Hemodynamic physiology during perioperative intracranial hypertension
Kalmar, A.F.
Study of the cerebral haemodynamic physiology during steep Trendelenburg position and CO2 pneumoperitoneum.

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Abstract

Background : The steep (40 degree) Trendelenburg position optimizes surgical exposure during robotic prostatectomy. The goal of the current study was to elucidate the influence of this patient positioning on cerebral blood flow and to assess the validity of different methods of evaluating cerebral perfusion.

Methods : Transcranial Doppler flow velocity waveforms and invasive arterial and central venous pressure (CVP) waveforms were successfully recorded during the whole operative procedure in 14 consecutive patients who underwent robotic endoscopic radical prostatectomy under general anaesthesia. The Zero Flow Pressure (ZFP) was determined by regression analysis of the pressure-flow plot and by different simplified formulas. The effective Cerebral Perfusion Pressure (eCPP), Pulsatility Index (PI) and Resistance Index (RI) were determined.

Results : While patients were in the Trendelenburg position, the ZFP increased in parallel with the CVP. The PI, RI, the gradient between the ZFP and CVP as well as the gradient between the CPP and the eCPP did not increase significantly (p<0.05) after 3 hours of steep Trendelenburg position. The ZFP calculated by the formula of Czosnyka overestimated the ZFP calculated by linear regression by 1.9 (3.7) mmHg, but did so consistently throughout the course of the operation.

Conclusion : During prolonged steep Trendelenburg position and CO₂ peritoneum, the gradient between the CVP and ZFP, and between the CPP and the eCPP remain invariant, as well as the PI and RI. Therefore, we conclude that this prolonged patient positioning does not compromise cerebral perfusion and that the CPP does not change over the course of the operation. The ZFP using the formula of Czosnyka and the eCPP are reliable parameters for assessing brain perfusion during prolonged steep Trendelenburg positioning.
Introduction

Robotic endoscopic abdominal surgery is increasingly being used\(^1\),\(^2\). To facilitate this technique, steep (40°) Trendelenburg positioning of the patient for several hours is often required, along with a CO\(_2\) pneumoperitoneum. This combination of interventions has the potential to significantly influence cerebral haemodynamic homeostasis.

The head down position increases arterial blood pressure, but at the same time increases the central venous pressure (CVP) to a lesser degree\(^3\) thereby impairing venous outflow from the brain, and increasing hydrostatic pressures within the brain vasculature. Increasing hydrostatic pressure will change the balance of Starling forces, and this is likely to increase the extracellular water content in dependent tissues, and in the brain this will result in an increase in intracranial pressure (ICP). At the same time, a degree of cerebral vasodilation is also likely, caused by autoregulation to maintain cerebral blood flow in the face of an impaired cerebral perfusion pressure (CPP), and exacerbated by possible increases in arterial PaCO\(_2\) caused by the CO\(_2\) pneumoperitoneum (which impairs diaphragmatic excursion, and also results in some systemic CO\(_2\) absorption). Any resulting vasodilation will further increase ICP.

It is not surprising then that the combination of steep Trendelenburg positioning and pneumoperitoneum has been shown to induce intracranial hypertension\(^4\) and cause significant reductions of cerebral tissue oxygen saturation in elderly patients\(^5\) and in patients with pre-existing raised ICP\(^6\). Patients presenting for robotic surgery are often elderly, with limited physiological reserve, and significant co-morbidities such as cerebrovascular disease, and these are thus patients in whom the procedure may critically disturb the cerebral perfusion.

On regaining consciousness shortly after prolonged steep Trendelenburg positioning, patients commonly exhibit a short-lived (~60 minutes) period of pronounced cognitive dysfunction [personal observations]. The subsequent rapid return to baseline function suggests that the cognitive dysfunction is the result of an insult, such as cerebral oedema, that rapidly disappears with normal positioning.

