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# Effects of prone position and positive end expiratory pressure on non-invasive estimators of ICP: a pilot study

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| **Abstract:** | Background: Prone positioning and positive end expiratory pressure (PEEP) can improve pulmonary gas exchange and respiratory mechanics. However, they may be associated with the development of intracranial hypertension. Intracranial Pressure (ICP) can be non-invasively estimated from the sonographic measurement of the optic nerve sheath diameter (ONSD) and from the Transcranial Doppler analysis of the pulsatility (ICPPI) and the diastolic component (ICPFVd) of the velocity waveform.<br>Methods: The effect of the prone positioning and PEEP on ONSD, ICPFVd, and ICPPI was assessed in a prospective study of 30 patients undergoing spine surgery. One-way repeated measures analysis of variance, fixed-effect multivariate regression models and receiver operating characteristic analyses were used to analyse numerical data.<br>Results: The mean values of ONSD, ICPFVd and ICPPI significantly increased after |

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| | change from supine to prone position. Receiver operating characteristic analyses demonstrated that, among the non-invasive methods, the mean ONSD measure had the greatest area under the curve signifying it is the most effective in distinguishing a hypothetical change in ICP between supine and prone positioning (0.86±0.034 [0.79 to 0.92]). A cutoff of 0.43 cm was found to be a best separator of ONSD value between supine and prone with a specificity of 75.0 and a sensitivity of 86.7.<br>Conclusions: Non-invasive ICP estimation may be useful in patients at risk of developing intracranial hypertension who require prone positioning. |

# Effects of prone position and positive end-expiratory pressure on non-invasive estimators of ICP: a pilot study

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**ABSTRACT**

**Background:** Prone positioning and positive end expiratory pressure (PEEP) can improve pulmonary gas exchange and respiratory mechanics. However, they may be associated with the development of intracranial hypertension. Intracranial Pressure (ICP) can be non-invasively estimated from the sonographic measurement of the optic nerve sheath diameter (ONSD) and from the Transcranial Doppler analysis of the pulsatility ($ICP_{PI}$) and the diastolic component ($ICP_{FVd}$) of the velocity waveform.

**Methods:** The effect of the prone positioning and PEEP on ONSD, $ICP_{FVd}$, and $ICP_{PI}$ was assessed in a prospective study of 30 patients undergoing spine surgery. One-way repeated measures analysis of variance, fixed-effect multivariate regression models and receiver operating characteristic analyses were used to analyse numerical data.

**Results:** The mean values of ONSD, $ICP_{FVd}$ and $ICP_{PI}$ significantly increased after change from supine to prone position. Receiver operating characteristic analyses demonstrated that, among the non-invasive methods, the mean ONSD measure had the greatest area under the curve signifying it is the most effective in distinguishing a hypothetical change in ICP between supine and prone positioning (0.86±0.034 [0.79 to 0.92]). A cutoff of 0.43 cm was found to be a best separator of ONSD value between supine and prone with a specificity of 75.0 and a sensitivity of 86.7**.**

**Conclusions:** Non-invasive ICP estimation may be useful in patients at risk of developing intracranial hypertension who require prone positioning.

***Keywords***: intracranial pressure; optic nerve sheath diameter; positive end expiratory pressure; prone position; pulsatility index; transcranial Doppler

## Introduction

Mechanical ventilation in the prone position and the use of positive end expiratory pressure (PEEP) are frequently used techniques which improve oxygenation in patients at risk of respiratory failure [1, 2]. Prone positioning improves oxygenation in patients with acute lung injury and acute respiratory distress syndrome by reducing ventilation–perfusion mismatch [3-5]. PEEP improves oxygenation by opening collapsed alveoli [6] and mitigates end-expiratory alveolar collapse during general anesthesia, reduces intrapulmonary shunt, increases functional residual capacity, and allegedly reduces the incidence of ventilator-associated pneumonia and lung injury [2, 7].

However, both prone positioning and PEEP can have undesirable effects on cerebral physiology. Prone positioning can increase intracranial pressure (ICP) in patients with intracranial pathology by impairing jugular venous outflow [8, 9]. PEEP can increase ICP and decrease mean arterial pressure, both resulting in decreased cerebral perfusion pressure (CPP) [10, 11], by increasing central venous pressure (CVP) and by impeding cerebral venous return to the right atrium. Consequently, in acutely brain injured patients, ventilation goals are often in conflict with ICP control strategies [12].

The gold standard technique for ICP measurement is an intraventricular catheter [13]; however, this method is invasive and can have complications [14, 15]. Non-invasive ICP (nICP) measurement is a promising technique, still under development in adult [16, 17] and pediatric population [18].Optic nerve sheath diameter (ONSD) measurement using ocular ultrasonography is a safe, quick, reliable and reproducible technique for the assessment of ICP [19, 20 21]. Transcranial Doppler Ultrasonography (TCD) can also non-invasively assess ICP and CPP. Increased ICP produces characteristic changes in cerebral blood flow velocity (FV) waveform that can be assessed by decreases in the diastolic FV and increases in the pulsatility index (PI=systolic FV – diastolic FV) / mean FV)[22] and several methods TCD derived have been proposed to assess non invasively ICP, showing good performance[23, 24].

