Impact of hyperoxia and phenylephrine on cerebral oxygenation: An experimental clinical study

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Abstract

Background: Oxygen supply to the brain is of special importance during intracranial surgery because it may be compromised by intracranial pathology. A high arterial blood pressure (mean arterial pressure above 80 mmHg) and a high arterial oxygen tension (PaO2 above 12 kPa) is therefore often targeted in these patients, when for example intracranial pressure is increased or when a mass effect on brain tissue from a tumour is present, and it is pursued by administering vasopressors such as phenylephrine and by increasing inspiratory oxygen fraction (FiO2). However, whether these interventions increase cerebral oxygenation remains uncertain. We aimed to investigate the effect of hyperoxia and phenylephrine on brain tissue oxygen tension (PbtO2) in patients undergoing craniotomy.

Methods: In this experimental study, we included 17 adult patients scheduled for elective craniotomy. After securing a stable baseline of the oxygen probe, PbtO2 was measured in white matter peripherally in the surgical field during general anaesthesia. Primary comparisons were PbtO2 before versus after an increase in FiO2 from 0.30 to 0.80 as well as before versus after a bolus dose of phenylephrine (0.1–0.2 mg depending on patient haemodynamics). Data were analysed with the Wilcoxon signed rank test.

Results: We obtained complete data sets in 11 patients undergoing the FiO2 increase and six patients receiving the phenylephrine bolus. PbtO2 was 22 (median; 5%–95% range, 4.6–54) mmHg during 30% oxygen, 68 (8.4–99) mmHg during 80% oxygen (p = .004 compared to 30% oxygen), 21 (4.5–81) mmHg before phenylephrine, and 19 (4.2–56) mmHg after phenylephrine (p = .56 compared to before phenylephrine).

Conclusion: In patients undergoing craniotomy under general anaesthesia, brain tissue oxygen tension increased with a high inspiratory oxygen fraction but remained unchanged after a bolus dose of phenylephrine.

KEYWORDS

cerebral oxygenation, hyperoxia, neurosurgery, oxygen, phenylephrine
1 INTRODUCTION

In patients undergoing intracranial surgery, oxygen supply to the brain is of special importance since intracranial pathology may increase the risk of brain tissue ischaemia. To ensure adequate oxygen supply, hypoxaemia and hypotension should likely be avoided, but it is unclear whether increases in arterial oxygen tension and mean arterial pressure beyond normal levels further increase oxygen delivery to the brain and, consequently, improve brain tissue oxygenation. Arguments to the contrary could be made, as an increase in arterial oxygen tension will trigger a reduction in global cerebral blood flow (CBF) in the healthy brain, and cerebral pressure autoregulation will offset an increase in mean arterial pressure by a compensatory increase in cerebrovascular resistance, keeping cerebral perfusion constant within certain limits. Furthermore, overdosing of oxygen has well-established harmful systemic effects.

Arterial pressure can be increased using phenylephrine, a selective alpha-1 adrenergic receptor agonist which induces of vascular smooth muscle constriction and is commonly administered to counteract anaesthesia-induced hypotension. However, it remains debated whether phenylephrine also causes constriction of cerebral blood vessels, thereby potentially reducing CBF despite an improvement in systemic haemodynamics. Bedside monitoring of CBF is generally not feasible, but several techniques exist for continuous assessment of cerebral oxygenation (and thereby indirectly CBF), two of which are used as part of standard clinical practice in various settings: non-invasive near-infrared spectroscopy (NIRS), and invasively measured brain tissue oxygen tension (PbtO2) based on a Clark-like electrode. While NIRS is based on the differential absorption of light by oxy- and deoxyhaemoglobin as measured by an optode on the forehead skin, the Clark-like electrode measures the partial pressure of oxygen invasively in the brain tissue using polarography. NIRS has thus far been used mainly within the perioperative setting and for monitoring of very preterm infants to detect and treat cerebral desaturation, however, the level of evidence for these practices is sparse. In contrast, due to their invasive nature, PbtO2 is mainly measured during neurocritical care, e.g. in patients with acute severe brain injury as a tool to optimise brain oxygen supply and monitor complications such as delayed cerebral ischaemia.