The driving pressure for brain perfusion, the CPP, is usually regarded as the difference between the mean arterial pressure (MAP) and the greater of the ICP and the CVP\(^7\). In normal patients and conditions the equation CPP = MAP – CVP provides a reasonable approximation of effective CPP (eCPP). If, however, significant cerebral perivascular oedema develops, the eCPP may deviate significantly from this theoretical value. Consequently, a CPP that is associated with adequate cerebral perfusion in the supine position may become inadequate after a long period of steep Trendelenburg position. Falling eCPP caused by worsening
perivascular oedema should be reflected in the evolution of the Zero Flow Pressure (ZFP), which is the theoretical arterial pressure at which blood flow in the cerebral circulation ceases, and may represent the effective downstream pressure of this system\(^8\). The evolution of the eCPP and ZFP can be estimated from analysis of the middle cerebral blood flow velocity (using Transcranial Doppler Sonography, TCD) and invasive arterial pressure waveforms.

There are essentially two major methods for determining the ZFP. The most fundamental method calculates the ZFP by regression analysis of the pressure-flow plot of the Flow Velocity (FV) and invasive arterial pressure (P).

**Figure 1 : Determination of the Zero Flow Pressure by regression analysis.**

\[
y = 0.7013x - 34.76
\]

\[R^2 = 0.9181\]

\[ZFP = 49.6\]

Each dot in figure 1 of the flow velocity waveform represents a pressure sample and corresponds to a data point in the regression analysis. The X-intercept of the regression line is the ZFP. An $R^2 > 0.91$ is used as a cut-off value to select heartbeats with adequate signal quality.

This method is the most precise, but requires perfect synchronization of the pressure and flow curves and requires elaborate computations. The second general method uses a formula to calculate ZFP from the systolic and diastolic pressure and flow values\(^9\) (figure 2). The basic principle is that, mathematically, perfusion pressure = flow x resistance. The two most commonly used formulas are those suggested by Czosnyka\(^10\) and Schmidt\(^11\). These methods are much simpler to implement than regression analysis and can easily be used for bedside assessments. As far as we are aware neither the general method nor the different available formulas for calculating ZFP have been validated in patients in the extreme Trendelenburg position.
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Figure 2 : Formulas to determine ZFP, RI and PI based on systolic and diastolic pressure and flow values

<table>
<thead>
<tr>
<th>Formula</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>(\text{eCPP}_{\text{Belfort}}) = (\frac{\text{BP}_s - \text{BP}_d \times \text{BP}_m - \text{BP}_d}{\text{FV}_m - \text{FV}_d})</td>
<td>Effective Cerebral Perfusion Pressure as described by Belfort.</td>
</tr>
<tr>
<td>(\text{ZFP}_{\text{Czosnyka}}) = (\frac{\text{BP}_s - \text{BP}_d \times \text{BP}_s - \text{BP}_d}{\text{FV}_s - \text{FV}_d})</td>
<td>Zero Flow Pressure as described by Czosnyka.</td>
</tr>
<tr>
<td>(\text{ZFP}_{\text{Schmidt}}) = (\frac{\text{BP}_m - \text{BP}_m \times \text{FV}_d + 14}{\text{FV}_m + 14})</td>
<td>Resistance Index as described by Schmidt.</td>
</tr>
<tr>
<td>(\text{RI}) = (\frac{\text{FV}_s - \text{FV}_d}{\text{FV}_s})</td>
<td>Resistance Index.</td>
</tr>
<tr>
<td>(\text{PI}) = (\frac{\text{FV}_s - \text{FV}_d}{\text{FV}_m})</td>
<td>Pulsatility Index.</td>
</tr>
</tbody>
</table>

These formulas to determine the effective Cerebral Perfusion Pressure (eCPP) as described by Belfort, the Zero Flow Pressure (ZFP) as described by Czosnyka and Schmidt and the Resistance Index (RI) and Pulsatility Index (PI) are a function of the mean (m), diastolic (d) or systolic (s) value of the Flow Velocity (FV) and invasive Arterial Blood Pressure (BP).

The aim of this study was therefore to assess the influence of extreme Trendelenburg positioning on ZFP, eCPP, arterial blood pressure and CVP over time. In addition we wanted to assess the influence of this position, and changes in PaCO2, on the pulsatility index\(^\text{12}\) and resistance index\(^\text{13}\), and to compare the different methods of calculating ZFP.

