOP values of a particular measurement before the hypoxic period (0 min), at minutes 4 and 10 during ten minutes of normobaric hypoxia and at the end of the 7-minute recovery (17 min). The half-sizes of the vertical abscissae correspond to the IOP standard deviations. IOP increases both during measurements in the hypoxic period and returned approximately to the resting value at 7 minutes of recovery if averaged across all the subjects.

Some observations show an increase in IOP (Ersanli et al. 2006; Karadak et al. 2008; Sommer et al. 2007; Bosch et al. 2010), whereas other experiments presented a decrease (Cymerman et al. 2000; Pavlidis et al. 2006). Bayer et al. 2004 reported no significant changes. The effect seems to vanish during acclimatization (Pavlidis et al. 2006; Sommer et al. 2007; Bosch et al. 2010; Cymerman et al. 2000). The observed changes in IOP were mostly evaluated as clinically insignificant, i.e., > −2 mmHg and < 2 mmHg (Qian et al. 2012).

The high altitude changes result in two important effects – a decrease in air pressure and a corresponding decrease in the partial pressure of the inspired oxygen. Recent studies mostly evaluated both factors together in the form of hypobaric hypoxia. Moreover, in the case of actual hiking, the climb to the given altitude was connected with the physical aerobic activity, which results in a IOP decrease (see above), and/or changes of other physical parameters in the surrounding environment. We therefore realised the study of hypoxia under normal atmospheric pressure and under well-controlled conditions in a laboratory, see Najmanová et al. (2019a). We found an increase in IOP in response to short-term (10 minutes) normobaric hypoxia (1.2 mmHg ± 1.9 mmHg at minute 4 and 0.9 mmHg ± 2.3 mmHg at minute 10 of hypoxia), which returned to the baseline 7 min after hypoxia, see Fig. 2. The increase was higher for subjects with a higher degree of induced oxygen desaturation. Although the average increase was clinically insignificant, clinicians should be aware that some patients who perform the activities connected with short-term hypoxia may run the risk of an unsafe increase in intraocular pressure. Hypoxic changes can also influence the accuracy of the IOP measurement.

The effect of position change on intraocular pressure

It is a known fact that IOP is significantly affected by body position (e.g. Jorge et al. 2010; Fang et al. 2018; Kiuchi et al. 2010; Lam et al. 2013; Lee et al. 2012; Lindén et al. 2018; Malihi & Sit 2012; Meurs et al. 2018; for a review of older studies see Prata et al. 2010). The majority of the studies refer to the higher IOP values in the supine compared to the sitting or upright position (e.g. Jorge et al. 2010; Fang et al. 2018; Galin et al. 1963; Kiuchi et al. 2010; Lam et al. 2013; Lee et al. 2012; Lindén et al. 2018; Linder et al. 1988; Meurs et al. 2018; Malihi & Sit 2012). Such an increase in IOP as well as its quick changes can be a risk factor for development and progression of glaucoma (e.g. Goldberg 2003; Hasegawa et al. 2006; Krist et al. 2001). IOP is usually measured in the sitting position due to technical facilities, however, many patients are transported in the supine position. Thus, the interpretation of measured values can be complicated by short-time IOP changes associated with the body reposition before measurement and it is therefore important to know the time response of IOP related to the position change. Recent studies have mostly focused on a comparison of IOP values in a different position, but have only rarely studied the longer-time response of IOP (e.g. Fang et al. 2018). We focused on the assessment of the IOP time response to the change in body position from a sitting to a supine and from a supine to a sitting immediately and during 30 minutes of rest in each position in healthy subjects. The results were published in Najmanová et al. (2019b). We observed an immediate increase in IOP as a response to both considered changes of body position (2.6 mmHg ± 2.4 mmHg after lying down and 2.1 mmHg ± 3.1 mmHg after sitting up) and the subsequent gradual decrease with time, see Fig. 3. The mean IOP was 1.41 mmHg ± 2.4 mmHg higher in the lying period than in the sitting period; the mean difference was smaller for those with a lower initial (sitting) IOP (0.9 ± 2.2 mmHg) than the higher initial (sitting) IOP (1.9 mmHg ± 2.5 mmHg), see Fig. 4. Moreover, we observed a gradual decrease of IOP during the entire experiment – the mean IOP in the final sitting was significantly lower (2.5 mmHg ± 1.9 mmHg) than in the initial sitting position. The results did not depend on gender.