Therefore, in patients without invasive ICP monitoring, nICP methods may be useful for determining whether PEEP or prone positioning is causing a pathological increase in ICP. In this study we compared 3 different non-invasive ICP estimation techniques to investigate the effect of prone position and/or PEEP on ICP in non-brain injured patients undergoing spine surgery.

## METHODS

The study was approved by the institutional ethics committee at Galliera Hospital, Genova, Italy and, before enrolment, written informed consent was obtained from all participants. Exclusion criteria were: age < 18 years, pre-existing ophthalmic diseases or a history of ophthalmic surgery, and pre-existing neurological disease. A total of thirty-three adult patients scheduled for elective spine surgery between May 2015 and August 2015 who were American Society of Anesthesiologists (ASA) class I to II were included in this study. Of these, three patients were excluded because it was not possible to obtain a suitable ultrasound temporal window in the operating room.

On arrival in the operating room, standard monitoring was applied, including electrocardiography, pulse oximetry, and non-invasive arterial blood pressure. The participants were pre-medicated with midazolam (0.05 mg/kg). General anesthesia was induced with propofol 1.5 mg/kg, and fentanyl 1 μg/kg. Cisatracurium besilate 0.15 mg/kg was administered intravenously to facilitate oro-tracheal intubation. After tracheal intubation, mechanical ventilation was performed with a tidal volume of 8 mL/kg and respiratory rate was adjusted to maintain an end-tidal carbon dioxide ($EtCO_2$) of 35 to 40 mm Hg during surgery. Anesthesia was maintained with remifentanil 0.05 to 0.2 μg/kg/min and 1 to 1.5 minimum alveolar concentration (MAC) of sevofluorane in 50% oxygen/air.

Patients were carefully turned from the supine to prone position by a team of five staff members (three staff nurses and two physicians); two on each side, one controlling the legs and feet and one (the anaesthetist) controlling head and airways and coordinating the procedure.

In the prone position, we limited the shoulder abduction to less than 90° to avoid overstretching of the brachial plexus. We placed the forearm in a neutral position to minimize the direct pressure on the ulnar nerve at the elbow and applied soft padding under the elbows, chest and pelvis.The potential for increased intrathoracic pressure caused by the increased abdominal pressure in prone position was minimized by using foam padding to limit abdominal compression. The head was put in neutral position on an open soft head ring (Horseshoe Head Pad - High - Adult Size) to avoid any direct pressure to the eyes, nose, and mouth.

Ultrasonographic measurement of ONSD was conducted by a single trained investigator (CR) with more than 30 ultrasound examinations of experience, as described in previous studies [25].

A linear 7.5 MHz ultrasound probe (7L4a, Mindray Medica Dc-n3) was carefully placed on the closed upper eyelid without exerting pressure on the eye, in the supine and prone positions. In the two-dimensional mode, ONSD was measured 3 mm behind the globe using an electronic caliper.The ONSD measurement in the prone position was performed by one operator (C.R) while an assistant held the head rotated 30 degrees rightward (to measure the right ONSD) and then 30 degrees leftward (to measure the left ONSD). Two measurements were performed for each optic nerve, one in the transverse plane and one in the sagittal plane. The final ONSD was taken as the mean of the four values measured in both eyes of each patient.

In the supine and prone position the temporal windows are easily accessible. The middle cerebral artery flow velocity (FV) of both sides was determined by Transcranial Doppler using a 2.5 MHz ultrasound probe (2P2, Mindray Medica Dc-n3), and the final FV measurement corresponded to the average of the two values of both sides. In addition, we assessed the duration of surgery, of anesthesia, the amount of intraoperative blood loss, and the volume of administered fluids.

Mean arterial pressure (ABPm), heart rate (HR), Airways Peak Pressure ($P_{peak}$), Airways Plateau Pressure ($P_{plat}$), End Tidal $CO_2$ ($ETCO_2$), middle cerebral artery flow velocities (systolic (FVs), mean (FVm), and diastolic (FVd)) by TCD, and ONSD were recorded at the following time points:

$T_0$: baseline, at least 10 minutes after induction of anaesthesia, in supine position and PEEP=0;

$T_1$: after 10 minutes of prone position ventilation, at zero end expiratory pressure (ZEEP), PEEP=0;

$T_2$: in prone position, after slow and gradual (2 $cmH_20$ every minute) application of PEEP=8 $cmH_20$, after 10 minutes of PEEP=8 $cmH_20$;

$T_3$: at the end of surgery, after 10 minutes of supine position, with PEEP=8 $cmH_20$, without disconnection of ventilation while returning to supine position.

PI was calculated according to the method of Gosling [26]:

PI= (FVs-FVd)/FVm;

nICP derived by PI ($PI_{ICP}$) was calculated according to a formula based on data described by Budohoski *et al.* [27].

$ICP_{PI}$=4.47·PI+12.68.

According to Czosnyka *et al.* [28], non invasive cerebral perfusion pressure (nCPP) has been calculated as:

nCPP=ABPm·FVd/FVm+14

Finally, ICP was then estimated as the difference between inflow (ABPm) and CPP:

$ICP_{FVd}$ = ABPm- nCPP= ABPm(1-Fvd/Fvm)-14.