Phenylephrine has been reported to reduce frontal lobe oxygenation as measured by NIRS in anaesthetised patients; however, this reduction could, at least in part, be caused by a reduced perfusion of the skin and scalp, which are more likely to be influenced by phenylephrine. Conversely, higher cerebral perfusion pressure is strongly associated with higher values of invasively measured PbtO2 in patients with traumatic brain injury, further supporting the hypothesis that the decrease in NIRS values is not caused a reduction in actual brain perfusion.

In the present study, the aim was to investigate the impact of hyperoxaemia and phenylephrine on cerebral oxygenation in neurosurgical patients during general anaesthesia. The primary outcome was PbtO2 during an inspiratory oxygen fraction (FIO2) of 0.30 versus 0.80, and before versus after an intravenous bolus of phenylephrine. The secondary outcome was cerebral oxygen saturation measured on the forehead over the frontal lobe using NIRS during the above-mentioned conditions. We hypothesised that a high FIO2 would increase, whereas a bolus dose of phenylephrine would decrease, brain tissue oxygenation.

2 METHODS

This study was an experimental clinical study in adult patients undergoing craniotomy. The protocol was registered on ClinicalTrials.gov (NCT03682198) before inclusion of the first participant, and approval was obtained from the Regional Ethics Committee of the Capital Region of Denmark (H-18007888) and the Danish Data Protection agency (VD-2018-97, I-Suite nr.: 6335). Written informed consent was obtained from all subjects, and external monitoring of consent, study documents and data was performed according to the ICH-GCP.

Patients were recruited from September 2018 to October 2020, at the Department of Neuroanaesthesiology, Rigshospitalet, Copenhagen University Hospital, Denmark. Eligible patients were adults (≥18 years) scheduled for elective craniotomy under general anaesthesia. Exclusion criteria were the following: Repeat craniotomy, perioperative hypotension (defined as a systolic blood pressure below 110 mmHg before surgery), preoperative hypoxia (defined as a peripheral oxygen saturation [SpO2] <90% without oxygen supplementation before surgery), and no negative pregnancy test for women <50 years. Arterial blood pressure and SpO2 were measured upon arrival in the operating room. To enable placement of the NIRS sensor in the surgical field, the craniotomy was required to have an expected size of at least 8 × 4 cm.

The INVOS™ 5100c Cerebral/Somatic Oximeter (Medtronic) was used for measurement of regional cerebral oxygen saturation (ScO2). An adult-sized sensor was placed on the patient’s forehead, over the non-affect ed hemisphere. After a baseline ScO2 was obtained, general
Anaesthesia was induced and maintained as per clinical standard with propofol 1–2 mg/kg bolus and remifentanil infusion with the patient in the supine position. Patients were intubated after deep neuromuscular blockade with either cisatracurium (0.15 mg/kg) or rocuronium (0.6 mg/kg) and placed in the relevant position for surgery (supine/prone/side). Anaesthesia was maintained using infusions of propofol (0.1–0.2 mg/kg/min) and remifentanil (0.25–0.5 μg/kg/min). Until the start of measurements, we aimed for an FiO2 of 0.50, which could be increased as needed to ensure a SpO2 ≥94% throughout the anaesthesia. A catheter was placed in the radial artery for continuous arterial pressure measurement and blood gas analysis. Normovolaemia was maintained with infusion of lactated Ringer’s solution, and blood transfusions were administered in case of a haemoglobin concentration below 5.0 mM or an estimated blood loss of >20% of total blood volume. A phenylephrine infusion (0.1 mg/ml) was used to keep mean arterial pressure >65 mmHg throughout the anaesthesia.

A Licox® PtO2 Monitor (Integra® Lifesciences) was connected to the oxygen probe of the Licox® Brain Tissue Oxygen Monitoring Complete Brain Probe Kit (either IM3EU or IM2EU) to measure PbtO2. The oxygen probe was placed by the neurosurgeon at depth of approximately 10 mm in the white matter peripherally in the surgical field. The introducer for the oxygen probe was not applied to minimise the risk of bleeding and for the convenience of the surgeon. If necessary, the probe was fixated to the surrounding surgical equipment. Once a stable baseline was achieved, PbtO2 and ScO2 were measured continuously. Intraoperative data from the anaesthesia machine (Primus, Dräger), patient monitor (Intellivue MX500, Philips), the cerebral oximeter and the Licox® monitor were recorded using ICM+® software (Cambridge Enterprise).

