and averaged TOF ratios significantly decreased to 0.72 (0.13) ($P < 0.004$) and 0.66 (0.16) ($P < 0.006$), at 2 and 3 min, respectively, after precurarization (Table 2). No visible muscle movement (scale 0) was observed following suxamethonium injection, except in 1 patient who had received 0.03 mg/kg rocuronium and showed very fine muscle movements of the fingertips (scale 1). There was a statistically significant difference in the onset times of suxamethonium-induced neuromuscular block between the 0.03 mg/kg group [79.5 (12.3) s, $P = 0.032$] and the 0.06 mg/kg group [93.9 (14.5) s].

Discussion

The present study could identify that a safe precurarizing dose of rocuronium for surgical patients was 0.03 mg/kg. The dose of about 0.06 mg/kg rocuronium that had been commonly studied for precurarization [5, 11, 12] induced a potentially risky neuromuscular block within 3 min while awaiting induction of anesthesia and was therefore regarded as overdosing. Furthermore, to effectively prevent suxamethonium-induced muscle fasciculation, rocuronium 0.03 mg/kg was proven to be a sufficient dose.

Suxamethonium has the superior feature of rapid onset of action and enables shortening the interval from the patient's loss of consciousness following hypnotics to tracheal intubation. Particularly in an emergent patient with a full stomach, the incidence of pulmonary aspiration during induction of general anesthesia will be three to four times higher than that for patients undergoing proposed elective surgery [16]. Therefore, establishing a fast and profound neuromuscular block is required for rapid sequence intubation. Although priming [17] and timing principles [18] using rapid-onset rocuronium have been reported to be effective for rapid sequence intubation, suxamethonium seems to be clinically preferred rather than rocuronium as a neuromuscular blocking agent for patients with specific risks of pulmonary aspiration. In fact, a survey of variation of rapid sequence induction techniques in Wales reported that suxamethonium was currently used for 97% of cesarean sections, 94% of bowel obstructions, and 85% of appendectomies; in contrast, rocuronium was used only in 2–12% of patients [2]. A retrospective case-review analysis of 250 patients undergoing appendectomy in a 1-year period also revealed that suxamethonium use was 80%, with 96% of these patients receiving rocuronium precurarization [3]. To prevent several side effects associated with suxamethonium-induced muscular fasciculation, including an increase in intragastric pressure, precurarization seems to be important. The barrier pressure, which is the difference between intragastric pressure (mean value, 10 cmH_2O) and lower esophageal sphincter pressure (36 cmH_2O) normally prevents reflux of gastric contents into the esophagus [19]. However, in patients with a full stomach, basal intragastric pressure may rise, and many induction anesthetics reduce the lower esophageal sphincter tone [1]. In addition, it should not be surprising that intragastric pressure rises as high as 40 cmH_2O as a result of suxamethonium-induced fasciculation [20]. Under specific conditions in which the lower sphincter is not closing tightly enough, precurarization may be necessary to prevent fasciculation because the increases in intragastric pressure are directly related to the intensity of fasciculation [20]. As just described, such a combination of precurarization with rocuronium and suxamethonium is still predominantly used for rapid sequence induction and therefore should be safely and effectively applied. The present study is considered meaningful to be able to optimize the precurarizing dose of rocuronium in clinical anesthesia. Based on the results of this study, rocuronium 0.03 mg/kg is sufficient to prevent fasciculation on the trunk and may avoid increasing intraabdominal pressure.

Table 1 Patient characteristics

	0.03 mg/kg group	0.06 mg/kg group
Age (years)	40.2 (12.0)	37.6 (11.5)
Weight (kg)	54.3 (5.4)	56.2 (8.0)
Height (cm)	158.5 (4.9)	161.2 (8.0)

Data are presented as mean (SD); no significant differences were seen between the groups

Table 2 Change in the train-of-four (TOF) ratios after precurarization

	1 min	2 min	3 min
0.03 mg/kg group	1.01 (0.01)	0.94 (0.09)	0.91 (0.12)
	(range, 0.98–1.03)	(range, 0.79–1.05)	(range, 0.70–1.06)
0.06 mg/kg group	0.98 (0.04)	0.72 (0.13)*	0.66 (0.16)*
	(range, 0.89–1.04)	(range, 0.54–0.97)	(range, 0.37–0.88)