**STATISTICAL ANALYSIS**

Continuous variables were expressed as mean±SD or median (interquartile range). Categorical variables were expressed as number (percentage). First, data were checked for normality using the D'Agostino-Pearson omnibus test, since it is one of the most powerful and versatile tests for verifying and quantifying how far the distribution of our sample is from Gaussian in terms of asymmetry and shape, and whether these discrepancies are statistically significant. Then Mauchly's Sphericity Test [29] was performed to control data for the sphericity assumption, that is to verify whether the variances of the differences between all possible combinations or pairs of groups (or said otherwise all the possible levels of the independent variable) are equal. In case of sphericity violation, data were corrected using the Greenhouse-Geisser correction or the Huynh-Feldt correction, according to the value of the epsilon. If the epsilon was less than 0.75, the first approach was used.

One-way repeated measures analysis of variance (rmANOVA) was used to evaluate the differences at the different time points of the ONSD, $ICP_{PI}$, $ICP_{Fvd}$, PI, FVs, FVd, FVm, nCPP, ABPm HR, $ETCO_2$, $P_{peak}$, and $P_{plat}$ values. This analysis was used since rmANOVA (known also as within-subjects ANOVA or ANOVA for correlated samples) is the equivalent of one-way ANOVA, in case of related, not independent groups, as for our sample. The impact of the different time-points was estimated with the Pillai's trace, the Wilks' lambda, the Hotelling-Lawley's trace and the Roy's largest root, together with the F-statistics. If the impact of the anesthesiological time-points was significant, Sidak's *post hoc* analyses were performed, since they are very powerful in correcting for multiple comparisons [30]. Partial $\eta^2$ was computed as a measure of effect-size and was interpreted with the Cohen's rule of thumb: small if in the range

0.02-0.13, medium if in the range 0.13-0.26, and large if >0.26. Observed statistical power was also calculated.

A generalized fixed effects regression model with repeated measures was used to estimate and compare the impact of the studied variables on the different estimates of ICP, adjusting for confounding parameters. This statistical technique enables to represent the observed quantities in terms of explanatory variables that are treated as if the quantities were non-random. This technique was chosen because of the small number of patients recruited and because each measurement was made by only one operator. For this reason, the data were treated as a pilot study modeling fixed patient effects. In other words, findings comparing patients should be intended to apply only to the specific patients in the study, without making any inference to hypothetical populations of patients and operators in the way that a random-effects model could have done in a larger study.

A two-way ANOVA, an extension of one-way ANOVA, was performed because this technique enables to assess the influence of two different categorical independent variables on one continuous dependent variable and whether there is any significant interaction between them. In our case, it was performed in order to assess the effect of body position (supine *versus* prone) and PEEP on the different non-invasive ICP estimates.

Receiver operating characteristic (ROC) analyses were performed, enabling a comparison ability of the different nICP estimators to capture potential changes of ICP during different anesthesia time-points. It is important to emphasize that in this study we did not compare the nICP estimators against a gold standard invasive ICP, rather, we used ROC analyses to see which nICP estimator was best able to distinguish between baseline and prone positioning or baseline and PEEP. Cutoff values were chosen using the Youden index, the most used criterion which tends to maximize the correct classification rate, besides being relatively easy to compute.

A p-value <0.05 was considered statistically significant. All statistical analyses were performed using commercial statistical software, namely MedCalc Statistical Software version 15.4 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2015) and IBM SPPS version 22.0.

**RESULTS**

The study recruited a total of 30 ASA 1-2 participants undergoing spine surgery. None of the patients had known intracranial or ocular pathology. Demographic and surgical data of the patients are shown in table 1.

The mean values of HR, ABPm, $P_{peak}$, $ETCO_2$, FVs, FVd, FVm, PI, nCPP, ONSD, $ICP_{FVd}$ and $ICP_{PI}$ at each time point are presented in table 2.

Four patients had a value of ONSD of 0.58 cm or above (the cutoff value for prediction of ICP above 20 mm Hg in previous studies)[19] at time-point $T_2$ (in particular, two patients had an ONSD of 0.58 mm and two of 0.60 mm). Among these four patients, three presented a concomitant increased nICP estimates measured with TCD-derived formulae ($ICP_{PI}$=18, 19, 21 mmHg and $ICP_{FVd}$ 23, 30, 36 mmHg, respectively). No complications (as evaluated with neurological and pupils examination) were observed in any of the enrolled patients.

Compared to baseline values ($T_0$), mean ONSD significantly increased when passing from supine to prone position ($T_0$-$T_1$; p-value <0.0001), after PEEP=8 application ($T_0$-$T_2$; p-value <0.0001), and when returning to supine position with PEEP=8 still applied ($T_0$-$T_3$) (p-value=0.002). ONSD in the prone position with zero PEEP ($T_1$) did not differ from ONSD in prone position with PEEP ($T_2$) (p-value=0.186) but was significantly higher than ONSD in supine position with PEEP applied ($T_3$) ($T_1$-$T_3$; p-value <0.0001). ONSD at $T_2$ was higher than ONSD at time $T_3$ ($T_2$-$T_3$; p-value <0.0001).