The study phase occurred at the end of surgery just before suture of the dura mater. Data was recorded during the following phases:

1. **Normoxia**: FiO2 was reduced to 0.30 and allowed to stabilise for 5 min, following which data was recorded for 5 min.
2. **Hyperoxia**: FiO2 was increased to 0.80 and allowed to stabilise for 5 min, following which data was recorded for 5 min.
3. **Phenylephrine**: Approximately 10 min after returning the FiO2 to the standard level (~0.50) and following 5 min of baseline data sampling, an intravenous bolus of 0.1 or 0.2 mg of phenylephrine was administered. The dose of phenylephrine was chosen individually based on what we estimated would result in an increase in mean arterial pressure (MAP) of at least 10 mmHg. We calculated the mean value of PbtO2 during the 5 min immediately before phenylephrine was administered (‘Before phenylephrine’), and compared it to the PbtO2 value that coincided with the maximal MAP within the first 5 min after the phenylephrine bolus (‘After phenylephrine’).

### Statistics and sample size

This study was part of a research project in which intracranial NIRS was also investigated; these results are described elsewhere. Sample size calculation was based on the co-registered NIRS study (NCT03682198), in which we calculated that paired data from 30 patients would be necessary to detect a minimal clinically relevant absolute difference of 15% between sites of measurement of ScO2 with a control value of 76%, a SD of 10%, a power of 80% and a 5% significance level.

Non-parametric statistics were used due to the small sample size, and unless otherwise stated data are reported as median (5%–95% range). The primary outcome of PbtO2 before versus after...

### FIGURE 1  Study flow chart

### TABLE 1  Patient characteristics

| Characteristic                                      | N = 17 |
|-----------------------------------------------------|--------|
| Age (years)                                         | 66 (35–75) |
| Female sex                                           | 8 (45%) |
| Body mass index (kg/m²)                              | 26 (23–36) |
| ASA classification (1/2/3/4)                         | 0/11/5/1 |
| History of hypertension                              | 2 (11.8%) |
| Other cerebral disease                               | 2 (11.8%) |
| Other cardiac disease                                | 1 (6%) |
| Chronic obstructive pulmonary disease                | 1 (6%) |
| Intracranial pathology                              |        |
| Cerebral tumour                                      | 13 (76%) |
| Cerebellar tumour                                    | 1 (6%) |
| Arteriovenous malformation                           | 2 (12%) |
| Epileptic focus                                      | 1 (6%) |

**Note**: Values are median (5%–95% range) or n (%). Abbreviation: ASA, American Society of Anesthesiologists.
interventions was evaluated using the paired Wilcoxon signed rank test. Statistical analyses were performed independently by two co-authors (SSP and MHO) using SAS Enterprise Guide 7.1 (SAS Institute) and R version 4.1.0 (R Core Team 2021).

2.2 | Follow-up

All patients were followed until hospital discharge for registration of all serious adverse events (SAEs), which were assessed by review of the electronic medical record.

3 | RESULTS

A total of 67 patients were screened for eligibility, of whom 50 were excluded (Figure 1). Due to slow recruitment and lack of funding, the study was terminated prematurely after inclusion of 17 patients. Of the study participants, 55% were male and the median age was 66 years (Table 1). The majority had an American Society of Anesthesiologists score of 2 (65%) and underwent neurosurgery due to a cerebral tumour (76%). The median blood loss was 300 ml, and 82% of patients required intraoperative phenylephrine on clinical indication (Table 2).

Fifteen of the seventeen patients underwent the oxygen intervention. The intervention was omitted in two patients due to circulatory instability and shortage of time, respectively. The PbtO2 baseline was unstable or exhibited non-physiological values in four patients; accordingly, sufficient data on PbtO2 during an FiO2 of 30% versus 80% was obtained in 11 patients.

The phenylephrine bolus was administered in 12 participants. In the remaining five patients, logistical (patient timing) or clinical considerations (bradycardia or surgeon’s advice) precluded phenylephrine administration. The dose was 0.1 mg in 11 patients and 0.2 mg in one patient. PbtO2 was obtained in six patients (Figure 1). The median MAP increase in these patients was 18 (5%–95% range 6–30) mmHg within 5 min after administration of phenylephrine.

