Original Article

Near-Infrared Spectrophotometry Is Useful to Detect the Beneficial Pharmacological Effects of Alprostadil on Spinal Cord Deoxygenation

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Purpose: The purpose of this study is to confirm our previous studies that near-infrared spectrophotometry (NIRS) can detect spinal cord ischemia earlier than evoked spinal cord potential (ESP), and to determine whether it can detect the pharmacological effect of prostaglandin E1 (PGE1) incorporated in lipid microspheres (alprostadil) on the spinal cord.
Materials and Methods: NIRS probes were placed on the posterior side of the lower lumbar vertebrae, and oxygenated hemoglobin (oxy-Hb) of the spinal cord was monitored continuously in 14 male New Zealand white rabbits. The amplitude of ESP was recorded every minute. All rabbits underwent a normothermic infrarenal aortic cross-clamping (AXC) for 20 min, and all were pretreated with either an intravenous 3 μg/kg/10 min alprostadil (group A; n = 4) or the same volume saline (group C; n = 10).
Results: ESP amplitude started to show a linear decrease 6 min after the onset of AXC and was comparable between groups (*P* = .839). Oxy-Hb decreased rapidly just after the onset of AXC, followed by monoexponential decline. It reached a plateau at 10 min after the onset of AXC. Oxy-Hb of group A was significantly higher than that of group C (*P* = .014).
Conclusions: NIRS can detect spinal cord ischemia earlier than ESP. It can detect the beneficial pharmacological effect of alprostadil on the spinal cord. (Ann Thorac Cardiovasc Surg 2008; 14: 376–381)

Key words: spinal cord ischemia, near-infrared spectrophotometry, evoked spinal cord potential, prostaglandin E1, alprostadil

Introduction

Spinal cord ischemia can be caused by various reasons: aortic cross-clamping (AXC) during thoracoabdominal aortic repair, spinal canal stenosis, trauma, tumor, and others. Increasing collateral blood flow to the jeopardized spinal cord seems to be a common beneficial therapeutic option to attenuate spinal cord ischemia. Prostaglandin E1 (PGE1) has emerged as one of the promising compounds that serve this purpose.[1)] To avoid PGE1-induced hypotension in clinical use, alprostadil (Palux™, Taisho Pharmaceutical Co., Ltd., Tokyo, Japan), which is PGE1 incorporated in lipid microspheres to minimize metabolization and inactivation in the lung,[2,3)] is also expected to have a beneficial effect on ischemic spinal cord injury. However, pathophysiology of the spinal cord during administration of alprostadil has not been fully understood.

To date, electrophysiological examinations have been used worldwide to identify spinal cord ischemia.[1,4–7)] However, although rare, complications related to epidural catheter are catastrophic. A less-invasive form of

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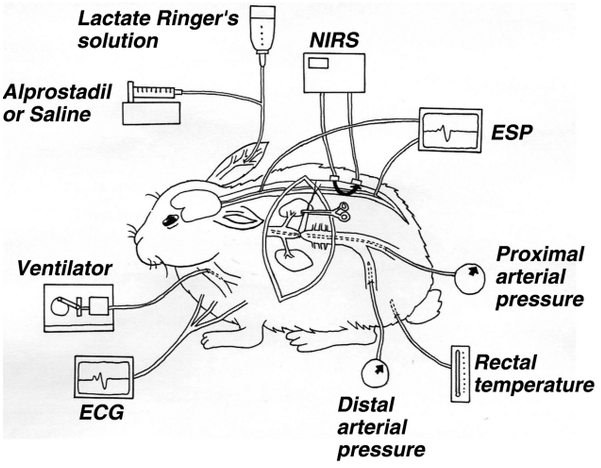

Fig. 1. A schematic diagram of a New Zealand white rabbit, typical of those used in this experiment.
NIRS, near-infrared spectrophotometry; ESP, evoked spinal cord potential; ECG, electrocardiogram.

monitoring, such as scalp-recorded somatosensory-evoked potential or peripherally recorded motor-evoked potential induced either magnetically or electronically, is affected by anesthetic techniques or electronic artifact.[6,7] Noninvasive and reliable monitoring of spinal cord ischemia may be ideal, but it has not been available. It has been reported that near-infrared spectrophotometry (NIRS) could detect spinal cord oxygenation/metabolism either directly, transcutaneously, or transesophageally.[8–11] Furthermore, we have demonstrated that NIRS could detect spinal cord ischemia more immediately than evoked spinal cord potential (ESP).[9,11] However, reproducibility of these approaches to evaluate pharmacological effects has not been tested.