Baseline mean value of $ICP_{FVd}$ was significantly lower compared to $ICP_{FVd}$ in the prone position before ($T_0$-$T_1$; p=0.036), and after prone position plus PEEP application ($T_0$-$T_2$; p-value =0.001), but not significantly different than $ICP_{FVd}$ in supine position with PEEP still applied ($T_0$-$T_3$; p-value = 0.998). After the application of PEEP in prone position, mean $ICP_{FVd}$ value did not change significantly ($T_1$-$T_2$; p=0.145), but returning to supine position ($T_3$), mean $ICP_{FVd}$ value was significantly lower compared to $T_2$ or $T_1$ ($T_1$-$T_3$; $T_2$-$T_3$; p<0.0001).

Compared to baseline, $ICP_{PI}$ was significantly higher in the prone position before PEEP ($T_0$-$T_1$; p<0.0001), after PEEP application ($T_0$-$T_2$; p<0.0001), and after returning to supine position with PEEP applied ($T_0$-$T_3$; p=0.040). $ICP_{PI}$ in the prone position without PEEP was significantly lower than after PEEP application ($T_1$-$T_2$; p= 0.024), but not different compared to the supine position with PEEP application ($T_1$-$T_3$; p=0.396). Finally $ICP_{PI}$ was significantly higher in the prone position with PEEP compared with the supine position with maintained PEEP=8 ($T_2$-$T_3$;

p=0.001).

The dependence of ONSD, $ICP_{FVd}$, nCPP PI and $ICP_{PI}$ on the different anaesthesiological variables is shown in table 3. After the corrections of the parameters for confounding factors, ONSD was significantly influenced just by the timepoints.All the nICP methods correlated with each other (p-value <0.0001).

The two-way ANOVA describes the effects of prone positioning and PEEP and their interactions on the considered parameters (table 4). Our results revealed that body position significantly influenced all the nICP methods, as well as ABPm and HR, airway pressures, and FVd and FVm. PEEP application has a significant effect on hemodynamic (ABPm, nCPP) and respiratory variables ($P_{peak}$ and $P_{plateau}$), but amongst the nICP estimators it influenced only $ICP_{PI}$ values. Finally, the synergistic action of PEEP and prone position seems to influence just ABPm.

From the ROC analyses, performed to detect changes in body position and of use of non-zero PEEP with nICP estimators, mean ONSD was best able to distinguish between the supine and prone position ($T_0$-$T_1$; p<0.0001) with an area under the curve (AUC) of 0.864±0.0338 [95% CI 0.789 to 0.920] (figure 1), whilst ROC analysis comparing the descriminative ability of nICP methods on detecting increases of PEEP (T2 vs T1), were not performed as no significant effect of PEEP application with ANOVA was found (table 2). $ICP_{PI}$ and $ICP_{FVd}$ presented with an AUC of 0.750±0.0447 [95% CI 0.663 to 0.825] and 0.694±0.0481 [95% CI 0.603 to 0.774],respectively. Finally, a cut-off of 0.43 cm was found useful to distinguish the mean ONSD value between supine and prone with a specificity of 75.0 and a sensitivity of 86.7 (figure 2).

## DISCUSSION

Our study demonstrates a moderate increase in non-invasive estimators of ICP in patients undergoing spine surgery, as assessed by ONSD- and TCD- based techniques. Changes in position from supine to prone caused a consistent increase in nICP estimators, with ONSD being the most sensitive. Application of PEEP (8 $cmH_20$) seemed to increase the $nICP_{PI}$ but not the other estimators of ICP.

Prone positioning and PEEP can be risk factors for the development of increased ICP. However, direct ICP monitoring is invasive and carries risks. Thus, its use in elective procedures is not indicated and a non-invasive method to assess ICP would be desirable [31]. Many attempts have been made to find a convenient, non-invasive "estimator" for ICP [32-35]. Among these, ONSD ultrasound and TCD has demonstrated to be repeatable, accurate for intraoperative use [20, 25, 36]. In particular, the correlation of ONSD and ICP has been established by several authors[23,31]. The subarachnoid space surrounding the retrobulbar portion of the optic nerve is distensible and can accordingly expand when cerebrospinal pressure increases. Various TCD-derived formulae have been proposed for the estimation of ICP [35], but it is still not clear which one works best. In an animal model [23] where an acute intracranial hypertension was induced, the $ICP_{FVd}$ method performed better than other formulae. Bellner et al. [37] found a strong correlation between $ICP_{PI}$ and invasive ICP, but Cardim et al.[38], comparing 4 different TCD derived formulae with invasive ICP in 46 patients with TBI, found that $ICP_{PI}$ was the weakest estimator.

The interactions between the intracranial and the respiratory systems during mechanical ventilation and PEEP application have been studied by several authors, showing conflicting results [39-44]. Continuous positive airway pressure has shown to decrease CPP and CBF in head injured patients [41]. However, Pulitanò *et al.* [42] in a recent study demonstrated that PEEP application (from zero to PEEP=8) in pediatric patients undergoing major neurosurgical interventions for tumors removal does not increase ICP, suggesting that PEEP application may be safe, provided that ABPm is maintained. Finally, Mascia and collaborators suggested that ICP significantly increases when PEEP is applied, only in patients where PEEP induces alveolar hyperinflation ("non-recruiters") with a consequent increase in $PaCO_2$ and ICP, whereas ICP remains constant in patients where PEEP causes alveolar recruitment ("recruiters") and unchanged $PCO_2$ [45].