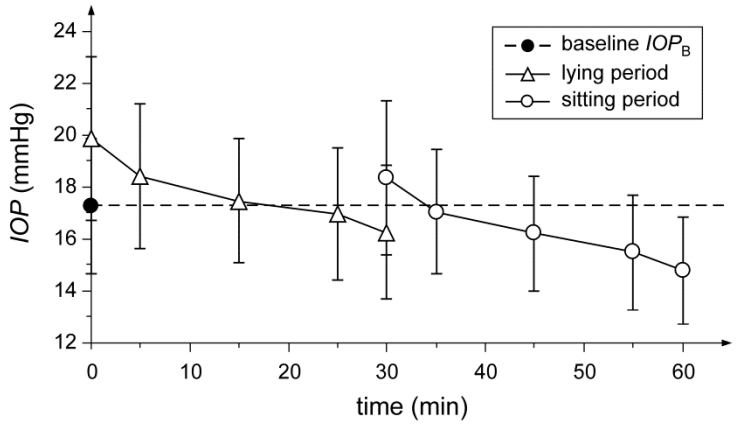

Fig. 3 Time course of mean IOP values during the lying (open triangles) and sitting (open circles) period. The graph indicates the IOP increases after each position change and then gradually decreases with time. The half-sizes of the vertical abscissae correspond to the IOP standard deviations. The black circle and dashed line represent the IOP baseline (in the initial sitting position).

The IOP significantly changed especially immediately after the position change. The immediate IOP changes, induced by body reposition, were higher than 2 mmHg and from a medical standpoint clinically significant (Qian et al. 2012). This effect should be considered when IOP is measured after the patient's reposition, that is there should be an adequate timing relationship between the reposition and the measurement. Based on our results (Najmanová et al. 2019b), the sufficient time interval must be longer than 5 min. This situation can occur, for example, during 24-hr monitoring of IOP (for a review see Itoop et al. 2016), where the position changes can be a distracting factor. Moreover, if the patients are calm a longer time before the measurement, the IOP value can be affected by a gradual decrease with time (Najmanová et al. 2019b). If the IOP is measured after an extended rest period, there is a risk that the IOP reading will be falsely lower. This effect is stronger for those with higher IOP, e.g. for glaucoma patients.

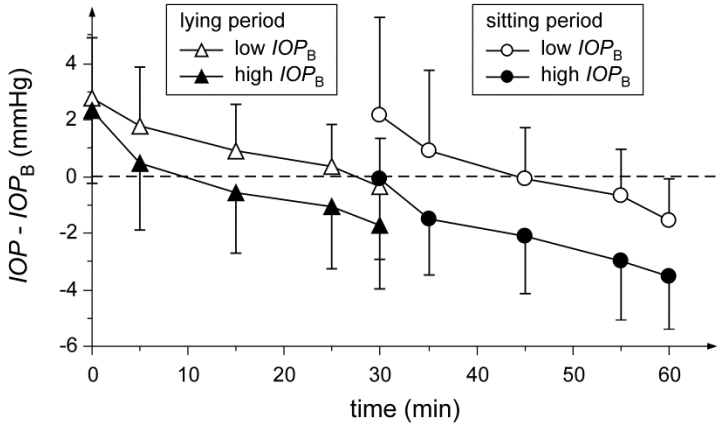

Fig. 4 Time course of mean IOP differences from the baseline for the lower (open symbols) and the higher (closed symbols) baseline group. The triangles represent data during the lying period and the circles during the sitting period. The higher baseline group shows higher differences between IOP in both periods than the lower baseline group. The sizes of vertical abscissae correspond to the IOP standard deviations. The dashed line represents a zero difference.