Methods

Patients
After Institutional Ethics’ Committee approval (Ethics’ Committee, OLV Clinic, Aalst, Belgium) and written informed consent was obtained, 21 consecutive patients who underwent robotic endoscopic prostatectomy in steep Trendelenburg position were included.

Anaesthetic management:
No premedication was administered. Upon arrival in the operating theatre, standard monitoring was applied: ECG, pulse oximetry and non-invasive automated arterial blood pressure. After anaesthesia was induced with propofol, 1–2 mg kg\(^{-1}\) and sufentanil 0.25 μg kg\(^{-1}\), rocuronium 0.6 mg kg\(^{-1}\) was administered and the trachea intubated. Anaesthesia was maintained with 1 MAC of sevoflurane. Additional boluses of sufentanil and rocuronium were administered as required at the discretion of the clinician. The lungs were ventilated in volume control mode with an O2/air mixture (F\(_{2}\)O\(_2\) 40%) and a PEEP of 5 cm H\(_2\)O. The tidal volume was adjusted to achieve a P\(_{\text{ET}}\)CO\(_2\) between 4.0 and 4.7 kPa. Normothermia was maintained with a forced-air warming system. Once stable profiles of capnography and blood pressure were reached, ventilatory and drug delivery settings were left unchanged.
Invasive pressure monitoring:
After induction, a 20-gauge arterial catheter (Arterial Cannula, REF 682245, Becton Dickinson, Swindon, UK) was inserted percutaneously into a radial artery. The catheter was connected via rigid pressure tubing (length 150 cm, internal diameter 1.5 mm), filled with saline, to a continuous-flush pressure-transducer system (Becton Dickinson Critical Care Systems, Singapore) to monitor beat-to-beat blood pressure. The right internal jugular vein was cannulated with a double-lumen central venous catheter (Arrow International Inc., Reading, PA, USA) for monitoring of central venous pressure. The external acoustic meatus was used as the zero reference point for both pressure transducers, to allow a precise determination of the cerebral perfusion pressure, independent of patient positioning. Both systems were calibrated against atmospheric pressure and both pressure transducers were connected to an S5-monitor (GE Healthcare, Helsinki, Finland).

Transcranial Doppler ultrasonography:
A middle cerebral artery was insonated via the temporal window using a 2MHz Transcranial Doppler ultrasound probe (dopbox, MedCaT, Erica, The Netherlands). The identity of the middle cerebral artery was confirmed using standard criteria and the position of the probe was fixed with the DiaMon® Sets (Compumedics, Singen, Germany) monitoring set to maintain a constant angle of insonation. All waveforms were recorded on a personal computer. The waveform sampling frequency was 100 Hz.

Surgical procedure:
After adequate positioning of the patient, the abdominal cavity was insufflated with CO₂ to a pressure of 10mmHg, and the patient was placed in mild Trendelenburg position after which the trocars were located at the classical points. Finally, the patients were slowly placed in steep Trendelenburg position (40° from horizontal). All operations were performed on the same table with the same degree of Trendelenburg.

The surgeon performed the procedure with the da Vinci Robot Surgical System (Intuitive Surgical, Sunnyvale, CA). The intraperitoneal pressure was adjusted by the surgeon as needed. At the end of the procedure, the position of the table was normalized and the pneumoperitoneum was released. The surgical wounds were closed and the patient was awakened either in the operating theatre or in the recovery room.

Data analysis:
All vital signs were monitored using an S5-monitor with automated electronic data recording using Collect Software (GE Healthcare, Helsinki, Finland). The arterial pressure and central venous pressure waveforms were sampled and digitized at 100Hz. All other variables were recorded digitally every 5 seconds. In the subsequent offline analysis, the data, which were stored in ASCII format, were imported into
Microsoft Excel spreadsheets. Using dedicated custom-developed software (written by A Kalmar), the pressure waveforms were synchronized with the velocity waveforms for visual inspection and analysis.

