Cerebral oxygenation during prostaglandin E₁ induced hypotension

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Purpose: To evaluate the cerebral oxygenation effects of hypotension induced by prostaglandin E₁ (PGE₁) during fentanyl-oxygen anaesthesia.

Methods: Ten patients who underwent elective cardiac surgery received infusion of PGE₁. After measuring the baseline arterial, mixed venous and internal jugular vein blood gases, systemic haemodynamics, and regional cerebral oxygen saturation (rSO₂) estimated by INVOS 3100^R, PGE₁ was continuously infused at 0.25-0.65 µg·kg⁻¹·min⁻¹ (mean dosage: 410 ± 41.4 mg·kg⁻¹·min⁻¹) intravenously. Ten, 20 and 30 minutes after the start of drug infusions, blood gases described above were obtained simultaneously with the measurement of systemic haemodynamics and rSO₂. Thirty minutes from the start of drug infusions, administration of PGE₁ was stopped. The same parameters were measured again 10, 30 minutes after the stop of drug infusion.

Results: PGE₁ decreased mean arterial pressure (MAP) to approximately 70% of the baseline value ($P < 0.05$). PGE₁ increased mixed venous saturation, but in contrast did not effect internal jugular pressure, internal jugular oxygen saturation and rSO₂.

Conclusions: These results suggest that PGE₁ is a suitable drug for induced hypotension because flow/metabolism coupling of brain and regional cerebral oxygenation were well maintained during hypotension.

Objectif : Évaluer les effets de l'hypotension, induite par la prostaglandine E₁ (PGE₁), sur l'oxygénation cérébrale pendant l'anesthésie avec fentanyl et oxygène.

Méthodes : Dix patients qui devaient subir une chirurgie cardiaque élektive ont reçu une perfusion de PGE₁. Après avoir procédé à la gazométrie artérielle de base, à celle du sang veineux mêlé et à celle de la veine jugulaire interne, évalué l'hémodynamie systémique et la saturation en oxygène cérébral régional (SO_{2r}) par INVOS 3100R, la PGE₁ a été administrée en perfusion intraveineuse continue à 0,25-0,65 µg·kg⁻¹·min⁻¹ (dosage moyen : 410 ± 41,4 µg·min⁻¹). Dix, 20 et 30 minutes après le début des perfusions de médicaments, les gaz du sang déjà cités ont été obtenus simultanément avec la mesure de l'hémodynamie systémique et la SO_{2r}. Trente minutes après le début des perfusions, l'administration de la PGE₁ a été arrêtée. Les mêmes paramètres ont été mesurés encore après 10 et 30 minutes après l'arrêt de la perfusion de médicament.

Résultats : La PGE₁ abaisse la tension artérielle moyenne (TAM) à 70 % de sa valeur de base environ ($P < 0,05$). La PGE₁ augmente la saturation en oxygène du sang veineux mêlé mais, au contraire, n'a pas d'effet sur la tension de la veine jugulaire interne, sur la saturation en oxygène de cette veine et sur la SO_{2r}.

Conclusion : Ces résultats montrent que la PGE₁ est un médicament approprié pour induire de l'hypotension parce que le couplage débit/métabolisme du cerveau et l'oxygénation cérébrale régionale ont été maintenus pendant l'hypotension.

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INDUCED hypotension is sometimes used during surgery to reduce blood loss and to provide a relatively bloodless surgical field to facilitate surgery and decrease operation time.¹⁻⁴ Many drugs have been used to induce hypotension including nitroglycerin (NTG), trimethaphan, nicardipine and prostaglandin E₁ (PGE₁).² Since anaesthetists are concerned about the cerebral haemodynamics during induced hypotension, there have been many reports describing the effects of drugs such as NTG and trimethaphan on cerebral haemodynamics during induced hypotension.^{2,9} For PGE₁, several studies demonstrated that the drug acted mainly on arterial smooth muscle,^{7,8,10} and induced hypotension rapidly.^{1,4,5,6}

Near infrared spectroscopy (NIRS) is a non-invasive technique which enables continuous monitoring of alterations in regional cerebral oxygenation in animal and human studies.¹¹⁻¹³ Recently, NIRS has been used to detect cerebral hypoxia in patients undergoing carotid endarterectomy.¹⁴

In a previous report, we compared the effects of PGE₁ and NTG on regional cerebral oxygenation using a four-wave length NIRS.¹⁵ However, with that spectrophotometer we were unable to obtain a quantitative value for regional cerebral oxygenation (rSO₂).