*Effects of prone positioning and PEEP on nICP estimators*

In our study, the mean ONSD, $ICP_{FVd}$ and $ICP_{PI}$ increased significantly after prone positioning and after PEEP application in the prone position (time-points $T_0$-$T_1$, and $T_0$-$T_2$, table 2). Isolated PEEP in the prone position did not change ONSD and $ICP_{FVd}$ (time-points $T_1$-$T_2$), but increased $ICP_{PI}$. The two-way ANOVA confirmed that all the nICP methods are strongly influenced by prone positioning, indicating that real ICP is likely to increase with prone positioning.

Among the methods we assessed, ONSD was dependent just on the different time-points rather than being influenced by other respiratory or hemodynamic variables (table 3). Moreover, sonographic ONSD seemed to have the highest sensitivity and specificity for the discrimination between the supine and prone body position (figure 1). An optimal cut off for discriminating between prone and supine positions was 0.43 cm (figure 2). As expected, $ICP_{FVd}$ is the method that is most influenced by hemodynamic variables (in particular by ABPm) and showed a good concordance with ONSD and an acceptable sensitivity and specificity for distinguishing between prone and supine body position (figure 1). As expected, $ICP_{PI}$ was strongly influenced by TCD-derived FV, as previously described [19]. The observation that $ICP_{PI}$ increased with PEEP application could indicate that it is the only nICP method that can be sensitive enough to detect suspected ICP changes in the setting of increased PEEP or alternatively it could reflect the fact that other factors (apart from ICP) may influence PI during PEEP, in particular $ETCO_2$ [46] (table 2,3). In this case, $ETCO_2$ had no significant changes at any studied time-points; we believe that $ICP_{PI}$ resulted to be so sensitive because it is mathematically dependent just from FV values ,which significantly changed after PEEP application.

*Influence of respiratory and hemodynamic parameters on nICP*

Our findings suggest that even in patients with no head injury, ICP may increase in the prone position. However, intracranial hypertension (ICP > 20 mm Hg as indicated by an ONSD above 0.58 cm[19]) rarely occurred in this cohort. Importantly, the increased estimated ICP detected with non-invasive methods in our case series was not related to an increase of $ETCO_2$ (ranging from 33.6±0.4 to 33.1±0.47 after prone positioning and to 32.5±0.4 after PEEP application, with no significant changes at any studied time-points). Moreover, our multivariate regression analysis confirmed that ETCO2 changes did not influence any of the nICP methods.

ABPm was lower in the supine position with PEEP application (T3) compared to baseline ($T_0$), prone positioning with zero PEEP ($T_1$) and prone positioning with PEEP application ($T_2$). This

was probably related to the change of position. However, ABPm as well as nCPP did not increase after prone positioning and PEEP application ($T_0$-$T_1$; $T_0$-$T_2$), suggesting that the increase of ICP registered by non-invasive methods is not the consequence of reduced ABPm, as suggested in a previous study [10].

*Limitations:*

There are several limitations in this study. The estimation of nICP using both TCD $ICP_{PI}$ and $ICP_{Fvd}$ were in fact calibrated using traumatic brain injury patients [25,26]. Therefore, absolute values of nICP in patients without any prior intracranial pathology may be artificially elevated. However, in our study we investigated differences in ICP in different body posture and PEEP conditions, rather than absolute values. Calibration error does not affect these differences. Moreover, to estimate accurately the effects of PEEP and prone positioning on cardiac and cerebral hemodynamics, a more aggressive monitoring should be considered, which should include the invasive measurement of ABPm, the measure of cardiac output, CVP to degree of venous drainage impairment. Moreover, even if in patients with normal respiratory function it is accepted that a constant and predictable gradient between partial pressure of carbon dioxide (PaCO2) and ETCO2 levels exists [47, 48], arterial blood samples with PCO2 determination would be desiderable. These monitoring techniques were not performed in our study as such invasive procedures are rarely indicated in elective neurosurgical procedures.
Furthermore, the data set would have been made more generally complete with the inclusion of an additional data collection time point, in supine positioning at the end of the procedure in the absence of PEEP.

Finally, this study should be considered as a pilot study and further studies with larger sample sizes and with different observers repeating the same measurements are warranted. However, despite the limited number of patients included we found high values of partial $\boldsymbol{\eta^2}$ and observed power for all the parameters (except $ETCO_2$) (table 2), suggesting that the number of patients was adequate for this study. Spinal surgery cases with prone positioning in patients with intracranial pathology where an invasive ICP monitoring device is already present, should be used to assess the role of noninvasive methods in this group of patients and to compare them with a gold standard.

## CONCLUSIONS

Our findings suggest that in patients without head injury, ICP may increase in prone position, whilst the effect due to PEEP of 8 cmH2O is negligible. TCD-derived formulae and ONSD ultrasound measurement can be both useful, safe, quick and easy techniques to non-invasively detect ICP, but ONSD seems to have the best performance in the detection of changes of body position. The increase in ICP that we detected was rarely estimated to be above 20 mmHg.