The purpose of this study is to confirm the reproducibility of NIRS to detect spinal cord ischemia more immediately than ESP. Another purpose is to evaluate whether NIRS can detect the pharmacological effect of alprostadil on the spinal cord in rabbit.

Materials and Methods

Experimental model

All experiments are approved by the Hokkaido University School of Medicine Animal Care and Use Committee, and conform to the U.S. National Institutes of Health guidelines regulating the care and use of laboratory animals. A schematic diagram of a typical experimental animal in this study is shown in Fig. 1. Fourteen male New Zealand white rabbits (3.5 ± 0.1 kg) were premedicated (subcutaneous 0.005 mg/kg atropine sulfate and 40 mg/kg ketamine hydrochloride), anesthetized (intravenous 2 mg/kg sodium pentobarbital), and paralyzed (intravenous 2 mg/kg suxamethonium chloride and maintained by intravenous 0.05 mg/kg pancuronium bromide). An endotracheal tube was introduced through a tracheostomy, and the animals were ventilated (38˚C, 0.5–1 L/min humidified oxygen, a respiratory rate of 30/min, the tidal volume of 10 ml/kg, and a positive end-expiratory pressure of 2.5 cm H_2O, Harvard Rodent Ventilator; Harvard Apparatus, Natick, MA). Adequacy of ventilation was confirmed by blood gas analysis at 37˚C. Lactate Ringer's solution (10 ml/kg/h) was continuously infused throughout the experiment. After heparinization (100 IU/kg), all rabbits underwent an infrarenal AXC through left retroperitoneal approach for 20 min, and all were pretreated with either an intravenous 3 μg/kg/10 min alprostadil (group A; n = 4) or the same volume saline (group C; n = 10) before AXC. Mean arterial pressure (MAP), both proximal and distal to AXC, heart rate, and rectal temperature, were continuously monitored and recorded throughout the operation. Rectal temperature was kept above 38˚C by a body temperature controlling system for rodent animals (Asahi Plate Warmer TK-43, Asahi Denshi Inc., Osaka, Japan).

NIRS and ESP monitoring

NIRS probes (OM-100A™, Shimadzu Corp., Kyoto, Japan) were placed on the posterior side of the lower lumbar vertebrae after the spinous process was removed. A photodetector and a light source were positioned longitudinally 20 mm apart to detect signals mostly originating in 10 mm depth from probes. We confirmed by preliminary anatomical study that the spinal cord was located within 10 mm from NIRS probes. Oxygenated hemoglobin (oxy-Hb) of the spinal cord was monitored continuously using three wavelengths of light (780, 805, and 830 nm). The data are expressed as percent change of the value at 20 min after the onset of AXC (plateau level). ESP catheters were inserted into the upper thoracic and lower lumbar epidural spaces, and ESPs were recorded every minute (MS-91™, Medelec Ltd, Surrey, England). The amplitudes of ESPs are expressed as percent change from the baseline value.