3.1 | Primary outcome

PbtO2 was higher during FiO2 0.80 compared to FiO2 0.30 (median 68 [5%–95% range 8.4–99] mmHg versus 22 [4.6–54] mmHg; p = .004) (Table 4, Figure 2). In contrast, PbtO2 did not change significantly after phenylephrine administration (19 [4.2–56] mmHg) versus before the intervention (21 [4.5–81] mmHg; p = .56) (Table 3, Figure 2).

3.2 | Secondary outcome

ScO2 was 76 (51–86)% during FiO2 0.3 compared to 77 (53–90)% during FiO2 0.8 (p = .002) (Table 4). Correspondingly, ScO2 was 76 (64–88)% before versus 76 (63–89)% after phenylephrine administration (p = .44) (Table 3). Changes in PbtO2 and ScO2 for each case are illustrated in Figure 2. The temporal changes in PbtO2 and ScO2 during phenylephrine administration (from 1 min before and until 5 min after) is illustrated in Figures 3 and 4.

3.3 | Serious adverse events

Two patients (12%) experienced one SAE each during their hospital stay. One had postoperative homonymous hemianopsia and was
**Figure 2** PbtO₂ and ScO₂ during FiO₂ 0.30 versus 0.80 and before versus after phenylephrine. Line plots of (A) PbtO₂ (mmHg) before (n = 6) versus after (n = 6) phenylephrine and during FiO₂ 0.30 (n = 12) versus 0.80 (n = 11). (B) ScO₂ (%) before (n = 10) versus after (n = 9) phenylephrine and during FiO₂ 0.30 versus 0.80 (n = 15).

**Table 3** Study outcome: Before versus after phenylephrine

|                      | Before phenylephrine (n_PbtO₂ = 6, n_ScO₂ = 9) | After phenylephrine (n_PbtO₂ = 6, n_ScO₂ = 9) | p-Value |
|----------------------|-----------------------------------------------|------------------------------------------------|---------|
| PbtO₂                | 21 (4.5–81)                                   | 19 (4.2–56)                                    | .56     |
| ScO₂                 | 76 (64–88)                                    | 76 (63–89)                                     | .44     |

Note: Data on PbtO₂ (mmHg) and ScO₂ (%) are reported as median (5%–95% range).

**Figure 3** Median PbtO₂ 1 min before and 1–5 min after phenylephrine intervention. Median PbtO₂ (mmHg) (IQR) 1 min before (depicted by −1 min) and 1–5 min after phenylephrine intervention administered (at 0 min).
discharged on postoperative Day 7 without further complications. Another patient had visual disturbances and ophthalmoparesis postoperatively and died on postoperative Day 9 due to intracranial hemorrhage and respiratory insufficiency. None of these complications were related to the interventions of the present study.

4 | DISCUSSION

In this experimental clinical study, brain tissue oxygenation increased significantly during an increase in the inspired oxygen fraction, and this increase was seen both in the oxygen tension measured directly in brain tissue (PbtO₂) and in non-invasive cerebral oxygen saturation values measured on the skin of the forehead (ScO₂). However, a bolus dose of phenylephrine to increase in MAP of 18 mmHg did not alter cerebral oxygenation significantly.

A high FiO₂ is applied with the intent of enhancing oxygen supply to end-organs such as the brain through an increase in physically dissolved oxygen in the blood. Oxygen is carried in two forms in the blood: physically dissolved, and haemoglobin-bound. With increased PaO₂, the amount of physically dissolved oxygen can increase substantially. Supplemental oxygen is used to treat hypoxaemia, that is, low PaO₂, and there is a well-documented relation between FiO₂ and PaO₂. However, a high FiO₂ could, least in part, be counteracted by direct vasoconstrictive effects of oxygen. This has previously been investigated in healthy volunteers, where a decrease in CBF during breathing of 100% oxygen due to cerebral vasoconstriction has been demonstrated, and has also been confirmed in a magnetic resonance imaging study where CBF decreased by 27% in young healthy adults given 100% oxygen. Although we did not measure CBF, we speculate that the observed increase in cerebral oxygenation was due to an increase in the arterial partial pressure and total content of oxygen (PaO₂ and CaO₂), which would have more than compensated for the potential reduction in cerebral perfusion.

