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Original article

Laryngoscopy mediated stress response induces opposite effects on cerebral and paraspinal oxygen saturation

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Abstract

Background: **Intraoperative sympathetic stimulation induces a cascade of metabolic and hormonal changes. It increases perfusion of vital organs, but also causes vasoconstriction of blood vessels supplying less vital organs, potentially leading to organ injury. To date, it is unknown how an endogenous stress reaction affects the spinal cord blood supply. Near-infrared spectroscopy (NIRS) can be applied paravertebrally to monitor the oxygenation of the collateral network, which contributes to the spinal cord blood supply. It has already been demonstrated that regional cerebral oxygen saturation (rS_cO_2) increases following sympathetic stimulation.**
Objectives: **We hypothesized that laryngoscopy would cause an increase in cerebral and paraspinal regional tissue saturations (rS_cO_2 and $rS_{ps}O_2$, respectively).**
Design: **Retrospective analysis of a previous conducted randomized trial.**
Setting: **Laryngoscopy in the operating room.**
Methods: **Data of 28 patients, scheduled for arterial dilation of the lower limb, were retrospectively analyzed. Before induction of anesthesia, standard monitoring, BIS and 8 NIRS sensors were applied (two on the forehead, six bilaterally on the back at T3-T4, T9-T10 and L1-L2). Sympathetic stimulation was induced by laryngoscopy.**
Main outcome measures: **Changes in rS_tO_2 following sympathetic stimulation induced by laryngoscopy.**
Results: **Following laryngoscopy, rS_cO_2 significantly increased and $rS_{ps}O_2$ significantly decreased at T9-T10 and L1-L2. The relative changes (regional tissue oxygen saturation (rS_tO_2) after intubation-rS_tO_2 before intubation)/ rS_tO_2 before intubation), at cerebral level, T9-T10 and L1-L2 were 9%, -5% and -3%, respectively ($p < 0.01$). $rS_{ps}O_2$ at T3-T4 did not change significantly. Changes (Δ) in mean arterial pressure following laryngoscopy were weakly correlated with ΔrS_cO_2 and moderately correlated with $\Delta rS_{ps}O_2$ at T9-T10 and L1-L2.**
Conclusions: **Intraoperative sympathetic stimulation may decrease the oxygen supply to the spinal cord.**
Trial registration: **The trial was registered at ClinicalTrials.gov (NCT 03767296).**

Keywords: **Adrenergic receptor, ephedrine, laryngoscopy, near-infrared spectroscopy, sympathomimetic agents.**

Introduction

Current guidelines advocate aiming for higher systemic blood pressures to prevent spinal cord ischemia in situations where regional blood perfusion of the spinal cord is at risk of being compromised[1]. This is usually obtained by pharmacological sympathetic stimulation, resulting in increased heart rate and blood pressure. The idea is that increased blood pressure automatically implies better regional spinal cord perfusion. Yet, evidence for such strategy is low (class III)[1].

Near-infrared spectroscopy (NIRS) enables the monitoring of changes in regional tissue

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IRB approval and written consent: Informed consent was obtained from every patient included.
Data from a previous conducted prospective randomized trial between 6 February and 7 September 2017 (registered at ClinicalTrials.gov (NCT 03767296))11 was retrospectively analyzed.
Ethical approval for the present retrospective observational study (ERB number: 2019/1603, November 2019) was provided by the Ethical Committee of the Ghent University Hospital, Ghent, Belgium (Chairperson Prof D. Matthijs).

oxygenation (rS_tO_2). Its use is widespread as a monitor of cerebral ischaemia[2], but more recently, as a result of changed anatomical understanding and new research insights[3-5], paravertebrally applied NIRS monitoring has also been advocated for non-invasive and indirect assessment of spinal cord perfusion. It measures the saturation of the collateral network, which is an extensive clew of interconnecting arteries and arterioles, located in the paravertebral tissues and contributing to the spinal cord blood supply[6].