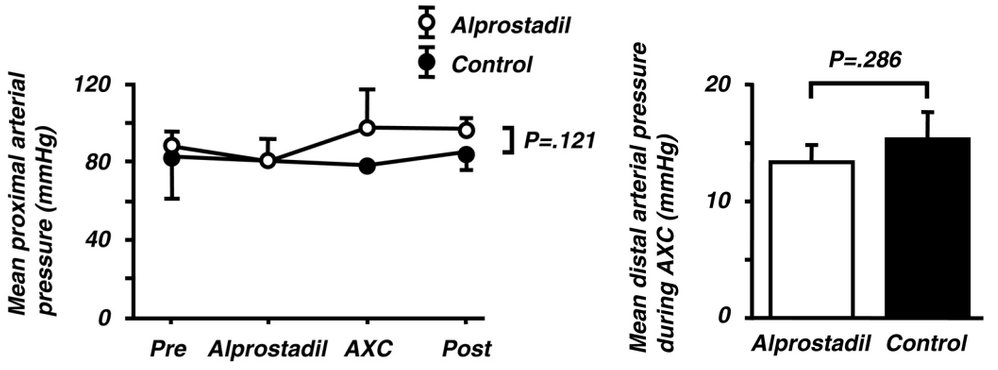

Fig. 2.
A: Time course of mean proximal arterial pressure. AXC, aortic cross-clamping.
B: Mean distal arterial pressure during aortic cross-clamping (AXC).

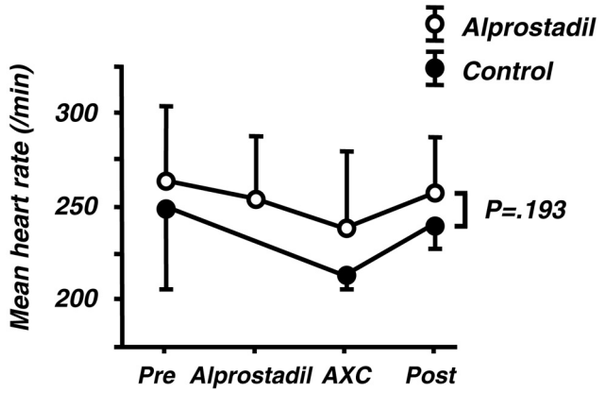

Fig. 3. Time course of mean heart rate. AXC, aortic cross-clamping.

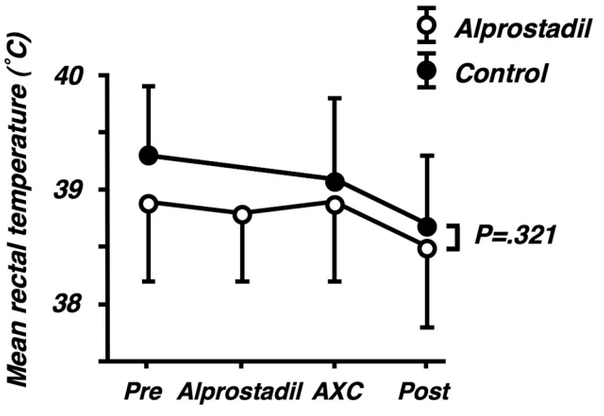

Fig. 4. Time course of mean rectal temperature. AXC, aortic cross-clamping.

Statistical analysis

All values are expressed as mean ± standard deviation. Statistical analysis was performed using StatView™ 5.0 (SAS Institute Inc., Cary, NC), except for repeated measures analysis of variance (ANOVA) using Greenhouse-Geisser's test to compare the intragroup differences of ESP or NIRS performed using SPSS version 14. Student's *t*-test was used for a comparison of the continuous variables. A *P* value of less than .05 was considered statistically significant.

Results

MAP was comparable between groups throughout the study. During AXC, mean proximal arterial pressure was higher ($P = .121$), and the distal one was lower ($P = .286$) in group A than in group C, though the differences were not significant (Fig. 2). Mean heart rate was minimum during AXC in both groups and higher in group A throughout the operation, but this difference had no statistical power ($P = .193$) (Fig. 3). Mean rectal temperature decreased gradually as the procedure progressed and was slightly lower in group A without statistical significance ($P = .321$) (Fig. 4).