Although the influence of hyperoxia on cerebral haemodynamics is well described, other clinical effects of hyperoxia on the brain have not been fully clarified. A long-term follow-up study of 1386 patients who were randomised to receive an FiO₂ of 0.30 versus 0.80 during laparotomy found no significant difference in the occurrence of stroke or transitory cerebral ischaemia. While observational studies have reported an alarmingly higher short-term mortality after 24 h of treatment aimed at PaO₂ >26.7 kPa as compared to patients titrated to a PaO₂ between 13.3 and 26.7 kPa, a large systematic review of 50 randomised clinical trials including a total of 21,014 acutely ill patients found no significant difference in major clinical outcomes (including stroke) when comparing liberal versus conservative oxygen therapy.

In extracerebral organs, oxygen is considered to be a vasoconstrictor. An FiO₂ of 1.00 results in an approximately 5% decrease in cardiac index and a 10% increase in systemic vascular resistance in patients undergoing general anaesthesia. Additionally, an increase in coronary artery resistance of 40% and a coronary blood flow reduction of 30% have been reported in patients with coronary artery disease breathing 100% oxygen as compared to ambient air. Hyperoxic conditions may also generate reactive oxygen species, which in addition to their direct damaging effects can degrade the endogenous vasodilator nitric oxide, thereby reducing its bioavailability and potentially triggering vasoconstriction.

Phenylephrine bolus administration affected neither PbtO₂ nor ScO₂ in the present study. As part of the standard treatment regimen, most patients (82%) already had a continuous phenylephrine infusion during anaesthesia to maintain an adequate arterial pressure. Thus, it
is reasonable to assume that all patients had arterial pressures that were located above the lower limit of autoregulation, and the results may not be applicable for patients with blood pressures below the lower level. Phenylephrine is a selective alpha-1 adrenergic receptor agonist, thus acting as a sympathomimetic agent, with receptors present in both the peripheral and cerebral vasculature. The cerebral perfusion pressure is the gradient driving the CBF and is determined as difference between arterial and intracranial pressure. CBF is largely autoregulated within normal ranges of cerebral perfusion pressure. It is debated whether CBF, and thus brain oxygenation, benefits from phenylephrine in situations without arterial hypotension or intracranial pressure elevations. Although phenylephrine increases vascular resistance and thereby cerebral perfusion pressure, there is sparse documentation for its clinical benefits during elective neuroanaesthesia. Phenylephrine has been shown to increase the blood velocity of the middle cerebral artery, possibly due to cerebral arterial vasoconstriction, although blood flow in the internal carotid artery was unaltered. In a randomised trial in 24 brain tumour patients who received either phenylephrine or ephedrine and underwent positron emission tomography, changes in the cerebral metabolic rate of oxygen were similar between the two groups in both the peritumoural and normal contralateral region. Whereas both ephedrine and phenylephrine increased CBF and the so-called brain tissue oxygenation ratio in the peritumoural region, this increase was more pronounced after ephedrine; in the contralateral region, only ephedrine increased CBF and brain tissue oxygenation ratio. The effect of phenylephrine on cerebral oxygenation has previously been investigated under various experimental conditions. One study in 16 piglets found that a phenylephrine bolus and subsequent infusion increased PbtO2 by 10–18 mmHg, and they also reported a concurrent decrease in ScO2 (median decrease 7%–21%). These results are not in line with ours; however, the piglets received a much larger dose of phenylephrine compared to their weight (0.2 mg followed by an infusion of 5.0–13.5 µg/kg/min in 25–34 kg piglets). Most patients in our study received 0.1 mg phenylephrine, a dose which increased MAP by a modest 18 mmHg. Thus, besides the limited sample size, the absence of a change in the PbtO2 after phenylephrine in our study may be explained by the presence of effective pressure autoregulation, or by the comparatively low dose of phenylephrine.

