Research Square

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Evaluation of Intracranial Pressure by Ultrasound of the Optic Nerve Sheath in an Animal Model of Intracranial Hypertension

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Research

Keywords: optic nerve sheath diameter, ultrasonography, brain injury, intracranial hypertension, animal model

DOI: https://doi.org/10.21203/rs.3.rs-80145/v1

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Abstract

Background: Invasive monitoring of intracranial pressure is currently the only accepted method for the safe diagnosis and treatment of intracranial hypertension, but it is subject to hemorrhage, infection and malfunction. Ultrasound of the optic nerve sheath diameter is a non-invasive alternative that is cost effective and available at the bedside. The objective of this study was to correlate intracranial pressure and ultrasonography of the optic nerve sheath in an experimental animal model of cerebral hematoma.

Materials and Methods: An experimental study was conducted on 30 male and female pigs wighing about 20 kg. The diameter of the optic nerve sheath was measured by ultrasound at different points of intracranial pressure. Intracranial pressure was simultaneously measured with an intraparenchymal catheter, and laboratory and hemodynamic data was collected from the animals. The values were correlated with each other to explore the application of this procedure in different clinical situations involving intracranial hypertension.

Results: All the variables obtained by ONSD ultrasonography (Left Optic nerve LON, Rigth optic nerve RON and Avarage of Optic Nerve sheath AON) were statistically significant to predict the ICP value. AON presentation changes in relation to baseline from the moment of balloon inflation. AON proved to be the best parameter for predicting ICP and presented the best correlation. AON showed a delay of 30 minutes compared to ICP decrease, as it maintained values higher than baseline values at the ballon deflation moment ($p = 0.016$). Thus, intracranial pressure can be predicted using the linear function: -80.5 + 238.2 × the optic nerve sheath diameter.

Conclusion: Optic nerve sheath diameter ultrasound is a reliable method for predicting intracranial pressure.

Background

Invasive monitoring of intracranial pressure (ICP) is the only method indiscriminately accepted for the safe diagnosis of ICP increase and the treatment of intracranial hypertension (ICHy).[1,2] Intraventricular catheters are considered the gold standard for ICP monitoring.[3]

Although there are clear benefits of the continuous and real-time monitoring provided by invasive methods, they are subject to non-negligible complications such as bleeding (1.1–5.8%), catheter malfunction (6.3–40%), and infection (0–15%), and after the fifth day, the risk of bacterial colonization increases significantly.[3,4,5,6,7]

When compared to computed tomography and nuclear magnetic resonance imaging, optic nerve sheath diameter (ONSD) ultrasound has many advantages. It is available at the bedside, it eliminates the need for transporting critical patients, and moves the patient from the decubitus position (a therapeutic measure). Compared to transcranial doppler, ONSD ultrasound is easier to apply and has a smaller learning curve; only about 25 cases are needed for physicians without experience with sonographic examinations to become proficient.[8]

A noninvasive method for monitoring ICP would avoid the need for placement of an intracranial device and the risks associated with this procedure. However, many noninvasive ICP monitoring techniques are limited by insufficient diagnostic accuracy, since most provide qualitative estimates of ICP but not quantitative values and as for non-dynamic nature.[3] The determination of a correlation between the values obtained by ONSD ultrasound with ICP would overcome this limitation. As such, the aim of this study was to identify such a correlation in an experimental animal model of cerebral hematoma.

Materials And Methods

We studied 30 piglets hybrids of the Landrace, Duroc, and Pietrain breeds. The selected animals were about 60 days of age, weighing between 18 and 22 kg, and with hemoglobin levels between 8.5 and 12.0 g/dL.

They were anaesthetized with propofol 5–10 mg/kg/h (1% Provine®), and fentanyl was used for analgesia (Fentanest®, Cristália) at an initial dose of 5 *μg*/kg followed by a continuous infusion of 0.08–0.15 mg/kg/min. The animals were intubated and mechanically ventilated at a controlled volume (Fan Dixtal® 5010), with a tidal volume of 10 ml/kg and a fraction of inspired oxygen of 0.40. The invasive monitoring of the mean arterial blood pressure (MABP) was performed using a right femoral artery catheter. End tidal CO_2 ($ETCO_2$), peripheral haemoglobin saturation (SpO_2), and systemic pH were continuously monitored.