In both groups, ESP amplitude started to show a linear decrease 6 min after the onset of AXC. There was no significant difference in ESP change between groups ($P = .839$) (Fig. 5). In contrast, oxy-Hb decreased rapidly just after the onset of AXC, followed by monoexponential decline during AXC. It reached plateau phase about 10 min after the onset of AXC. Oxy-Hb of group

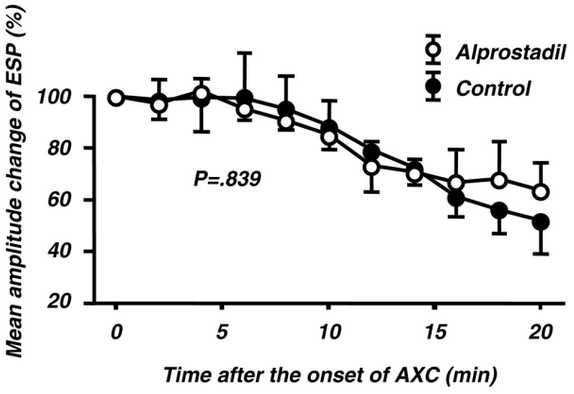

Fig. 5. Time course of mean amplitude change from baseline of evoked spinal cord potential (ESP).
AXC, aortic cross-clamping.

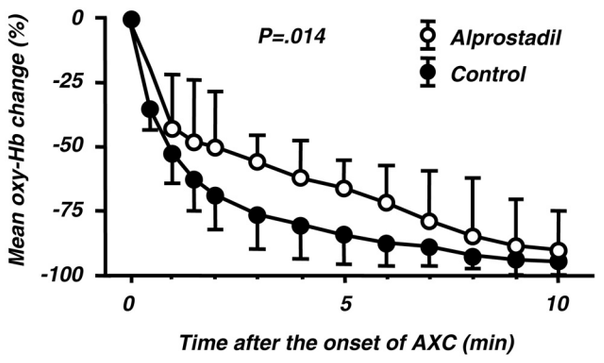

Fig. 6. Time course of mean percent change of oxygenated hemoglobin (oxy-Hb) in the spinal cord.
AXC, aortic cross-clamping.

A was significantly higher than that of group C during AXC (P = .014) (Fig. 6).

Discussion

One of the major findings in the current study, that NIRS could detect spinal cord ischemia earlier than ESP, is consistent with our previous reports using direct or transesophageal NIRS monitoring of the spinal cord.[9,11] Although the data in this article are very preliminary because of the small numbers, NIRS monitoring of spinal cord ischemia seems reproducible and reliable. Furthermore, NIRS could detect the beneficial pharmacological effect of PGE1 on spinal cord oxygenation.

NIRS, a novel optical modality, cannot reflect spinal cord function itself, but it can provide prompt information about spinal cord oxygenation/metabolism.[8–11] Traditionally, we have measured ESP to identify spinal cord ischemia during thoracoabdominal aortic surgery.[4,5] For measuring ESP, two epidural catheters should be inserted in the upper and lower thoracic vertebral level one day before surgery, which seems not only invasive, but also inherent with catheter-induced catastrophic complications. Less-invasive forms of monitoring such as somatosensory-evoked potential or motor-evoked potential are affected by various factors: anesthetic techniques, temperature, ischemia of the extremities, and electronic artifacts.[6,7] Furthermore, it takes several minutes to detect spinal cord dysfunction with electrophysiological techniques.[6,7] NIRS signals are independent on these factors. The current setting of NIRS monitoring is invasive, but transesophageal form seems noninvasive and feasible for clinical use, as we have already reported.[11] The only drawback is optical artifact that may be caused by extensive dissection between the esophagus and the aorta, which seems infrequent except in the AXC sites.

Today, PGE1 has been widely used to enhance tissue blood flow in various fields. The underlying mechanisms are believed to be dilating resistance vessels, antiplatelet effect, and inhibition of peripheral sympathetic nerves.[12,13] Moreover, PGE1 has a neuroprotective effect by scavenging free radicals[14,15] or inhibiting neuronal apoptosis.[16] One of the drawbacks in the clinical application of PGE1 may be PGE1-induced systemic hypotension that may have a potential risk to decrease spinal cord blood flow altogether. However, it has been demonstrated that the autoregulation of spinal cord blood flow is maintained during PGE1-induced hypotension.[12,17] Indeed, Grabitz and his colleagues reported that PGE1 could delay the time until the loss of ESP signals in patients who underwent thoracoabdominal aortic repair[1] or that it could mimimize the duration of loss of ESP signals in dog;[18] thus they concluded that PGE1 could protect the jeopardized spinal cord. Another drawback may be that 60%–95% of PGE1 is metabolized and inactivated in a single pulmonary circulation, which necessitates large amounts of intravenous administration.[2,19] Lipo-PGE1 (alprostadil), incorporated in 0.2 μm microparticles made of soybean oil, is developed in Japan to minimize metabolization and inactivation in the lung.[2,3] Growing evidence suggests that alprostadil has beneficial effects in the