Data are presented as percent (%) of control and mean (SD) (range)

* $P < 0.05$ when compared with the baseline value

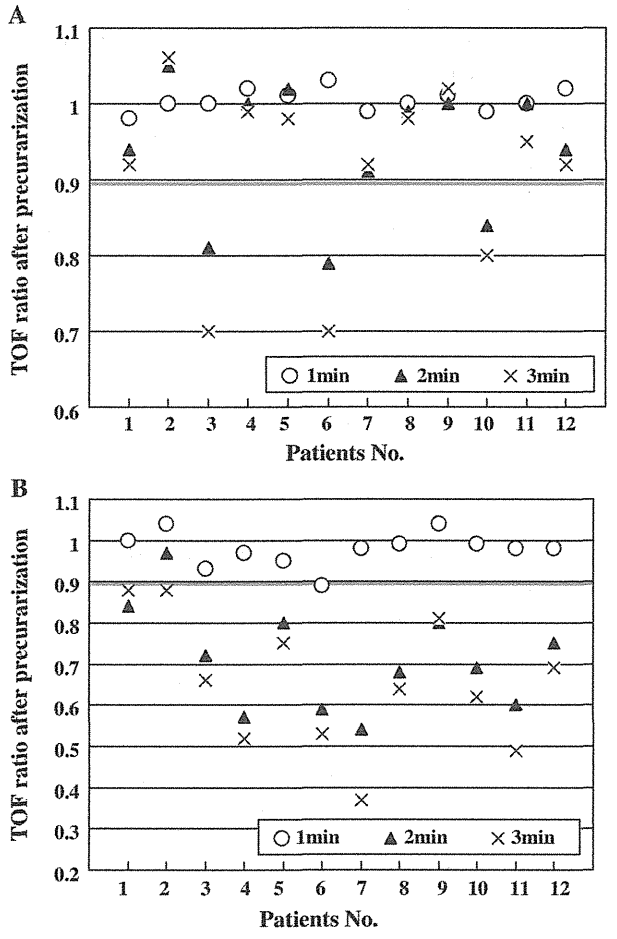

Fig. 1 Detailed train-of-four (*TOF*) ratios after precurarization in each patient in 0.03 mg/kg group (**a**) and 0.06 mg/kg group (**b**). Data were normalized by each baseline train-of-four ratio recorded before precurarization. *Circles*, *triangles*, and *multisymbols* on the graph show the train-of-four ratios observed 1, 2, and 3 min after precurarization, respectively

It was reported that rocuronium was the best drug to prevent muscle fasciculation following suxamethonium injection [5]. In the study, a pretreatment of 0.06 mg/kg rocuronium and an interval of 4 min to suxamethonium injection could completely prevent fasciculation in 85% of patients. Suxamethonium-induced fasciculation certainly would be effectively inhibited if the pretreatment dose of rocuronium was greater than a nonparalyzing dose. However, the intensity of neuromuscular block induced by the precurarizing dose of rocuronium was not clarified even though neuromuscular function was monitored throughout the study [5]. Three minutes after the precurarizing dose of 0.06 mg/kg rocuronium, we could show that an averaged TOF ratio was significantly depressed from 1.0 to 0.68. A TOF ratio below 0.9 observed at the adductor pollicis muscle exposes awake patients to the potentially unpleasant experience of difficulty in swallowing. At that time, the upper esophageal sphincter muscle resting tone markedly decreases [15]. Although precurarization should be applied to patients with a full stomach, it seems very possible that the risk of pulmonary aspiration of gastric contents may be even higher when rocuronium is overdosed [9]. It is therefore suggested, from our results, that the appropriate dose of rocuronium for safe and effective precurarization is 0.03 mg/kg.

Precurarization with a nondepolarizing neuromuscular blocking agent can prevent fasciculation; however, this simultaneously reduces the neuromuscular blocking potency of suxamethonium and also delays the onset of depolarizing neuromuscular block [21]. In the present study, a faster onset of suxamethonium-induced neuromuscular block was obtained in patients pretreated with 0.03 mg/kg rocuronium. It should be considered that too large a precurarization dose may conversely make suxamethonium less effective and delay the timing of tracheal intubation.