Patients at risk to develop intracranial hypertension undergoing spine surgery (such as patients with previous neurological diseases, brain tumors, hydrocephalus, or politraumatic patients who need spine fixation) should be counseled to the risks prone positioning may pose with regard to intracranial hypertension. In these patients, as well as for critically ill patient with both elevated ICP and respiratory illness treated by ventilation in the prone position (such as patients with ischemic stroke and brain swelling complicated by aspiration pneumonia leading to ARDS.), a non-invasive ICP monitoring through ONSD ultrasound or TCD could be a valid option.

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**Figure captions:**

Figure 1.On the left panel, univariate Receiving Operator Curve (ROC) analysis for the supination/pronation status the different non invasive parameters. On the right panel, univariate ROC analysis taking in account the use of PEEP.

Figure 2: cut off value for mean ONSD to distinguish the mean ONSD value between supine and prone. The method showed a specificity of 75.0 and a sensitivity of 86.7
0, supine without PEEP; 1, prone without PEEP.

*Table 1. Demographic and surgical data of the patients.*

When not specified, values are expressed as mean value ±Standard Deviation (median).
Abbreviations: COPD, Chronic Obstructive Pulmonary Disease.

*Table 2: Variation of the different parameters at the different anesthesia timepoints.*
Results are given as mean±standard deviation. Partial $\eta^2$ and observed statistical power are also reported. [a]Statistically significant compared to T0. [b]Statistically significant compared to T1. [c]Statistically significant compared to T2.

Abbreviations: airways peak pressure ($P_{peak}$), airways plateau pressure ($P_{plat}$), End Tidal $CO_2$ ($ETCO_2$), heart rate (HR), intracranial pressure measured through PI ($ICP_{PI}$) e FVd method ($ICP_{FVd}$), mean arterial pressure (ABPm), middle cerebral artery flow velocities (systolic (FVs), mean (FVm), and diastolic (FVd)), non invasive cerebral perfusion pressure (nCCP), optic nerve sheet diameter (ONSD), pulsatility index (PI), Timepoint (T).

*Table 3: Fixed effect multivariate regression. Models have been corrected for confounding variables, namely age, sex, BMI, type and time of surgery, fluids administration, ASA classification and co-morbidities. P-values statistically significant are reported in Bold.*

Abbreviations: airways peak pressure ($P_{peak}$), airways plateau pressure ($P_{plat}$), End Tidal $CO_2$ ($ETCO_2$), heart rate (HR), intracranial pressure measured through PI ($ICP_{PI}$) e FVd method ($ICP_{FVd}$), mean arterial pressure (ABPm), non invasive cerebral perfusion pressure (nCCP), optic nerve sheet diameter (ONSD), pulsatility index (PI).

*Table 4: two-way ANOVA assessing the effect of PP, PEEP and their interaction on different parameters*

Abbreviations: Abbreviations: airways peak pressure ($P_{peak}$), airways plateau pressure ($P_{plat}$), End Tidal $CO_2$ ($ETCO_2$), heart rate (HR), intracranial pressure measured through PI ($ICP_{PI}$) e FVd method ($ICP_{FVd}$), mean arterial pressure (ABPm), middle cerebral artery flow velocities (systolic (FVs), mean (FVm), and diastolic (FVd)), non invasive cerebral perfusion pressure (nCCP), optic nerve sheet diameter (ONSD), pulsatility index (PI).

Table 1

| | |
|---|---|
| Sex F/M (n) | 13/17 |
| Age (years) | 54 ±16.4 (54.5) |
| Height (cm) | 172.7±12.6 (176.0) |
| Weight (kg) | 73.8 ± 16.2 (75.0) |
| Comorbilities, n (%):<br>Hypertension<br>asthma<br>COPD<br>Previous transient ischemic attack<br>Smoker | <br>7 (23.33%)<br>3 (10%)<br>2 (6.67%)<br>1 (3.33%)<br>3 (10%) |
| Type of surgery n (%):<br>Micro-discectomy<br>Lumbar fixation<br>Laminectomy | <br>16 (53.3%)<br>7 (23.3%)<br>7 (23.3%) |
| Duration of surgery (min) | 111.7 ±52 (90.0) |
| Fluid administration (ml) | 1533.3 ± 412.2 (1500.0) |

Table 1. *Demographic and surgical data of the patients.* When not specified, values are expressed as mean value ±Standard Deviation (median).
Abbreviations: COPD, Chronic Obstructive Pulmonary Disease.