Pressure and velocity waveforms of each individual heart beat over the whole operation were evaluated for perfect synchronization. Hysteresis in the pressure-flow velocity plots was minimized (for each heartbeat, the point of maximal positive slope of both waveforms was automatically synchronized) and the ZFP was calculated for every heart-cycle as extrapolated by regression analysis of the pressure-flow plot\textsuperscript{16} (Figure 1). These data are presented as \( \text{ZFP}_{\text{reg}} \). Because signal quality is of critical importance for reliable determination of derived values from pressure and flow parameters, we only analyzed those waveforms where the \( R^2 \) of the regression line was > 0.91.

In those heartbeats with \( R^2 > 0.91 \), the effective Cerebral Perfusion Pressure (eCPP) was calculated using the formula of Belfort\textsuperscript{17}, the ZFP using the formulas described by Czosnyka\textsuperscript{10} and Schmidt\textsuperscript{11}, the Resistance index\textsuperscript{13} (RI) as described by Pourcelot and the pulsatility index\textsuperscript{12} (PI) as described by Gosling and King (Figure 2).

The MAP and CVP were determined for each heartbeat (as the arithmetic mean of sampling values within each heartbeat) and the CPP was calculated as the difference between MAP and CVP. These calculated values were determined at 10 minutes intervals from 5 minutes before institution of Trendelenburg position to 30 minutes after resuming the supine position. For each interval, the mean (SD) was calculated for the values within a time window of 30 seconds (= 6 ventilation cycles).

All curves were first synchronized with onset of Trendelenburg positioning (\( T_0 \)), and then later re-synchronised upon resumption of the supine position (represented as S in Figure 3). The baseline value, reported as “Pre”, was defined as the average of the 30 second interval at 5 minutes before steep Trendelenburg repositioning (i.e. during the period when the patient was still in horizontal position, just prior to shallow Trendelenburg).

The relationship between the Pulsatility Index and the Pe’CO2 after institution of the Trendelenburg position was determined by linear regression analysis (Figure 4).

Statistical analysis:
Data were analysed using the two-sided Student T-test for paired comparisons and statistical significance level was set at 5 %. Data were analyzed using Excel 2007.
Results

Twenty-one patients were enrolled in the study. No reliable TCD signal could be obtained in 7 patients, who were thus excluded from further analysis. Data of the 14 included patients were normally distributed and are presented as mean (SD). Patient age was 63 (8) years. The total time spent in steep Trendelenburg position was 149 (83) min. All patients left the post-anaesthesia care with an Aldrete\textsuperscript{18} score of 10/10 and were discharged from hospital after an uneventful postoperative period.

| Table 1: Parameters measured before, during and after the Trendelenburg period. |
|---------------------------------|-------|-------|-------|
| MAP (mmHg)                     | 85(12) | 91(11) | 73(14)* |
| CVP (mmHg)                     | 9 (5)  | 25(8)  | 8(4)   |
| CPP (mmHg)                     | 76(12) | 67(13) | 63(14)* |
| eCPP\textsubscript{Belfort} (mmHg) | 73(15) | 61(10) | 61(20)  |
| ZFP\textsubscript{linear regression} (mmHg) | 13(7)  | 28(11)  | 8(15) |
| ZFP\textsubscript{Czosnyka} (mmHg) | 14(8)  | 30(11)  | 10(14) |
| ZFP\textsubscript{Schmidt} (mmHg) | 8(7)   | 8(5)    | 4(6)   |
| Pe'CO\textsubscript{2} (kPa)    | 4.1(0.3) | 4.9(0.5)  | 4.8(0.6)* |
| Pulsatility Index              | 0.73 (0.20) | 0.72(0.17) | 0.75(0.19) |
| Resistance Index               | 0.48(0.09) | 0.48(0.07) | 0.49(0.08) |

The perioperative changes in Invasive Mean Arterial Pressure (MAP) and Central Venous Pressure (CVP) – measured at the level of the mid-ear, Cerebral Perfusion Pressure (CPP) calculated as CPP=MAP-CVP, effective CPP as described by Belfort, Zero Flow Pressure (ZFP) calculated by linear regression and as described by Czosnyka and Schmidt, End-tidal CO\textsubscript{2} pressure (Pe'CO\textsubscript{2}), Pulsatility Index and Resistance Index of the patients in the period before (Pre-Tren), during (Tren) and after (Post-Tren) institution of steep Trendelenburg position. The values are shown as mean(SD) of the 14 patients included in the study. *: significantly different from pre-Trendelenburg period, p<0.05.