treatment of peripheral arterial disease and spinal canal stenosis, especially in Japan.[2,3,20] However, little work has been made to evaluate spinal cord oxygenation/metabolism quantitatively during intravenous injection of alprostadil. This may be the first report to disclose pathophysiology of the spinal cord during the intravenous administration of alprostadil assessed by NIRS monitoring.

Study limitations

First, the number of animals included in the study is rather limited, which weakens the significance of the results. Either experimental or clinical prospective randomized trial in a larger cohort will be necessary to confirm our results. Second, the lack of postoperative neurological and histological outcome prevents us from confirming the accuracy of our results. However, our experimental setting was so invasive that almost all rabbits could not survive the operation or seemed moribund, thus preventing us from judging spinal cord function appropriately. Moreover, normothermic infrarenal AXC for 20 min in rabbit is well known to cause spinal cord injury most of the time.[21] Therefore we judged that comparing histological findings in this experimental setting would have little value, so we designed this study to validate intraoperative data alone. It would be interesting to modify our experimental setting to AXC for 12–15 min and verify histological findings. Third, mean proximal arterial pressure and heart rate during AXC were slightly higher and mean rectal temperature was slightly lower in group A, though they were not significant. These factors could be advantageous for spinal cord ischemia in this group. Nevertheless, the differences seemed trivial, so we judged that the contribution of these variables to our results might be minimum.

Conclusions

In the current preliminary experiment, we confirm the reproducibility of NIRS to detect spinal cord ischemia more immediately than ESP. We also confirm that NIRS monitoring can provide immediate information of delayed deoxygenation of the spinal cord caused by PGE1. Although conceptually promising, validation of the beneficial effects of PGE1 on spinal cord ischemia requires further studies in a larger cohort. Furthermore, the technical advance of NIRS monitoring toward clinical use to confirm this effect seems mandatory. We hope our paper will stimulate further study and technical advance in this field.

References

1. Grabitz K, Freye E, Stühmeier K, Sandmann W. Spinal evoked potential in patients undergoing thoracoabdominal aortic reconstruction: a prognostic indicator of postoperative motor deficit. *J Clin Monit* 1993; **9**: 186–90.
2. Yone K, Sakou T, Kawauchi Y. The effect of Lipo prostaglandin E1 on cauda equina blood flow in patients with lumbar spinal canal stenosis: myeloscopic observation. *Spinal Cord* 1999; **37**: 269–74.
3. Mizushima Y, Yanagawa A, Hoshi K. Prostaglandin E1 is more effective, when incorporated in lipid microspheres, for treatment of peripheral vascular diseases in man. *J Pharm Pharmacol* 1983; **35**: 666–7.
4. Matsui Y, Goh K, Shiiya N, Murashita T, Miyama M, et al. Clinical application of evoked spinal cord potentials elicited by direct stimulation of the cord during temporary occlusion of the thoracic aorta. *J Thorac Cardiovasc Surg* 1994; **107**: 1519–27.
5. Shiiya N, Yasuda K, Matsui Y, Sakuma M, Sasaki S. Spinal cord protection during thoracoabdominal aortic aneurysm repair: results of selective reconstruction of the critical segmental arteries guided by evoked spinal cord potential monitoring. *J Vasc Surg* 1995; **21**: 970–5.
6. Griepp RB, Ergin MA, Galla JD, Lansman S, Khan N, et al. Looking for the artery of Adamkiewicz: a quest to minimize paraplegia after operations for aneurysms of the descending thoracic and thoracoabdominal aorta. *J Thorac Cardiovasc Surg* 1996; **112**: 1202–15.
7. Meylaerts SA, Jacobs MJ, van Iterson V, De Haan P, Kalkman CJ. Comparison of transcranial motor evoked potentials and somatosensory evoked potentials during thoracoabdominal aortic aneurysm repair. *Ann Surg* 1999; **230**: 742–9.
8. Yamada S, Sanders DC, Maeda G. Oxidative metabolism during and following ischemia of cat spinal cord. *Neurol Res* 1981; **3**: 1–16.
9. Kunihara T, Miyatake T, Kubota T, Suto Y, Shiiya N, et al. An evaluation of spinal cord ischemia of rabbit by near-infrared spectrophotometry. *Ther Res* 1998; **19**: 2155–60.
10. LeMaire SA, Ündar A, Junkerman J, Schmittling ZC, Wolinsky JP, et al. Use of near-infrared spectroscopy to monitor spinal cord oxygenation during intercostal artery ligation: preliminary experimental results. *Ann Thorac Surg* 2002; **73**: S375.
11. Kunihara T, Shiiya N, Matsui Y, Yasuda K. Preliminary report of transesophageal monitoring of spinal cord ischemia using near-infrared spectrophotometry. *J Cardiovasc Surg (Torino)* 2004; **45**: 95–6.
12. Tsuji T, Matsuyama Y, Sato K, Iwata H. Evaluation of spinal cord blood flow during prostaglandin