Therefore in this study, we evaluated the effect of PGE₁ on cerebral haemodynamics with another device with NIRS which a quantitative value for rSO₂ could be obtained.

Patients and Methods

After obtaining the approval of the ethical committee of our institution and written informed consent, 10 consecutive patients who underwent elective cardiac surgery were studied (age: 64 ± 1.7 yr, height: 157.8 ± 2.2 cm, weight: 55.9 ± 2.4 kg, coronary artery bypass graft surgery four cases, aortic valve replacement three cases, mitral valve replacement three cases).

No patient had pulmonary, renal or hepatic disease. No patient had neuronal disease as shown by preoperative brain computed tomography and magnetic resonance imaging.

All patients received premedication with 10 mg diazepam *po* one hour before the induction of anaesthesia. Five electrodes were placed for electrocardiography (ECG) (Model HP 1166A, Hewlett Packard, Andover, MA, U.S.A.) and two peripheral veins were cannulated in the operating room with 18-gauge indwelling catheters. The left radial artery was cannulated with a 22-gauge indwelling catheter to monitor arterial blood pressure. Anaesthesia was induced with 30 $\mu\text{g} \cdot \text{kg}^{-1}$ fentanyl and 0.2 $\text{mg} \cdot \text{kg}^{-1}$ midazolam *iv* and tracheal intubation was facilitated by 0.2 $\text{mg} \cdot \text{kg}^{-1}$ vecuronium. After induction of anaesthesia, a pul-

monary arterial catheter (Vigilance®, Swan-Ganz CCO Thermolulution Catheter, Baxter, Co. U.S.A.) was inserted via the right internal jugular vein. In order to monitor jugular oxygen saturation (SjvO₂), a 4.0 French fiber-optic oximetry oxygen saturation catheter (Dural-lumen oximetry catheter®, Baxter, Co. U.S.A.) was inserted retrograde into the jugular bulb.¹⁶ This catheter was connected to Explorer™ system (Baxter, Co. U.S.A.) and was calibrated *in vivo* by drawing a blood sample from the catheter. The position of the jugular bulb catheter was verified by X-ray.

The partial pressures of the arterial, mixed venous and jugular venous blood gases were analyzed using Stat Profile Ultmita® (NOVA biomedical Co. U.S.A.). In all patients, the lungs were ventilated with oxygen 100% and the end-tidal CO₂ was monitored (Ultima®, Datex, Helsinki) and maintained between 35-40 mmHg. Electroencephalograph (EEG: Neuropack eight; Nihon Koden Co. Ltd., Tokyo, Japan) was utilized to assess neuronal activity (according to the International Ten-Twenty Electrode System, electrodes were attached at A1, A2, Fp1 and Fp2 position) during the study.

Rectal and nasopharyngeal temperatures were monitored continuously (Hewlett Packard, Andover, MA, U.S.A.). Tympanic membrane temperature was also monitored by Mon-a-Therm® (Mallinckrodt Co, St. Louis, MO).

The spectrophotometer probe (INVOS 3100; Somanetics, Troy, MI; distances between the light source and the two receivers were 3 cm and 4 cm) was attached to the mid-forehead with adhesive and a rubber strap, and regional cerebral oxygen saturation (rSO₂) was recorded throughout the procedure.¹⁷

Study protocol

The study was carried out after the induction of anaesthesia and before the start of surgery. Lactated Ringer's solution was infused at a rate of 5 $\text{ml} \cdot \text{kg}^{-1} \cdot \text{hour}^{-1}$.