Two 3-mm holes were made 1 cm lateral to the metopic suture: one for a multiparameter cerebral catheter to measure intracranial pressure, temperature, and tissue oxygen (microsensor-type microchip, Neurovent-PTiO®; Raumedic), which was placed in a hole anterior to the coronal suture and inserted 1.5 cm deep into the frontal lobe, and the other for a paediatric 8-French bladder catheter, which was placed in a hole 1 cm posterior to the coronal suture and inserted 2 cm deep into the parietal lobe.

In this nontraumatic model, after each animal was prepared, the paediatric catheter balloon was progressively inflated with 0.9% saline solution over 15 min using continuous pump infusion until 4 ml or 7 ml was infused. The experiment included three randomized groups according to the volume inflated into the balloon: 4 mL, 4 mL + 3 mL, and 7 mL.

Each group consisted of 10 animals that underwent intracerebral hematoma simulation, clinical treatment with saline (3% NaCl) solution, and simulation of surgery. .

In the 4 mL group, an intracranial hematoma was simulated with a volume of 4 mL,. This would be equivalent to the collection of approximately 80 ml in an adult human, taking into account the ratio between the animal’s brain weight at 2 months with a body weight of 18 kg (mean of 75 g) and a normal adult brain weight (1500 g) (with a body weight/body weight ratio of 5%). The hypertonic saline solution was infused 1 hour after the end of the inflation of the balloon. One hour after the end of the infusion of hypertonic saline solution, a final intervention was performed, the balloon was deflated, simulating a surgical procedure. In the 7 mL group, a volume of 7 ml was used, equivalent to a volume of approximately 140 ml in an adult human. In the 4 mL + 3 mL group 30 minutes after the initial volume of 4 ml, we added 3 ml, simulating re-expansion and generating an end volume of 7 ml.

. Diameters of the left and right optic nerve sheaths were measured 3 times at 9 timepoints after the beginning of the experiment: basal, balloon 1 (immediately after the first inflation of the balloon), balloon 2 (immediately after the second balloon inflation or 30 minutes after balloon 1), pre-saline, saline (immediately after infusion of saline), post-saline, pre-intervention, intervention (immediately after balloon deflation), and post-intervention. The average value of these three measures (LON, RON) was used for statistical analysis; the average optic nerve sheath value (AON) was calculated from the mean LON and RONTable 1 shows the volume inflated into the balloons at each time point.

The image plane was chosen to achieve the best longitudinal image of the optic nerve for cross-sectional diameter measurements. A LOGIQ Book XP portable ultrasound system (GE Healthcare, Milwaukee, WI) was used

for this study, and 1 of 2 high frequency transducers were selected with10 MHz linear array. The images were digitally acquired and stored on the system's hard drive. The same probe was used throughout the experiment. Ultrasound was performed on both eyes of each animal by an operator blinded to the ICP and balloon volume

After the end of the experiment and data collection, the animals received an anesthetic overdose of propofol and fentanyl, sacrificed with intravenous administration of 20 ml of 19.1% potassium chloride solution.

The protocol was approved by the Research Ethical Committee at Sao Paulo University Medical School .

Results

All animals were hemodynamically stable during the experimental procedure (physiological variables such as MABP, temperature, ETCO2, SaO2 was in normal value during rhe experiments). The mean ICP values of the three groups differed statistically throughout the studied timepoints. Despite similar final volumes of insufflation (7 mL), the 4 mL + 3 mL and 7 mL groups presented different mean ICP values. The 4 mL + 3 mL group presented higher mean ICP values at the balloon 2 timepoint, when it reached 7 mL of insufflation. This suggests that rebleeding is an additional factor involved in the increase of ICP in hematomas of the same final volume. This could explain any differences in evolution between patients with intracranial hematomas similar in volume and location at the time of the first evaluation.

In the 4 mL group, mean ICP values did not exceed 17 mmHg, which leads us to conclude that 4 mL was insufficient to generate ICHy in the study animals.

In the 4 mL + 3 mL group, the mean ICP values showed a significant increase in relation to the baseline of the first inflation until the time of the intervention, returning to the baseline values after balloon deflation. These results show that the saline solution did not significantly influence the ICP, unlike emptying of the balloon.