The present study aimed to investigate the effect of a strong endogenous sympathetic stimulation on cerebral and paravertebral oxygen saturation. Therefore, we analyzed NIRS data during laryngoscopy in order to identify the effects of a laryngoscopy-mediated stress response on regional cerebral oxygen saturation (rS_cO_2) and paravertebrally measured regional oxygen saturations ($rS_{ps}O_2$).

Methods

After approval of the Ghent University Hospital Ethics Committee for additional analysis (ERB number: 2019/1603) and informed consent was obtained, data from a previously conducted prospective randomized trial (registered at ClinicalTrials.gov (NCT 03767296))[7] were retrospectively analyzed.

All 28 patients included in that study[7] were scheduled for an endovascular dilatation of arterial blood vessels of the lower limb. Exclusion criteria were BMI>30, previous aortic surgery, severe valvular disease, paraplegia or paraparesis and patients requiring renal replacement therapy. Baseline mean arterial pressure (MAP) was measured during the preoperative visit. Before induction of anesthesia, two disposable NIRS sensors (INVOS 5100C, Medtronic, Dublin, Ireland) were applied bilaterally on the forehead, as was one bispectral index sensor (BIS, Medtronic, Ireland). A further six NIRS sensors were applied bilaterally on the back of the patient, all in a paravertebral position, at thoracic level T3-T4, T9-T10 and the remaining two at lumbar level L1-L2. Baseline NIRS levels were obtained before induction of anesthesia, with the patient in a supine position without supplemental oxygen. At this moment non-invasive blood pressure readings were obtained and set to repeated measurements at one-minute intervals. For induction of anesthesia, all patients received a standard dose of sufentanil (0.15 μg/kg) and propofol (1-2 mg/kg) until loss of consciousness, followed by cisatracurium (0.15 mg/kg). After three minutes of manual ventilation with an inspiratory fractional oxygen concentration (F_iO_2) of 1.0 and BIS-titrated sevoflurane administration, the patient was intubated. Following intubation, F_iO_2 was immediately reduced to 0.4. Tidal volumes were set at 8 mL/kg ideal body weight. Respiratory rate was titrated to maintain end-tidal CO_2 readings between 35 and 45 mmHg. Sevoflurane was used for maintenance of anesthesia, with a target BIS range of 40-60.

Hemodynamic and respiratory data were acquired using a personal computer running dedicated data acquisition software (Dräger Data Grabber, Dräger Medical GmbH, Lübeck, Germany).

Primary outcome was the laryngoscopy-induced change in rS_tO_2 (rS_cO_2 and $rS_{ps}O_2$) as measured by NIRS. Blood pressure, heart rate, BIS and peripheral oxygen saturation (S_pO_2) were chosen as secondary endpoints.

Primary and secondary outcome data before and after laryngoscopy were compared. For the pre-laryngoscopy data, the value just before introduction of the laryngoscope was noted. For the post-laryngoscopy data, the maximum changed value within two minutes was recorded.

The relative changes (Δ) following laryngoscopy were calculated with the formula (post-laryngoscopy value minus pre-laryngoscopy value)/pre-laryngoscopy value.

Statistical analysis

Based upon the data of the previous trial[7], a post-hoc power analysis was performed for the present study. With a sample size of 28 and an alpha of 0.05, analysis revealed a power of 0.99 at the cerebral level and a power of 0.06, 0.98 and 0.99 at T3-T4, T9-T10 and L1-L2, respectively.

Normality was tested with the Shapiro-Wilk test. Differences before and after laryngoscopy in primary and secondary outcomes were analyzed with the Wilcoxon Signed Ranks test and are presented as median [min, max]. Correlation between ΔMAP and ΔrS_tO_2 was performed with the Spearman correlation test. P-values < 0.05 were considered significant.

Results

All 28 patients from the previous trial were included in the present analysis. Patients' characteristics are presented in Table I.

Heart rate, MAP and BIS increased significantly following laryngoscopy, as depicted in Table II. SpO_2 did not change.