After the induction of anaesthesia, baseline value was defined as the time when mean arterial pressure (MAP) was approximately equal to the pre-anaesthetic value for five minutes.

After measuring baseline partial pressures of the arterial, mixed venous and jugular venous blood gases, systemic haemodynamics and rSO₂, PGE₁ was infused at 0.25-0.65 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (mean dosage was 410 ± 41.4 $\text{mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) until MAP decreased to approximately 70% of the baseline value.^{1,4,18} Ten, 20 and 30 min after the start of drug infusions, the partial pressures of the arterial, mixed venous and jugular venous blood gases were obtained simultaneously, and the systemic haemodynamics values were also obtained. The

rSO₂ value was monitored continuously. Thirty minutes after the start of drug infusions, drug administration was stopped. Ten and 30 min after the stop of drug infusions, the same variables were measured as during the drug infusion.

Data analysis

All data are expressed as means $\pm$ SEM. Changes in mean values were compared with the baseline values using repeated measures analysis of variance. Statistical significance was set at $P < 0.05$.

Results

During induced hypotension, no changes were observed in EEG (data not shown).

Administration of PGE₁ decreased mean arterial pressure (MAP) to approximately 70% of the baseline value ($P < 0.05$). Ten minutes after discontinuation of PGE₁ infusion, MAP returned to the baseline value. PaO₂ was decreased after the PGE₁ infusion compared with the baseline value ($P < 0.05$), and the decrease in PaO₂ lasted after discontinuation of PGE₁ infusion ($P < 0.05$). Cardiac index was increased at 20 and 30 min after the PGE₁ infusion compared with baseline ($P < 0.05$), and the increase lasted after discontinuation of

PGE₁ infusion ($P < 0.05$). The heart rate, mixed venous oxygen saturation (SvO₂) and the partial pressure oxygen of mixed vein (PvO₂) were increased after the PGE₁ infusion compared with baseline ($P < 0.05$), and lasted after the discontinuation of PGE₁ infusion ($P < 0.05$). There were no differences between pre-and post-infusion values of central venous pressure, internal jugular venous pressure, plasma glucose, haemoglobin, PaCO₂, regional cerebral oxygenation (rSO₂), jugular oxygen saturation (SjvO₂) or the partial pressure of oxygen (PjvO₂). Arterio-mixed venous and arterio-jugular venous differences of lactate levels were maintained at the baseline value throughout the drug infusion. There were no differences in rectal, oesophageal or tympanic membrane temperatures.

Discussion

Our study demonstrated that PGE₁ was a useful drug for induced hypotension because SjvO₂ and rSO₂ values were well maintained during hypotension. PGE₁ did not increase internal jugular vein pressure (IJP). Since IJP has been reported to reflect intracranial pressure (ICP),² PGE₁ may not have a major effect on ICP in man. Even though Nakano *et al.*⁷ and Maruno *et al.*⁵ reported that PGE₁ increased ICP in dogs, the