In the 7 mL group ICP was elevated in relation to baseline after the influx of 7 mL at the balloon 1 timepoint and was maintained until the moment of pre intervention. From the moment of injection, the ICP returned to the baseline value until the end of the experiment. Again, saline solution did not significantly influence ICP, unlike the intervention that simulates surgery (balloon deflation). Thus, balloon deflation was the only method that controlled the ICHy obtained in the 4 mL + 3 mL and 7 mL groups, reducing the ICP values to the levels observed at baseline.

The variation in the mean diameter of the optic nerve sheaths was statistically different between the 3 groups (4 ml flask, 4 + 3 ml flask and 7 ml flask over the different moments of the experiments ($p = 0.021$). The mean diameter of the optic nerve sheath showed the highest values in the 4 mL + 3 mL group, and the 4 mL group presented the smallest measurements of the optic nerve sheath at all times.

At balloon 1, when inflating 4 mL, we did not observe a significant increase in the ONSD similar to that observed with the ICP. AON presentation changes in relation to baseline from the moment of balloon inflation ($p = 0.007$). In the moment after deflation of the balloon, we observed a significant reduction in AON in relation to the other moments of the experiment ($p = 0.007$). The ICP also showed statistically significant differences between the same moments. AON presented a variation similar to the ICP measurements in the 2 groups in which it was possible to generate intracranial hypertension (4 mL + 3 mL and 7 mL) presenting sustained elevation at the moments when the balloon was inflated. However, in the reduction and return to baseline values, AON showed a

delay of 30 minutes compared to ICP decrease, as it maintained values higher than baseline values at the ballon deflation moment (p = 0.016).

All the variables obtained by ONSD ultrasonography (LON, RON and AON) were statistically significant to predict the ICP value. AON proved to be the best parameter for predicting ICP and presented the best correlation. Thus, ICP can be predicted using the linear function:

ICP = -80.5 + 238.2 × AON

Discussion

Experimental models of cerebral hematomas have been used since the 1960s. Initially, autologous blood was injected directly into the brain, a simple and effective technique for producing cerebral parenchymal hematoma. In larger animals such as dogs, cats, pigs and monkeys, the injection was performed in the frontal lobe.[9,10,11] In smaller animals such as rats and mice, the site of choice was the caudate nucleus.[12,13,14,15,16,17,18] These models allowed researchers to extrapolate the data obtained in animals to humans in a context closer to clinical practice than models that simulated trauma mechanisms. However, although the use of autologous blood allows the evaluation of biochemical effects of the blood on neurons, it does not provide a simple or direct way to evaluate the effects of surgery for remotion of the hematoma.

The use of an inflated balloon in the cerebral parenchyma[19] instead of blood[20] allowed us to simulate more uniform lesions, in addition to simulating the effect of surgical treatment with balloon emptying [21] The method does have limitations, however, as it does not include surgical access via craniotomy or corticectomy and hemostasis.

The choice of pigs for the animal models took into account the well-developed cortical and white matter rotations more similar to the human brain compared to other animals, the possibility of using intracranial volumes 20 to 30 times greater compared to murine models, the uniform state of health in pigs at this age, and the relatively low cost.

In our experimental model, we used a simulation of early rebleeding with reexpansion. As cerebral hematoma is a dynamic lesion, there may be rebleeding, ventricular flooding, and worsening of cerebral edema, with consequent elevation of ICP. This necessitates the development of techniques to monitor the evolution of this hematoma and the behavior of the brain in the face of these changes, both from anatomically and functionally. There are ongoing clinical trials focused on the reduction of controlled blood pressure in patients with cerebral hematomas that are seeking to avoid the expansion of hematomas and minimize the brain lesions induced by intracranial hypertension.[22,23] However, there are no studies analyzing the effects of hematoma expansion directly on intracranial pressure behavior.

Even without grade 1 level of evidence, invasive ICP monitoring remains the standard recommendation for the management of patients with suspected ICHy.[24] ONSD ultrasound would be a valuable adjunct to the gold-standard invasive technique..