Table III presents the absolute values of rS_tO_2, measured before and after laryngoscopy, and the relative changes. Laryngoscopy provoked an

opposite effect on rS_tO_2, with an increase in rS_cO_2 ($p<0.01$) and a decrease in $rS_{ps}O_2$ at T9-T10 and L1-L2 ($p<0.01$ for both). No significant effect was observed at level T3-T4.

Correlation analysis showed a weak positive correlation between ΔMAP and ΔrS_cO_2 ($r=0.49$, $p<0.05$) and a moderate negative correlation between ΔMAP and $\Delta rS_{ps}O_2$ at both T9-T10 and L1-L2 ($r=0.59$ and $r=0.69$, respectively, $p<0.01$ for both). No correlation was found between ΔMAP and $\Delta rS_{T3-T4}O2$ (Figure 1).

Table I. — Patients' characteristics.

Sex (male/female)	13/15
Length (cm)	168 [150, 190]
Weight (kg)	70 [42, 100]
BMI ($kg.m^{-2}$)	25.4 [17.5, 30.0]
Age (y)	67 [48, 87]
Arterial hypertension	24 (86)
Atrial fibrillation	5 (18)
Myocardial infarction	7 (25)
Diabetes mellitus	11 (39)
Pacemaker	1 (4)
ACE-inhibitors	12 (43)
b-blocking agents	14 (50)
Diuretics	8 (29)
Ca^{2+}-antagonists	5 (18)
Statins	17 (61)

Data are expressed as median [min, max] or number (percentage). BMI: body mass index; ACE: Angiotensin-converting enzyme.

Discussion

Laryngoscopy mediated stress response was accompanied with an increase in rS_cO_2. However, despite higher MAPs, a decrease in $rS_{ps}O_2$ was observed.

NIRS technology was used to observe the effect of laryngoscopy on rS_cO_2 and $rS_{ps}O_2$. Based on data of previous studies[3], measuring $rS_{ps}O_2$ at low thoracic and lumbar levels seems to adequately reflect the oxygenation of the collateral network. Therefore, the T9-T10- and L1-L2-level were both chosen for sensor application. The level of T3-T4 was chosen as a control measurement.

NIRS measures rS_tO_2 of the underlying region at a depth of approximately 2.5 to 3 cm. Hence, the question may rise if oxygenation of the subcutaneous tissue has been measured instead of oxygenation of the collateral network. Indeed, although the spatial resolution technique reduces the influence of outer layers, not all extraspinal structures may have been excluded. Therefore, patients with a BMI of more than 30 were excluded to minimize this possible confounding factor, in accordance with the exclusion criteria stated in previous studies on NIRS and spinal cord oxygenation[8].

Also, the study population existed of vascular burdened patients with concomitant diseases such as diabetes mellitus (39%) and atherosclerosis (100%) (Table I). The inherent microangiopathy accompanying both conditions may influence reactivity of the targeted vascular structures (at

Table II. — Secondary outcome parameters before and after laryngoscopy with its relative change.

	Pre-laryngoscopy	Post-laryngoscopy	Relative change (%)	p-value
HR (bpm)	63 [58-77]	81 [69-93]	22 [13-40]	< 0.001
MAP (mmHg)	84 [64-95]	108 [83-122]	23 [8-38]	< 0.001
S_pO_2 (%)	99 [97-100]	99 [98-100]	0 [0.02-0.03]	ns
BIS	39 [27-46]	49 [35-68]	25 [16-55]	< 0.001

Data are presented as median [Q1-Q3]. HR: heart rate; bpm: beats per minute; MAP: mean arterial pressure; SpO2: peripheral oxygen saturation; BIS: bispectral index; relative change: (post-laryngoscopy – pre-laryngoscopy) /pre-laryngoscopy; ns: not statistically significant. Q1-Q[3]

Table III. — Regional tissue oxygen saturation (rS_tO_2) before and after laryngoscopy with its relative change.