Effect of drinks on IOP

Drinking of water (e.g. Read & Collins 2010; Brucculeri et al. 1999), caffeine in the form of coffee or tea (Avisar 2002) or energetic drinks (Ilechie & Tetteh 2011) can influence IOP values. It has been demonstrated that drinking water significantly increases IOP with the maximal effect in minute 10 (2.24 mmHg ± 0.31 mmHg) (Read & Collins 2010) or 15 (Brucculeri et al. 1999) after ingestion of 1000 ml or 14 ml per kg of body weight. IOP was maintained significantly (however not clinically, < 2 mmHg) higher than the baseline for at least 30 min (Read & Collins 2010) or 45 min after water ingestion (Brucculeri et al. 1999). The study (Avisar 2002) determined that consumption of 180 mg of caffeine in 200 ml beverage causes an increase compared to the baseline up to 3.6 mmHg ± 1.1 mmHg and 3.4 mmHg ± 1.0 mmHg in minute 60 after caffeine ingestion in the case of normal tension glaucoma subjects or a subject with eye hypertension. The significant increase still persists in minute 90. As such patients are more sensitive, we suspect that normal healthy people will represent a smaller IOP rising. In contrast, caffeine consumption in the form of an energy drink (85 mg of caffeine in 250 ml of

beverage – Red Bull®) caused a decrease in IOP in young healthy subjects which persists up to 90 min. This mean decrease (up to 1.7 mmHg ± 1.9 mmHg) was below clinical significance, however, the individual changes can be clinically significant. This effect can be due to a combination of caffeine and other ingredients, especially taurine with a hypotensive effect (Veselovsky et al. 2007). Thus, the consumption of water increases IOP, whereas the consumption of energy drinks with a combination of caffeine and taurine decreases IOP. Caffeine consumption seems to increase IOP especially in the case of glaucoma or eye hypertension patients.

Conclusion

Within this report, we focused partly on the effects of corneal parameters on IOP measurement using a rebound tonometer ICARE and non-contact tonometer ORA and on the repeatability of the IOP measurement. It was determined that the most important factors affecting IOP readings from both equipment are corneal hysteresis and central corneal thickness. As the central corneal thickness is correlated with corneal rigidity, the rigidity can also affect the measured values. Thus, for the proper determination of IOP by the studied equipment, it is important to know if the biomedical properties of the measured cornea and corneal thickness are within the normal range. Repeatability of the measurement using ICARE PRO is comparable with the repeatability of the Goldmann applanation tonometer, whereas the repeatability of both ORA outputs is worse. We determined that the values from the different tonometers are not interchangeable.

The second part of the report focused on the influence of different short-term physiological stress factors on IOP. Such factors can affect the IOP values immediately before the measurement and distort the results. From a clinical view, the most important seems to be position change and short-term physical activity. Other effects such as short-term hypoxia or maximal activity cause clinically insignificant mean changes of IOP, although individual changes may exceed the save range and may be a risk factor especially for glaucoma patients. In

addition, the higher individual response, especially in the case of maximal activity (or activity close to maximal) may increase the uncertainty of measurement. The incidence of all the discussed effects is limited to a small time interval and then vanishes. Based on recent studies and our experiments, it seems that a 20 min long interval is enough to reduce the above-described effect to zero or to a clinically acceptable difference. Too long a period of calm (more than 30 min) can induce, however, a gradual decrease in IOP, which can cause a false lower IOP. With regard to the significant effect of different beverage consumption on IOP, the measured subjects should not consume caffeine or energy drinks on the day of measurement or a higher amount of water approximately one hour before the measurement.

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