Table 2

| Parameter | Mean T0 (supine) | Mean T1 (Prone) | Mean T2 (Prone+PEEP) | Mean T3 (Supine+PEEP) | Partial $\eta^2$ | Observed power |
|---|---|---|---|---|---|---|
| HR | 72.93±2.48 | 66.93±2.67[a] | 67.48±2.86 | 78.28±3.05[b,c] | 0.53 | 0.99 |
| ABPm | 79.07±2.98 | 79.67±1.87 | 79.73±2.34 | 69.27±2.50[a,b,c] | 0.45 | 0.97 |
| Ppeak | 15.83±0.40 | 18.13±0.38[a] | 24.10±0.37[a,b] | 20.90±0.57a[,b,c] | 0.95 | 1.00 |
| Pplateau | 11.87±0.47 | 13.83±0.45[a] | 17.83±0.45 [a,b] | 15.77±0.44 [a,b,c] | 0.81 | 1.00 |
| $ETCO_2$ | 33.60±0.42 | 33.10±0.47 | 32.53±0.43 | 32.43±0.41 | 0.16 | 0.40 |
| FVs | 89.80±2.75 | 87.70±2.86 | 86.40±2.60 | 90.13±2.27[c] | 0.28 | 0.71 |
| FVd | 47.77±1.88 | 38.03±2.02[a] | 33.87±2.29[a,b] | 44.03±1.75[b,c] | 0.70 | 1.00 |
| FVm | 61.87±2.08 | 54.53±2.08[a] | 51.27±2.11[a,b] | 58.47±2.03[c] | 0.67 | 1.00 |
| PI | 0.68±0.03 | 0.92±0.05[a] | 1.06±0.07[a,b] | 0.81±0.05[c] | 0.60 | 1.00 |
| nCPP | 71.97±2.67 | 67.87±1.81 | 65.10±2.25 | 61.60±2.52[a] | 0.34 | 0.84 |
| ONSD | 0.40±0.01 | 0.48±0.01[a] | 0.49±0.01[a] | 0.42±0.01[a,b,c] | 0.92 | 1.00 |
| ICPFVd | 7.07±0.82 | 11.80±1.46[a] | 14.83±1.74[a] | 7.53±0.89[b,c] | 0.43 | 0.96 |
| ICP PI | 15.50±0.16 | 16.67±0.23[a] | 17.40±0.31[a,b] | 16.13±0.22[a,c] | 0.64 | 1.00 |

*Table 1: variation of the different parameters at the different anesthesia timepoints.*
Results are given as mean±standard deviation, with their 95% confidence interval. Partial $\eta^2$ and observed statistical power are also reported.

[a]Statistically significant compared to T0. [b]Statistically significant compared to T1. [c]Statistically significant compared to T2.

Table 3

| PARAMETERS | PI p-value | ONSD p-value | FVDICP p-value | nCPP p-value | ICP-PI p-value |
|---|---|---|---|---|---|
| **Intercept** | 0.054 | 0.169 | 0.283 | 0.266 | **0.000** |
| **Timepoint** | 0.144 | **0.000** | 0.364 | 0.414 | 0.174 |
| **HR** | 0.954 | 0.974 | 0.807 | 0.730 | 0.236 |
| **$ETCO_2$** | 0.590 | 0.989 | 0.658 | 0.556 | 0.499 |
| **ABPm** | 0.798 | 0.431 | **0.012** | **0.000** | 0.792 |
| **Ppeak** | 0.364 | 0.154 | 0.300 | 0.308 | 0.693 |
| **Pplat** | 0.535 | 0.561 | 0.243 | 0.335 | 0.686 |

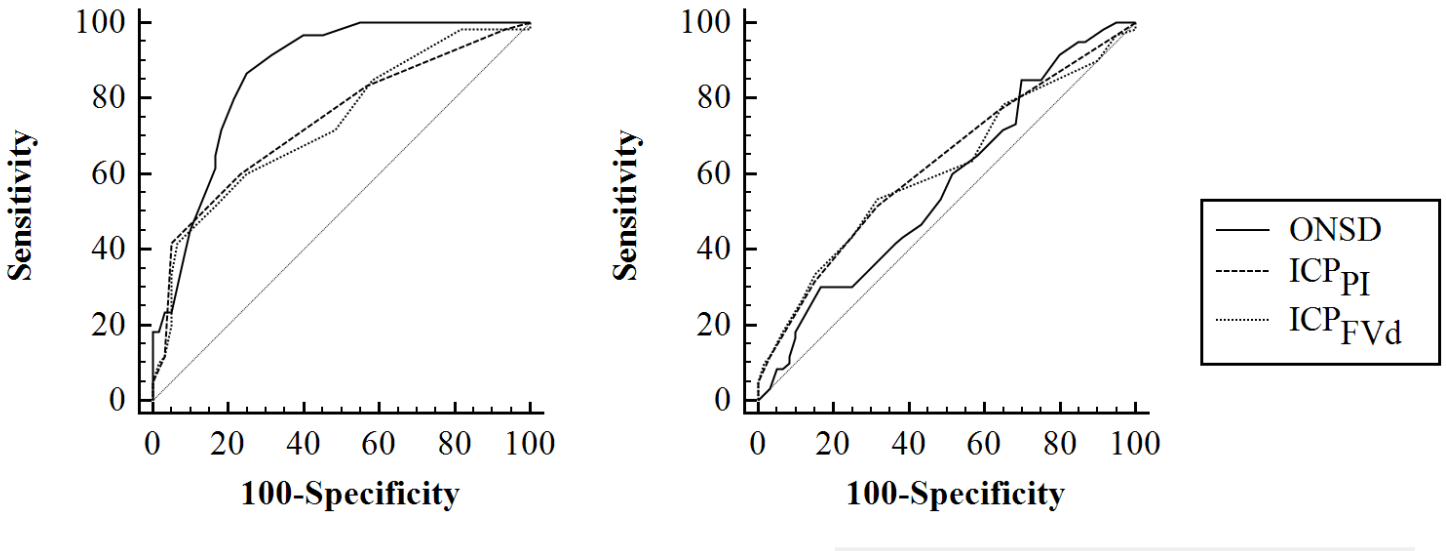
*Table 3: Fixed effect multivariate regression*. Models have been corrected for confounding variables, namely age, sex, BMI, type and time of surgery, fluids administration, ASA classification and co-morbidities. p-values statistically significant are reported in Bold.