rS_tO_2	Pre-laryngoscopy	Post-laryngoscopy	Relative change (%)	p-value
rS_cO_2	68 [61-75]	76 [70-81]	9 [6-12]	<0.01
$rS_{T3-T4}O_2$	82 [78-89]	83 [76-89]	-1 [-2, 1]	ns
$rS_{T9-T10}O_2$	78 [72-85]	74 [70-82]	-5 [-7, 1]	<0.01
$rS_{L1-L2}O_2$	81 [71-88]	77 [72-85]	-3 [-6, -1]	<0.01

Data are presented as median [Q1-Q3]. rS_cO_2: regional cerebral oxygen saturation, $rS_{T3-T4}O_2$: regional oxygen saturation at T3-T4, $rS_{T9-T10}O_2$: regional oxygen saturation at T9-T10; $rS_{L1-L2}O_2$: regional oxygen saturation at L1-L2, relative change: (post-laryngoscopy – pre-laryngoscopy)/pre-laryngoscopy, ns: not statistically significant.

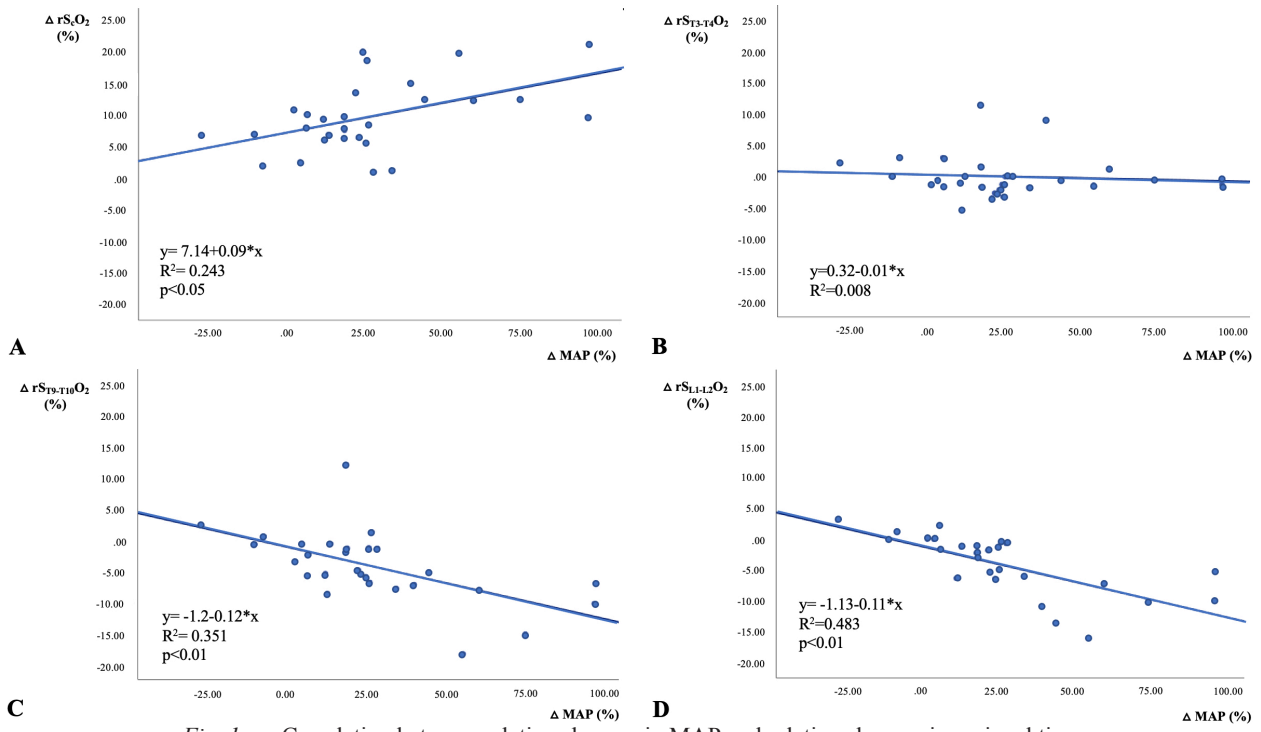

Fig. 1 — Correlation between relative changes in MAP and relative changes in regional tissue saturation.