Currently, a neurosurgical unit that receives requests for patient evaluations receives information that includes Glasgow Coma Scale values, vital signs, and possibly imaging tests. The ONSD ultrasound could dramatically

change the way these cases are handled by discarding or confirming the ICHy diagnosis, allowing for better patient screening, and setting priorities with greater accuracy and safety. An estimate of the ICP value obtained from the bedside measurement of the optic nerve would support treatment providers in their decision making.

In addition, the cost of ONSD ultrasound is lower than that of other imaging methods used for the evaluation of ICP (computed tomography and nuclear magnetic resonance imaging). It can also be performed at the bedside without the transport of critical patients, and it involves a fast learning curve. Ballantyne et al.[25] studied ONSD ultrasound in healthy adults and observed that intra and inter-rater variability fell drastically after 17 measurements.

Preliminary reports proposed that ONSD between 5.1 mm and 5.2 mm were associated with radiological signs of increased ICP in African and Asian patients with TBI1, 2. Specificity for most of these studies approached 100% with sensitivities ranging from 70%to 80%.[26,27]

ONSD is especially important in low and middle-income country where disease as traumatic brain injury is epidemic and ICP monitoring usually is not available. One of the objectives of this study was to evaluate the ability of ONSD ultrasound to diagnose ICHy compared to the standard invasive monitoring of ICP.

An increased diameter of the optic nerve sheath can be compared with papilledema (optic disc edema). However, unlike papilledema, the expansion of the optic nerve sheath occurs seconds after an acute increase in ICP.

ONSD ultrasound has been used to quantify variations in the optic nerve sheath and thus to detect elevations of ICP. Several authors have demonstrated a correlation between millimetric increases in the optic nerve sheath and ICHy.[28] In 2012, Dubourg et al.[29] began a meta-analysis of studies comparing ONSD ultrasound and ICP catheter. The goal of the meta-analysis was to obtain an accurate ONSD ultrasound value for ICHy detection. They considered the clinical use of ONSD ultrasound only for screening purposes, never as a potential substitute for invasive ICP monitoring.[28,29,30,31,32,33,34] This is due to the fact that many of the models allowed only a qualitative and non-quantitative diagnosis of ICHy. Limiting factors of these models included the comparison of ONSD ultrasound with imaging tests[35] and lumbar puncture with manometry .[36,37] Even when compared to an ICP catheter, the selection of the sample for demographic characteristics, diagnosis, neurological status, and the impossibility of reproducing the same situations in a controlled environment were limiting factors in obtaining a quantitative prediction model of ICP using ONSD ultrasound.

There are few models of quantitative prediction of ICP through ONSD ultrasound. Wang et al.[37] studied 316 patients with suspected ICHy due to various diagnostic hypotheses (headache, infection, cerebrovascular diseases, cranial nerves, etc.) submitted to ONSD ultrasound and, soon after, lumbar puncture for ICP measurement. There were 221 patients randomized to the “model” group, in which a statistical model was obtained to predict ICP from ONSD ultrasound: ICP = -111.92 + 77.36 × ONSD. The values obtained using the “control” group were compared to those obtained in the “test” group (94 patients). The correlation obtained was 0.76 ($p < 0.001$). In addition to insufficient correlation for practical application, the comparison with lumbar puncture imposes a series of limitations, such as the impossibility of simultaneous measurement with ONSD ultrasound and variations in positioning.

In experimental animal models, this correlation would theoretically be much simpler to obtain. Kasapas et al.[38] studied 20 rabbits with invasive ICP monitoring with intraparenchymal catheter and ONSD ultrasound in ICHy

models using a SwanGanz catheter to simulate intracranial hematoma. They obtained an exponential correlation: $r^2 = 0.62 \pm 0.119$ ($p < 0.001$). In 2015, Ilie et al. used an ICHy model with autologous blood injection in 6 dogs. They compared ICP data from an epidural catheter and failed to obtain a linear relationship.

The correlation obtained in the present study was linear, and therefore higher than those observed in previous studies.

To date, the use of ONSD ultrasound is restricted to the average of the measurements obtained in each eye. No study has reported differences in the laterality of the ONSD measurements or in the localization of lesions with mass effect. The possibility of this correlation was studied by Strumwasser et al.,[23] but a correlation was not found. In our experiments, AON was the best parameter for predicting ICP and presented the best correlation.