We set the administration interval between the precurarizing dose of rocuronium and suxamethonium to 3 min in accordance with conventional practice. Timing of administration is important, because the benefits of precurarization may be weakened if suxamethonium is given too soon or, equally, if it is given too late. Based on the characteristics of rapid onset and intermediate duration of action of rocuronium, a longer waiting time for suxamethonium accelerates rocuronium to dissociate from the neuromuscular junction. Further studies are warranted to clarify a relationship between the precurarizing dose of rocuronium and the waiting time to suxamethonium administration.

In this study, the neuromuscular effects of precurarizing doses of rocuronium were observed during maintenance of anesthesia. Twitch responses evoked by the repetitive TOF mode gradually increase during baseline stimulation and reach a plateau at around 10 min [14]. In the middle of the staircase phenomenon, neuromuscular block induced by a small dose of rocuronium might not be correctly evaluated; therefore, the present study required stabilizing the responses before precurarization. In the protocol of this study, not only the effects of precurarization but also other influencing factors on the degree of neuromuscular block must be considered. The duration of anesthesia with opioid and propofol before an administration of neuromuscular blocking agent increases the intensity of neuromuscular block [22]. In addition, the longer duration of baseline nerve stimulation can further decrease the onset of action of rocuronium [23]. It is likely that the peripheral vasodilation caused by anesthetics and muscle blood flow increased by muscle contractions to nerve stimulation may be involved in the augmentation of neuromuscular block. It is possible that an optimal precurarizing dose of

rocuronium may be larger in awake patients who are not peripherally stimulated by a nerve stimulator.

The patients enrolled in this study were all Japanese women. Asian people are more sensitive to rocuronium-induced block than Caucasian people [24]. Racial differences may therefore impact on the optimal dose of rocuronium for precurarization. In addition, women are more sensitive to rocuronium and require about 30% less rocuronium than men to achieve the same degree of neuromuscular block [25]. However, it was reported that a precurarizing dose of rocuronium affected men and women equally [26].

In conclusion, precurarization with 0.03 mg/kg rocuronium induces no significant depression of the TOF ratios in most patients during a waiting time of 3 min and can certainly prevent suxamethonium-induced fasciculation. We consider that 0.06 mg/kg rocuronium causes a marked neuromuscular block that potentially triggers pulmonary aspiration of gastric contents.

Acknowledgments This study was performed using the departmental fund.

Conflict of interest No relationships between authors and any company or organization with a vested interest in the outcome of the study.