Our study has several strengths, including the simultaneous measurement of cerebral oxygenation using two different techniques. ScO2 is continuous and non-invasive, while PbtO2 relies on an invasive technique and is gradually becoming the golden standard for brain oxygenation monitoring. Furthermore, we used ICM+ software for logged data recording, ensuring continuous, synchronised data on all variables. This study also comes with some limitations. First, due to the large size of the craniotomy needed to make the measurements during the procedure for the overall research project, the planned number of patients were not included within the timeframe of the study period; this reduced statistical power may have limited our ability to determine the effects of phenylephrine with certainty. The large craniotomy required may also have introduced a risk of selection bias among the included patients, as large craniotomies were needed for certain surgical approaches and for large tumours; our study findings may therefore not be generalisable to all neurosurgical procedures. Secondly, there were several challenges with the intracranial probe, resulting in data on only six patients for the primary analysis on phenylephrine. In some cases, placement of the intracranial probe in the field of surgery, without its introducer, resulted in unstable baseline values. It has previously been proposed that micro-haematomas are formed around the tip after insertion of the probe, and this may explain the reported calibration time of 1–3 h. As there is constant manipulation of the brain tissue in the surgical field, some probes may not have been able to calibrate correctly, and since our study was performed at the end of surgery, the measurements may have been affected by changes in brain tissue homeostasis that occurs in the post-surgical phase, including inflammation and other reactive changes. Additionally, bending of the Licox probe caused the signal to decrease to improbably low values (2 to 3 mmHg) in some patients; these values were considered erroneous and had to be excluded from the analyses.

In perspective, this study does not challenge the common use of high intraoperative FiO2 to secure cerebral oxygenation, as our data implied an increased oxygenation during a high FiO2. However, the intraoperative use of the Licox oxygen probe is problematic for short-term surgery, as a calibration period of up to 3 h is needed to ensure a stable baseline in some cases, and the probe requires little to no manipulation of surrounding tissue. Furthermore, based on the limited data from patients who received the phenylephrine intervention with complete PbtO2 measurements, no clinically relevant decline in oxygenation of brain tissue was detected, although this finding is based on a very small sample and must be interpreted with great caution. Clinical studies of neurological outcomes, such as stroke, covert stroke, or postoperative cognitive dysfunction related to the use of vasopressors will require large sample sizes to detect any difference in functional clinical outcomes. However, intraoperative hypotension is a more urgent clinical problem to address in patients at risk of adverse neurological or cardiac outcomes than the subtle differences that may exist between different vasopressor strategies.

5 | CONCLUSION

In patients undergoing intracranial surgery, an increase in inspired oxygen fraction was associated with increased cerebral oxygenation as measured invasively using a Clark-electrode as well as non-invasively using NIRS. A bolus dose of phenylephrine did not significantly alter cerebral oxygenation. The interpretation of the results warrants caution due to the small sample size and technical challenges regarding the intraoperative use of the Clark-electrode.

AUTHOR CONTRIBUTIONS

Sofie S. Pedersen: Protocol writing; data collection; data processing; manuscript writing. Christian S. Meyhoff: Protocol writing; data processing; manuscript writing. Markus Harboe Olsen: Protocol writing; data collection; data processing; manuscript writing. Zara R. Stisen: Data collection; manuscript writing. Anton Lund: Protocol writing; manuscript writing. Kirsten Møller: Protocol writing; manuscript writing. Jane Skjæth-Rasmussen: Protocol writing; data collection; manuscript writing. Finn B. Moltke: Protocol

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Sofie S. Pedersen: Reports indirect research funding from Boehringer Ingelheim outside the submitted work. Christian S. Meyhoff: Co-founder of a start-up company, WARD247 ApS, with the aim of pursuing the regulatory and commercial activities of the WARD-project (wireless assessment of vital signs). WARD247 ApS has finalised terms for licence agreement for any WARD-project software and patents. One patent has been filed: ‘Wireless Assessment of Respiratory and circulatory Distress (WARD)—Clinical Support System (CSS)—an automated clinical support system to improve patient safety and outcomes’. Christian S. Meyhoff also reports direct and indirect research funding from Merck Sharp & Dohme Corp., Radiometer and Boehringer Ingelheim, as well as lecture fees from Radiometer, all outside the submitted work. Markus Harboe Olsen: Unrestricted grant from Neurescue ApS outside the submitted work. Zara R. Stisen: None to be reported. Anton Lund: None to be reported. Kirsten Møller: None to be reported. Finn B. Moltke: None to be reported. Martin Kryspin Sørensen: None to be reported.

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