The hypothesis that there is a potential delay in changes in the optic nerve sheath compared to ICP has not been confirmed. The linear correlation itself speaks against this, and the best parameter to predict the ICP, the AON, did not show a delay in the follow-up ICP values.

One criticism of our study was the absence of a control group for comparison. We considered that the measures obtained at baseline, without ICHy, characterized to a certain extent a control group, preventing the sacrifice of more animals for this single purpose, which, in addition to raising costs, would incur an ethical dilemma.

Another criticism was the use of only one examiner to obtain ONSD measurements. However, there are no other animal-model studies with more than one examiner. Even in humans, there is no recommendation for more than one examiner in clinical practice. Padayachy et al.[39] found a good correlation between 2 examiners (r: 0.89 $p < 0.001$). Bäuerle et al.[40] found differences of less than 5% in the measurements obtained, also with a good correlation between 2 examiners ($r > 0.82$ $p < 0.01$). Ballantyne et al. (2002) studied 67 patients with 3 examiners taking 3 measurements of each eye. The mean variability found among the examiners (+/- 0.2 mm) was considered inherent to the device. In addition, after 17 measurements, intra- and inter-rater variability fell dramatically.

Finally, the achievement of measures in a single transversal plane can also represent a limitation. Many studies[26,28,29] use 2 planes of measurement for the optic, transverse, and sagittal nerve sheath, and the mean of the two is used for statistical analysis. In pigs, the sagittal plane is more difficult to measure due to the divergent strabismus of the animals under anesthesia. In our study, we tried to compensate for this limitation with 1 additional measurement to calculate the mean of each side (LON and RON).

Conclusion

ONSD presents a linear correlation with ICP and is a reliable parameter for the prediction of ICP. The mean of the ONSD values on each side (AON) is the best parameter for predicting ICP under the formula **ICP = -80.5 + 238.2 x AON.**

Declarations

Authors' contributions

BCPJ, WSP, AFA, AB, MJ, MR, EBSS, MO, AMR, and DAG designed the paper. All authors participated in drafting and reviewing. All authors read and approved the final version of the manuscript.

Funding

None.

Datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval

The protocol was approved by the Research Ethical Committee at Sao Paulo University Medical School. The care and handling of the animals were in accord with the National Institutes of Health guidelines.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

The datasets generated and/or analysed during the current study are available in the Iniversity of Sao Paulo repository.

(https://teses.usp.br/index.php?option=com_jumi&fileid=17&Itemid=160&id=47A3749E4974&lang=en)

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Table

Table 1

Diameters of the left and right optic nerve sheaths were measured at 9 timepoints after the beginning of the experiment:

	basal	balloon 1	balloon 2	pre saline	saline	post saline	pre intervention	intervention	post intervention
4 mL	0	4	4	4	4	4	4	0	0
4 mL + 3 mL	0	4	7	7	7	7	7	0	0
7 mL	0	7	7	7	7	7	7	0	0

basal, balloon 1 (immediately after the first inflation of the balloon), balloon 2 (immediately after the second balloon inflation or 30 minutes after balloon 1), pre-saline, saline (immediately after infusion of saline), post-saline, pre-intervention, intervention (immediately after balloon deflation), and post-intervention. The volume (mL) inflated in the balloon in each group at each timepoint is shown above