Table 4

| PARAMETER | Supine versus prone effect (p-value) | With PEEP versus without PEEP effect (p-value) | Supine versus prone effect X with PEEP versus without PEEP effect (p-value) |
|---|---|---|---|
| **ABPm** | 0.026* | 0.049* | 0.047* |
| **FVd** | 0<0.001*** | 0.050* | 0.914 |
| **FVm** | 0.001** | 0.111 | 0.974 |
| **FVs** | 0.269 | 0.854 | 0.756 |
| **ETCO2** | 0.646 | 0.048* | 0.491 |
| **HR** | 0.011* | 0.253 | 0.595 |
| **PPeak** | <0.001*** | <0.001*** | 0.305 |
| **PPlat** | <0.001*** | <0.001*** | 0.912 |
| **PI** | <0.001*** | 0.009** | 0.922 |
| **ICPFVd** | <0.001*** | 0.177 | 0.321 |
| **ICP IP** | <0.001*** | 0.004** | 0.830 |
| **Mean ONSD** | <0.001*** | 0.084 | 0.410 |
| **nCPP** | 0.898 | 0.006** | 0.107 |

*Table 4: two-way ANOVA assessing the effect of PP, PEEP and their interaction on different parameters.*

Figure 1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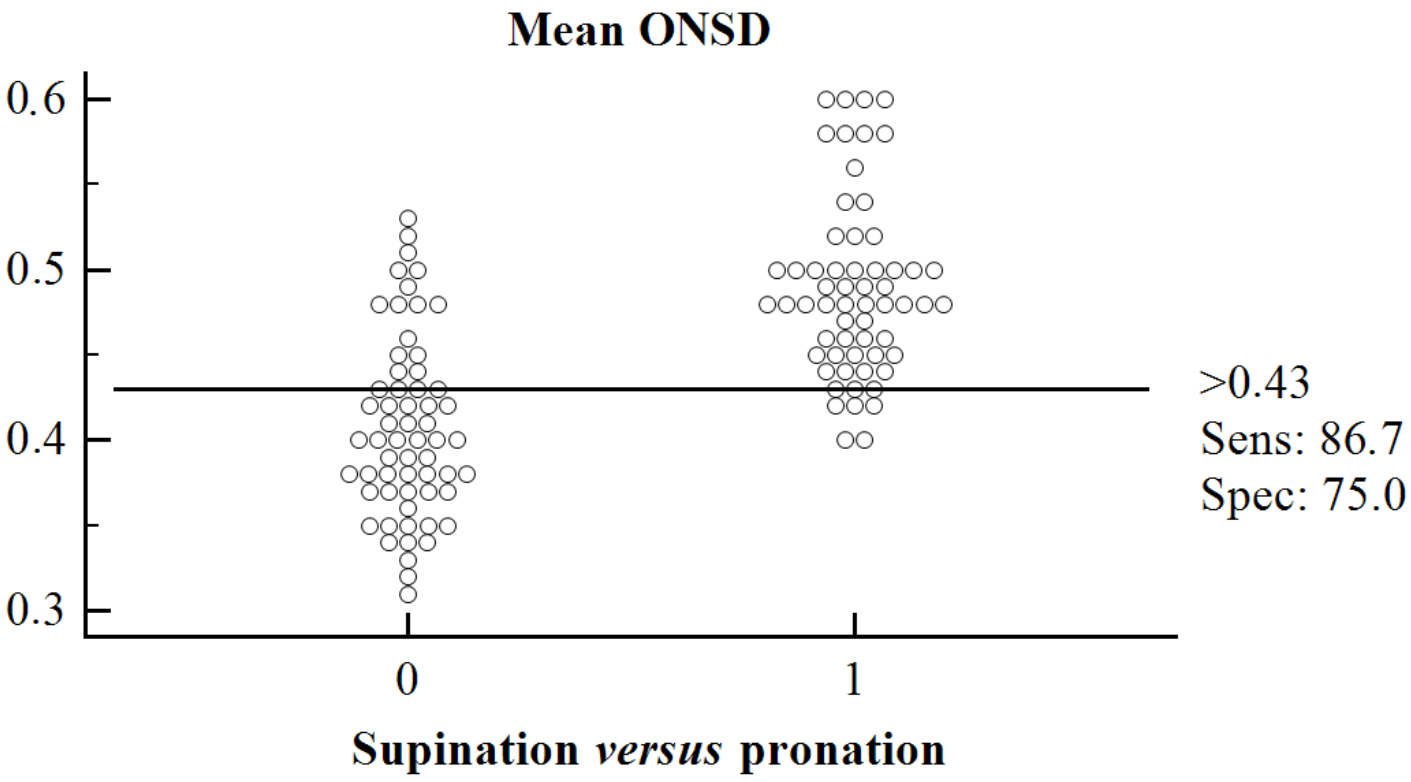
ICP$_{PI}$
ICP$_{FVd}$

Figure 2


Mean ONSD
0.6
0.5
0.4
0.3
>0.43
Sens: 86.7
Spec: 75.0
0
1
Supination versus pronation