E1-induced hypotension with power Doppler ultrasonography. *Spinal Cord* 2001; **39**: 31–6.
13. Hadhádzy P, Vizi EX, Magyar K, Knoll J. Inhibition of adrenergic neurotransmission by prostaglandin E1 (PGE1) in the rabbit ear artery. *Neuropharmacology* 1976; **15**: 245–50.
14. Topsakal C, Kilic N, Ozveren F, Akdemir I, Kaplan M, et al. Effects of prostaglandin E1, melatonin, and oxytetracycline on lipid peroxidation, antioxidant defense system, paraoxonase (PON1) activities, and homocysteine levels in an animal model of spinal cord injury. *Spine* 2003; **28**: 1643–52.
15. Ohnishi ST, Sakamoto A, Ohnishi T, Ogawa R. Inhibition of lipid peroxidation by prostaglandin oligomeric derivatives. *Prostaglandins Leukot Essent Fatty Acids* 1992; **45**: 217–21.
16. Kawamura T, Akira T, Watanabe M, Kagitani Y. Prostaglandin E1 prevents apoptotic cell death in superficial dorsal horn of rat spinal cord. *Neuropharmacology* 1997; **36**: 1023–30.
17. Ide R, Fukusaki M, Yamaguchi K, Matsumoto M, Ogata K, et al. Effect of controlled hypotension induced by prostaglandin E1 on evoked spinal cord potential and spinal cord blood flow. *Masui* 1997; **46**: 1342–6. (in Jpse.)
18. Grabitz K, Freye E, Prior R, Schrör K, Sandmann W. Does prostaglandin E1 and superoxide dismutase prevent ischaemic spinal cord injury after thoracic aortic cross-clamping? *Eur J Vasc Surg* 1990; **4**: 19–24.
19. Hammond GL, Cronau LH, Whittaker D, Gillis CN. Fate of prostaglandins E(1) and A(1) in the human pulmonary circulation. *Surgery* 1977; **81**: 716–22.
20. Iwamoto J, Takeda T, Ichimura S. Effect of administration of lipoprostaglandin E(1) on physical activity and bone resorption in patients with neurogenic intermittent claudication. *J Orthop Sci* 2001; **6**: 242–7.
21. Perdrizet GA, Lena CJ, Shapiro DS, Rewinski MJ. Preoperative stress conditioning prevents paralysis after experimental aortic surgery: increased heat shock protein content is associated with ischemic tolerance of the spinal cord. *J Thorac Cardiovascular Surg* 2002; **124**: 162–70.