Figures

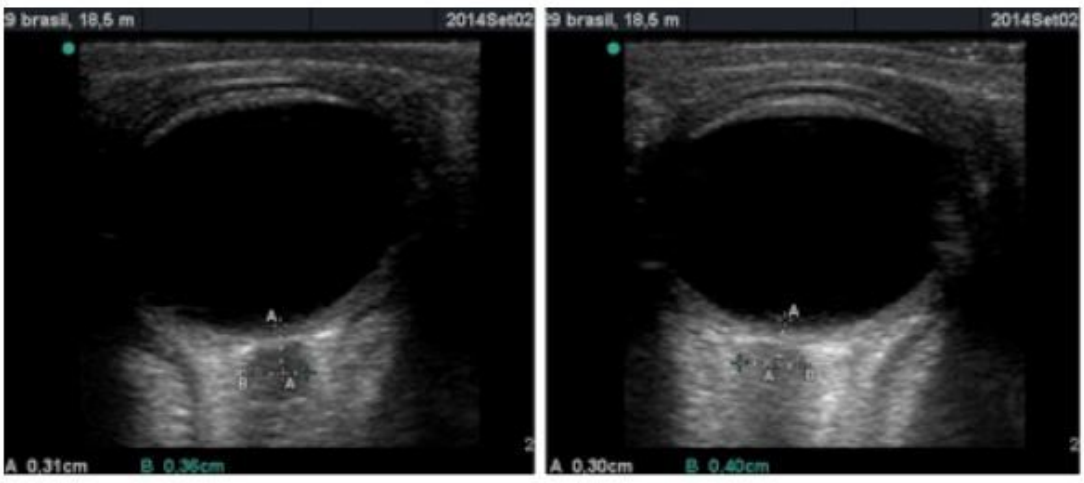

Figure 1

ONSD of experimental animals before (baseline) and after insufflation of 7mL balloon (balloon 1); A: distance from the papilla; B: hem measurement

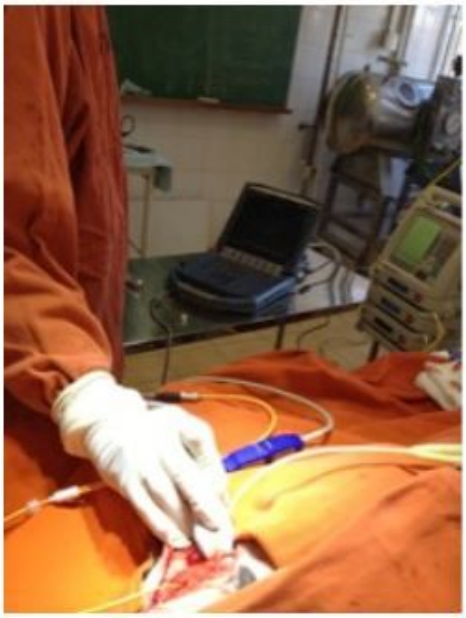

Figure 2

Positioning of the intraparenchymal catheter with a multi-sensor Neurovent-PTO, French size 8 pediatric catheter, and ultrasound transducer LOGIQ Book XP.

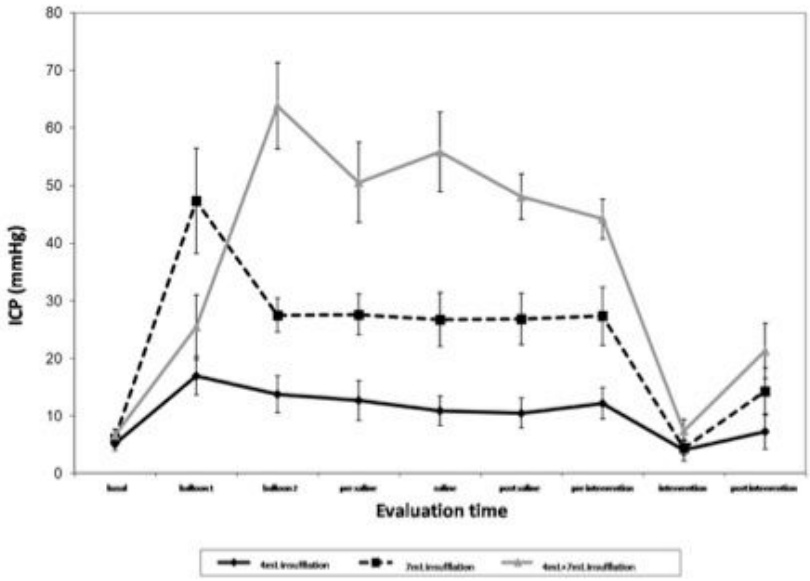

Figure 3

Mean values of the intracranial pressure (ICP) in each group at different time points during the experiment.