TABLE Physiological variables

	Before infusion (baseline)	10 min	during infusion of PGE ₁ 20 min	30 min	discontinuation of PGE ₁ infusion 10 min	30 min
MAP(mmHg)	98.8 $\pm$ 3.7	72.4 $\pm$ 3.4*	68.7 $\pm$ 3.1*	66.5 $\pm$ 2.9*	93.4 $\pm$ 4.0	101.2 $\pm$ 3.2
H.R(beat·min ⁻¹)	62 $\pm$ 4.7	73 $\pm$ 3.3*	79 $\pm$ 3.8*	85 $\pm$ 3.0*	84 $\pm$ 2.7*	81 $\pm$ 2.5*
CI(L·min ⁻¹ ·M ⁻²)	2.4 $\pm$ 0.2	2.5 $\pm$ 0.2	2.8 $\pm$ 0.2*	3.0 $\pm$ 0.2*	3.1 $\pm$ 0.2*	3.1 $\pm$ 0.2*
CVP(mmHg)	7.0 $\pm$ 1.0	6.9 $\pm$ 0.8	7.1 $\pm$ 0.9	6.9 $\pm$ 0.7	7.4 $\pm$ 0.9	7.0 $\pm$ 0.8
IJP(mmHg)	9.7 $\pm$ 1.0	9.5 $\pm$ 1.0	9.6 $\pm$ 1.0	10.0 $\pm$ 0.8	10.7 $\pm$ 1.2	10.1 $\pm$ 0.9
PaO ₂ (kPa)	70.6 $\pm$ 2.1	65.9 $\pm$ 3.9*	62.8 $\pm$ 4.1*	62.9 $\pm$ 3.6*	65.9 $\pm$ 3.6*	65.3 $\pm$ 3.6*
PaCO ₂ (kPa)	5.1 $\pm$ 0.2	4.9 $\pm$ 0.2	5.1 $\pm$ 0.2	5.1 $\pm$ 0.2	5.2 $\pm$ 0.2	5.2 $\pm$ 0.2
Hb(mg·dl ⁻¹)	12.4 $\pm$ 0.4	12.4 $\pm$ 0.4	12.3 $\pm$ 0.3	12.2 $\pm$ 0.3	12.1 $\pm$ 0.4	12.4 $\pm$ 0.4
PjvO ₂ (kPa)	4.8 $\pm$ 0.3	5.1 $\pm$ 0.4	5.3 $\pm$ 0.3	5.5 $\pm$ 0.5	5.5 $\pm$ 0.5	5.6 $\pm$ 0.3
SjvO ₂ (%)	62.5 $\pm$ 3.8	63.9 $\pm$ 4.0	69.1 $\pm$ 3.0	68.8 $\pm$ 4.1	70.9 $\pm$ 3.8	71.9 $\pm$ 3.9
PvO ₂ (kPa)	6.5 $\pm$ 0.3	8.4 $\pm$ 0.4*	9.3 $\pm$ 0.6*	9.1 $\pm$ 0.4*	8.8 $\pm$ 0.4*	8.7 $\pm$ 0.5*
SvO ₂ (%)	82.6 $\pm$ 1.6	90.3 $\pm$ 0.9*	92.4 $\pm$ 1.6*	92.1 $\pm$ 0.7*	91.1 $\pm$ 1.0*	90.3 $\pm$ 1.5 *
Plasma glucose (mg·L ⁻¹)	110 $\pm$ 14.3	112 $\pm$ 14.0	111 $\pm$ 10.6	122 $\pm$ 13.1	126 $\pm$ 12.6	122 $\pm$ 10.7
ET(°C)	36.1 $\pm$ 0.1	36.0 $\pm$ 0.1	35.9 $\pm$ 0.1	35.8 $\pm$ 0.2	35.8 $\pm$ 0.2	35.8 $\pm$ 0.3
RT(°C)	36.4 $\pm$ 0.2	36.4 $\pm$ 0.2	36.2 $\pm$ 0.3	36.0 $\pm$ 0.2	36.0 $\pm$ 0.2	36.0 $\pm$ 0.2
TT(°C)	36.0 $\pm$ 0.2	36.0 $\pm$ 0.2	35.8 $\pm$ 0.2	35.8 $\pm$ 0.2	35.8 $\pm$ 0.2	35.8 $\pm$ 0.3
plasma lactate						
AJ diff.(mmol·L ⁻¹)	-0.07 $\pm$ 0.06	-0.08 $\pm$ 0.05	-0.12 $\pm$ 0.06	-0.17 $\pm$ 0.11	-0.07 $\pm$ 0.06	-0.07 $\pm$ 0.06
AV diff.(mmol·L ⁻¹)	-0.09 $\pm$ 0.08	-0.09 $\pm$ 0.06	-0.14 $\pm$ 0.07	-0.15 $\pm$ 0.10	-0.10 $\pm$ 0.09	-0.11 $\pm$ 0.09
rSO ₂ (%)	67.7 $\pm$ 1.5	69.3 $\pm$ 1.9	69.3 $\pm$ 1.9	69.6 $\pm$ 1.3	70.6 $\pm$ 1.7	70.7 $\pm$ 1.8

mean $\pm$ S.E.M.