Correlation analysis, demonstrating a weak positive correlation between changes (Δ) in MAP and ΔrS_cO_2 (A), no correlation between ΔMAP and $\Delta rS_{T3-T4}O_2$ (B) and a moderate negative correlation between ΔMAP and both $\Delta rS_{T9-T10}O_2$ (C) and $\Delta rS_{L1-L2}O_2$ (D). Δ: relative change, rS_cO_2: regional cerebral oxygen saturation, $rS_{T3-T4}O_2$: regional oxygen saturation at T3-T4, $rS_{T9-T10}O_2$: regional oxygen saturation at T9-T10; $rS_{L1-L2}O_2$: regional oxygen saturation at L1-L2. MAP: mean arterial pressure.

cerebral and paravertebral level), hence influencing the changes in rS_tO_2

following laryngoscopy. Moreover, 86% of our study population suffered from arterial hypertension and were treated with antihypertensive medication (Table I). It might be that the antihypertensive drugs have affected the vascular wall and hereby have affected the measured changes in rS_tO_2 following laryngoscopy. Despite these possible confounding factors, our measurements all trended in the same direction.

We have previously demonstrated that administration of ephedrine, a commonly used α- and ß- sympathomimetic drug failed to improve $rS_{ps}O_2$ (-0.7% and -1.3% at T9-T10 and L1-L2, respectively) despite substantially rising MAP (12 mmHg)7. The results of the current study confirm this sympathetic mediated response in $rS_{ps}O_2$(-4% at both T9-T10 and L1-L2) with increased blood pressure (MAP increase of 24 mmHg). These findings suggest that an increased sympathetic stimulation seems indeed associated with decrease in $rS_{ps}O_2$ and this effect appears more pronounced with a more important rise in MAP.

This is an unexpected finding as the current strategy to preserve spinal cord blood supply is to augment MAP, presuming that increasing blood pressure automatically implies better tissue perfusion[9].

To date, research on how physiologic responses affect $rS_{ps}O_2$ remains scarce. The current initial data suggest that an endogenous stress response following laryngoscopy may induce a decrease in $rS_{ps}O_2$, indicating that sympathetic stimulation may adversely affect (para)spinal tissue oxygenation.

Limitations

In this study, the spinal cord oxygenation was not directly measured. Instead, we measured $rS_{ps}O_2$, which reflects the oxygenation of the underlying paravertebral tissues. Since this vasculature takes part in the collateral network, several landmark papers postulate that it contributes substantially to the spinal cord blood supply[3-5].

Nevertheless, the spinal cord blood supply is not solely dependent on blood supply from the collateral network. Hence, the observed changes of $rS_{ps}O_2$ following laryngoscopy – presumably due to vasoactive changes in the paravertebral vasculature- may not necessarily imply that the spinal cord blood supply is at stake. Therefore, further investigation is needed to study the effect of sympathetic stimulation on $rS_{ps}O_2$ with simultaneous imaging of the spinal cord perfusion, using fMRI, for example

Arterial partial pressure of carbon dioxide (P_aCO_2) plays a significant role in vascular tone and might therefore influence rS_cO_2. We did not obtain P_aCO_2 data, but as part of our routine anesthetic monitoring, end tidal CO_2 was measured and per

protocol maintained at a level between 35 and 45 mmHg. No outliers of end tidal CO_2 were detected in our dataset.

Post-hoc power analysis is sometimes criticized as a means of assessing validity of determining whether the sample size of a secondary data analysis is adequate for a proposed analysis[10]. Sensitivity analysis has been proposed as a possible means to address this problem. The most relevant variables potentially influencing the current study results would be outlayers and missing data, none of which were present in this study[11].

Conclusion

Although paraspinal NIRS monitoring has to date not been validated to indirectly assess spinal cord oxygen saturation, the results of the present study should be an incentive to specifically analyze the effects of sympathetic stimulation on $rS_{ps}O_2$.

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The authors declare no conflicts of interest.

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