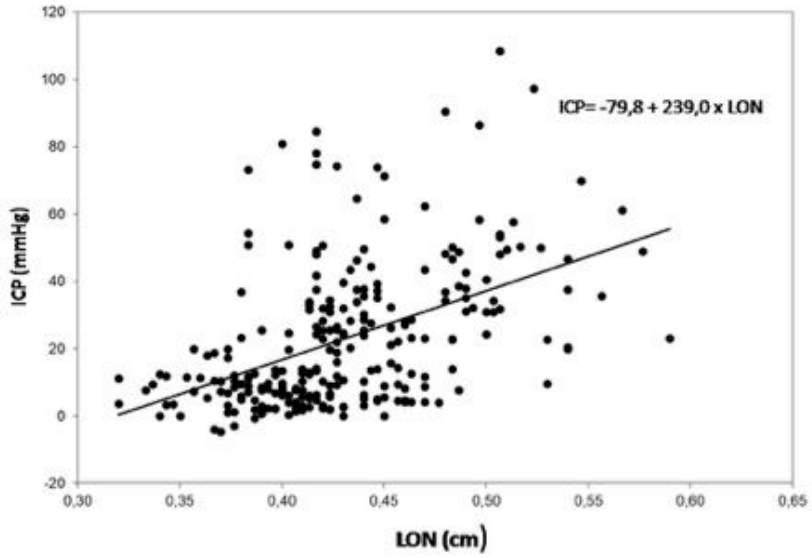

Figure 4

Dispersion diagram of the intracranial pressure (ICP) as a function of the diameter of the left optic nerve sheath (LON).

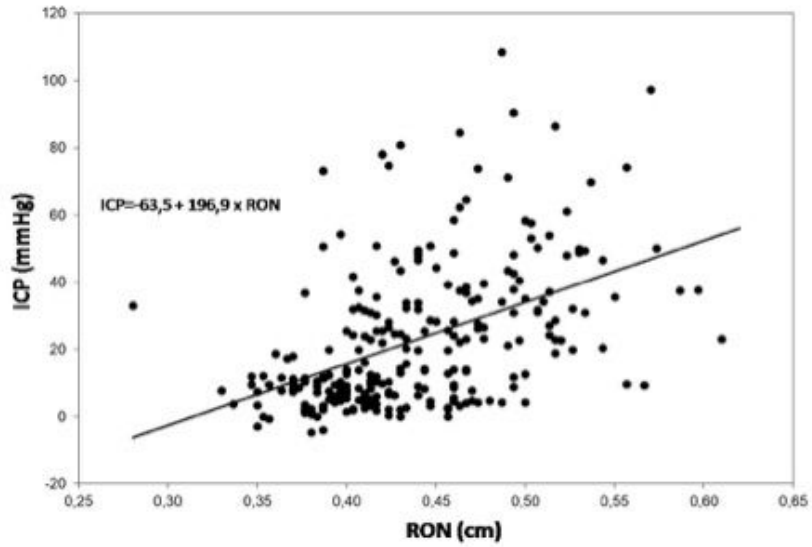

Figure 5

Dispersion diagram of the intracranial pressure (ICP) as function of the diameter of the right optic nerve sheath (RON).

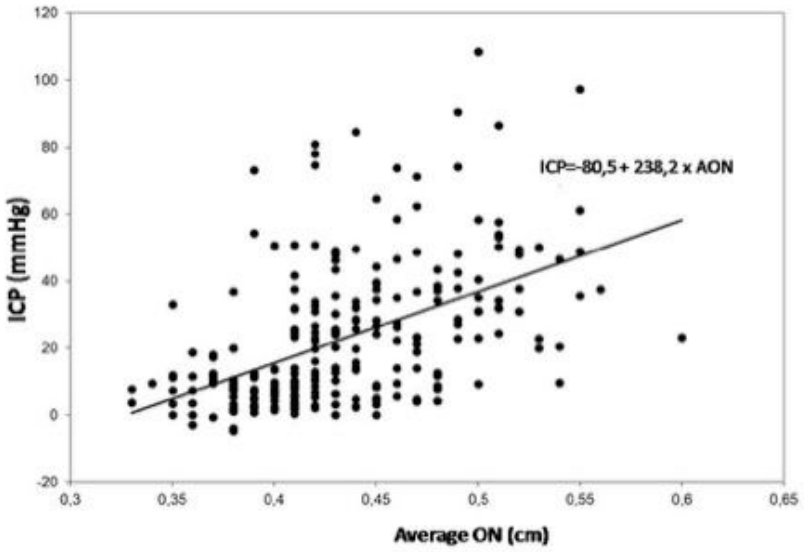

Figure 6

Dispersion diagram of the intracranial pressure (ICP) as function of the average optic nerve sheath value (AON).