* $P < 0.05$ compared to control value

MAP: mean arterial pressure, HR: heart rate, C.I: cardiac index, CVP: central venous pressure, IJP: internal jugular venous pressure, Hb: hemoglobin, PjvO₂: the partial pressure of jugular venous blood gas, SjvO₂: jugular venous oxygen saturation, PvO₂: the partial pressure of mixed venous blood gas, SvO₂: mixed venous oxygen saturation, ET: esophageal temperature, RT: rectal temperature, TT: tympanic membrane temperature, AV diff.: arteriovenous differences in lactate level, AJ (diff.: arterio-jugular differences in lactate concentration, rSO₂: regional cerebral oxygenation estimated by INVOS 3100^R

discrepancy between our results and theirs may be explained by the differences in study protocol, such as experimental animal species, infusion doses of PGE₁ and anaesthetic management.

There is some controversy concerning the effect of PGE₁ on CBF during induced hypotension.⁴⁻⁷ Olesen reported that PGE₁ increased CBF 11.2% of control value in awake humans.¹⁰ In contrast, Yamamoto *et al.* reported that PGE₁ decreased CBF in dogs.¹⁹ However recent studies by Kitaguchi *et al.* and Sha *et al.* claimed that PGE₁ did not increase CBF in anaesthetized humans.^{4,6} Even though we did not measure cerebral blood flow in this study, the lack of alteration in S_{ijv}O₂, rSO₂ and EEG suggested that PGE₁ did not provoke major alteration in blood flow and metabolism in brain during the induced hypotension.

In this study we assessed regional cerebral oxygenation by NIRS. Recently, NIRS has become a tool as a non-invasive real-time, on-line monitor for the determination of the cerebral oxygenation state in animals or humans.^{11,12,17} Although many studies using NIRS evaluated its reliability as a detector of intracranial phenomena,^{13,15,20,21} there is controversy concerning the influence of extracranial factors, such as facial muscle movements.²² Increasing the distance between photoprobes is thought to reduce the interference of extracranial factors.²³ Kirkpatrick *et al.* reported that interruption of extracranial blood flow by clamping the external carotid artery had no effect on NIRS measurement.¹⁴ In our study, we utilized the new probe which had a long emitter-detector distance, and facial muscle activities were completely blocked by muscle relaxant. Therefore, the influence of extracranial factors were considered to be minimal in our study.

There is also controversy concerning the technical factors with NIRS.²⁴ Recently, Pollard *et al.*²⁵ suggested that NIRS monitors should be considered as trend monitors for intracranial phenomena. Therefore, we did not attempt to estimate cerebral blood flow and cerebral blood volume as described by Owen-Reece.²⁶

Our previous report showed that PGE₁ increased regional cerebral oxygenation state, but in this study PGE₁ it did not. This discrepancy might be attributed to the different algorithms of the equipment. Matcher *et al.* found differences between the results from the different algorithms.²⁷ Another reason is that the sensitivity of the monitor might not be sufficient to detect minor changes in tissue oxygenation, and that the absolute value of rSO₂ indicated by the machine may be disturbed.²⁸ Thus, even though we could not detect any cerebral action of PGE₁ in this study, further investigation with a high-sensitivity NIRS device may detect some effect of PGE₁ on local cerebral perfusion.

In this study we observed that PGE₁ did not change rSO₂ or S_{ijv}O₂, but SvO₂. McDaniel *et al.* reported that the brain was an organ which made only a minor contribution to the SvO₂.²⁹ Also, Croughwell *et al.* reported that there was a poor correlation between SvO₂ and S_{ijv}O₂ during cardiac surgery.³⁰ Considering these previous reports, the discrepancy between S_{ijv}O₂ and SvO₂ is not contradictory. Probably, PGE₁ has differential effects on S_{ijv}O₂ and SvO₂.

In conclusion, PGE₁ was found to be a suitable drug for induced hypotension because flow/metabolism coupling of brain and regional cerebral oxygenation were well maintained during hypotension.

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