The course of the investigated parameters is shown in Figures 3a-c as mean values at 10 minute intervals.

MAP increased significantly from 85 (12) mmHg before Trendelenburg positioning to 107 (14) mmHg at T\textsubscript{1} (10 minutes after T\textsubscript{0}) (P<0.05). Thereafter it was not significantly (p>0.05) different from pre-Trendelenburg values (figure 1). After resumption of the supine position, the MAP was significantly (p<0.05) lower than before T\textsubscript{0}.

CVP and ZFP\textsubscript{reg} increased significantly (p<0.05) after T\textsubscript{0}.
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Figure 3: The Course of the investigated parameters at 10 minute intervals.

A

The course of the Central Venous Pressure (CVP), Zero Flow Pressure calculated by linear regression (ZFP), Zero Flow Pressure as described by Czosnyka and Schmidt and the End-Tidal CO\textsubscript{2} pressure (Pe'CO\textsubscript{2}).

B

The course of the Pulsatility Index, Resistance Index and End-Tidal CO\textsubscript{2} pressure (Pe'CO\textsubscript{2}).

C

The course of the Central Venous Pressure (CVP), Invasive Mean Arterial Pressure (MAP), Cerebral Perfusion Pressure determined as (CPP=MAP-CVP) and the effective Cerebral Perfusion Pressure as described by Belfort (eCPP Belfort).

The parameters are shown as Mean values at 10 minutes intervals. All data are synchronized at the moment of initiating Trendelenburg positioning and resynchronized at resumption of the supine position. The parameters are shown as Mean values at 10 minutes interval from 5 minutes before to 165 minutes after institution of Trendelenburg position. At reassuming the supine position, the curves are resynchronized and values are shown for another 20 minutes.
The gradient between these parameters remained stable – mean $ZFP_{\text{reg}}$ was 2.8 (8.6) mmHg greater than CVP during Trendelenburg positioning ($p>0.05$). Neither parameter changed significantly during the period of Trendelenburg positioning (fig 3a).

The $ZFP_{\text{Czosnyka}}$ increased significantly ($p<0.05$) after $T_0$ and correlated closely with $ZFP_{\text{reg}}$ (fig 3a). After resumption of the supine position, it was not significantly different ($p>0.05$) from the value before Trendelenburg. The $ZFP_{\text{Schmidt}}$ did not change significantly ($p>0.05$) after $T_0$ and showed poor correlation with the ZFP (fig3a).

The eCPP did not change significantly ($p>0.05$) during Trendelenburg compared to the pre-Trendelenburg value. eCPP was significantly lower after Trendelenburg compared with baseline: eCPP 73 (15) mmHg at baseline versus 59 (23) mmHg at S1, $P<0.01$ (fig 3c).

Over the course of the operation, eCPP values were consistently lower than the calculated CPP (=MAP-CVP), although this difference did not reach statistical significance. Moreover, the gradient between the CPP and the eCPP did not increase significantly over the course of the operation (fig 3c).

The Pulsatility Index and Resistance Index did not change significantly ($p>0.05$) over the course of the operation (fig 3b). The Pe'CO$_2$ increased significantly ($p<0.05$) during Trendelenburg position, compared to baseline (fig 3b). There was a negative correlation between the Pulsatility Index and the Pe'CO$_2$ (fig 4).

**Figure 3 : Linear regression analysis of the Pulsatility index in function of the Pe'CO$_2$.**

![Graph showing linear regression analysis](image)

This negative slope confirms that the CO$_2$ reactivity of the cerebral blood flow is preserved.
Discussion

Steep Trendelenburg position (40°) optimizes surgical exposure in several procedures, and is well tolerated by most patients. In this observational study of a group of 14 patients undergoing robotic prostatectomy we have evaluated the influence of the steep Trendelenburg position combined with a CO₂ pneumoperitoneum on the cerebral haemodynamic homeostasis. We have also evaluated and compared different methods for estimating zero flow pressure that were hitherto only validated in subjects positioned in more benign positions.

We have previously observed that patients are frequently disorientated after awakening after being in the Trendelenburg position for a long time, but that this resolves spontaneously within an hour. This rapid return to normal cognitive function, coupled with the fact that cerebral brain oxygenation remains optimal during robotic prostatectomy, lead us to suspect that the period of disorientation may have been caused by cerebral oedema resulting from increased venous pressure during steep Trendelenburg positioning. In contrast with peri-orbital oedema (which is probably also caused by venous hypertension), cerebral oedema is a far less benign problem, given the fixed volume of the cranial cavity. It is thus important to know whether this cerebral oedema, if present, is sufficient to compromise cerebral perfusion.

Buhre and colleagues demonstrated that the Zero Flow Pressure is determined by two Starling resistors in series, one at the precapillary arteriolar level influenced by vascular tone, and one at the level of collapsible cerebral veins influenced by the greater of the ICP and CVP. A Starling resistor is any collapsible conduit surrounded in its middle section by an external pressure that is greater than the outlet pressure. The precapillary Starling resistor determines the effective downstream pressure as long as the ICP (CVP) does not exceed the critical closing pressure of the arteriolar system. It remains to be seen whether the resistance of the second starling resistor (at the level of the cerebral veins) remains at an acceptable level in the context of prolonged steep Trendelenburg position. Weyland and coworkers have shown that the Zero Flow Pressure of the cerebral circulation can be reasonably assessed from instantaneous pressure-flow velocity plots by extrapolation. This ZFP should be slightly higher than the CVP. If prolonged steep Trendelenburg position has a significant effect on the ZFP, the ZFP-CVP gradient should increase over time. Our observations show (Figure 3a) that this gradient does not increase significantly (P>0.05), even after 3 hours of head-down positioning. This suggests that any cerebral perivascular oedema that may develop does not significantly hamper the cerebral perfusion.

The evolution of changes in cerebral vascular resistance can also be assessed by estimating the effective Cerebral Perfusion Pressure (eCPP), described by Belfort and colleagues (Figure 2). This eCPP should be slightly lower than the calculated...
CPP (CPP = MAP - CVP). As shown in figure 3c, the eCPP is indeed slightly lower than the CPP, but the gradient between the CPP and the eCPP does not change significantly and neither the Pulsatility Index nor the Resistance Index increase significantly over the course of the operation (fig 3b). Moreover, the negative relationship between the PI and the Pe'CO_2 suggest that the CO_2-reactivity of the cerebral system is also preserved (fig 4). All these observations suggest that the cerebral microcirculation and cerebral autoregulation are preserved during prolonged Trendelenburg positioning.

Inversely, the observation that the CPP, calculated as CPP = MAP - CVP gives a very similar result to the eCPP calculated by the formula of Belfort (figure 2), suggests that even after prolonged steep Trendelenburg positioning, this time-honoured method of determining the CPP, based on the values of the MAP and CVP, remains valid.

Throughout the whole procedure, ZFP\textsubscript{Czosnyka} was remarkably similar to ZFP\textsubscript{reg}. In contrast, although ZFP\textsubscript{Schmidt} was similar to ZFP\textsubscript{reg} during the pre-Trendelenburg period, it did not change significantly during Trendelenburg positioning, and remained at about 1/3 of the ZFP\textsubscript{reg} (Figure 3a). These results suggest that when patients are in this position, the method of Czosnyka provides a reasonable estimate of ZFP whereas that of Schmidt does not.

In conclusion, even after prolonged combined Trendelenburg positioning and pneumoperitoneum, we found no evidence of cerebral oedema, and no increased resistance to cerebral blood flow other than that caused by the hydrostatic pressure due to the head-down position. In these situations, the clinically convenient method to determine the ZFP described by Czosnyka remains valid, as does the conventional method for calculating CPP.
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