References

1. Ng A, Smith G. Gastroesophageal reflux and aspiration of gastric contents in anesthetic practice. Anesth Analg. 2001;93:494–513.
2. Koerber JP, Roberts GE, Whitaker R, Thorpe CM. Variation in rapid sequence induction techniques: current practice in Wales. Anaesthesia. 2009;64:54–9.
3. Istvan J, Belliveau M, Donati F. Rapid sequence induction for appendectomies: a retrospective case-review analysis. Can J Anaesth. 2010;57:330–6.
4. Erkola O, Salmenperä A, Kuoppamäki R. Five non-depolarizing muscle relaxants in precurarization. Acta Anaesthesiol Scand. 1983;27:427–32.
5. Martin R, Carrier J, Pirlet M, Claprood Y, Tetrault JP. Rocuronium is the best non-depolarizing relaxant to prevent succinylcholine fasciculations and myalgia. Can J Anaesth. 1998;45:521–5.
6. Demers-Pelletier J, Drolet P, Girard M, Donati F. Comparison of rocuronium and D-tubocurarine for prevention of succinylcholine-induced fasciculations and myalgia. Can J Anaesth. 1997;44:1144–7.
7. Engbæk J, Viby-Mogensen J. Precurarization: a hazard to the patient? Acta Anaesthesiol Scand. 1984;28:61–2.
8. Motsch J, Fuchs W, Hoch P, Kaas V, Hutschenreuter K. Side effects and changes in pulmonary function after fixed dose precurarization with alcuronium, pancuronium or vecuronium. Br J Anaesth. 1987;59:1528–32.
9. Musich J, Walts LF. Pulmonary aspiration after a priming dose of vecuronium. Anesthesiology. 1986;64:517–9.
10. Kopman AF, Khan NA, Neuman GG. Precurarization and priming: a theoretical analysis of safety and timing. Anesth Analg. 2001;93:1253–6.
11. Motamed C, Choquette R, Donati F. Rocuronium prevents succinylcholine-induced fasciculations. Can J Anaesth. 1997;44:1262–8.
12. Findlay GP, Spittal MJ. Rocuronium pretreatment reduces suxamethonium-induced myalgia: comparison with vecuronium. Br J Anaesth. 1996;76:526–9.
13. Tsui BCH, Reid S, Gupta S, Kearney R, Mayson T, Finucane B. A rapid precurarization technique using rocuronium. Can J Anaesth. 1998;45:397–401.
14. Suzuki T, Fukano N, Kitajima O, Saeki S, Ogawa S. Normalization of acceleromyographic train-of-four ratio by baseline value for detecting residual neuromuscular block. Br J Anaesth. 2006;96:44–7.
15. Eriksson LI, Sundman E, Olsson R, Nilsson L, Witt H, Ekberg O, Kuylenstierna R. Functional assessment of the pharynx at rest and during swallowing in partially paralyzed humans. Simultaneous videomanometry and mechanomyography of awake human volunteers. Anesthesiology. 1997;87:1035–43.
16. Janda M, Scheeren TWL, Nöldge-Schomburg GFE. Management of pulmonary aspiration. Best Pract Res Clin Anaesthesiol. 2006;20:409–27.
17. Yavaşcaoğlu B, Cebelli V, Kelebek N, Uçkunkaya N, Kutlay O. Comparison of different priming techniques on the onset time and intubating conditions of rocuronium. Eur J Anaesthesiol. 2002;19:517–21.
18. Suzuki T, Aono M, Fukano N, Kobayashi M, Saeki S, Ogawa S. Effectiveness of the timing principle with high-dose rocuronium during rapid sequence induction with lidocaine, remifentanil and propofol. J Anesth. 2010;24:177–81.
19. Hunt PCW, Cotton BR, Smith G. Comparison of the effects of pancuronium and atracurium on the lower esophageal sphincter. Anesth Analg. 1984;63:65–8.
20. Miller RD, Way WL. Inhibition of succinylcholine-induced increased intragastric pressure by nondepolarizing muscle relaxants and lidocaine. Br J Anaesth. 1971;34:185–8.
21. Hartman GS, Fiamengo SA, Riker WF. Succinylcholine: mechanism of fasciculations and their prevention by D-tubocurarine or diphenylhydantoin. Anesthesiology. 1986;65:405–13.
22. Plaud B, Debaene B, Donati F. Duration of anesthesia before muscle relaxant injection influences level of paralysis. Anesthesiology. 2002;97:616–21.
23. Symington MJ, McCoy EP, Mirakhur RK, Kumar N. Duration of stabilization of control responses affects the onset and duration of action of rocuronium but not suxamethonium. Eur J Anaesthesiol. 1996;13:377–80.
24. Collins LM, Bevan JC, Bevan DR, Villar GC, Kahwaji R, Smith MF, Donati F. The prolonged duration of rocuronium in Chinese patients. Anesth Analg. 2000;91:1526–30.
25. Xue FS, Tong SY, Liao X, Liu JH, An G, Luo LK. Dose-response and time course of effect of rocuronium in male and female anesthetized patients. Anesth Analg. 1997;85:667–71.
26. Mencke T, Soltesz S, Sauer M, Menzebach A, Silomon M, Nöldge-Schomburg G. Are women more sensitive to a precurarization dose of rocuronium than men? Acta Anaesthesiol Scand. 2008;52:1051–5.

J Anesth (2011) 25:376–379
DOI 10.1007/s00540-011-1129-0

ORIGINAL ARTICLE

Onset of rocuronium-induced neuromuscular block evaluated subjectively and accerelomyographically at the masseter muscle

Osamu Kitajima · Takahiro Suzuki · Naoko Fukano · Shigeru Saeki · Setsuro Ogawa · Yoshikazu Noda

Received: 25 November 2010 / Accepted: 8 March 2011 / Published online: 12 April 2011

Abstract
Purpose The main aim of this study was to compare the onset times of rocuronium evaluated subjectively and by acceleromyography at the masseter muscle (MM).
Methods Forty female patients were sequentially enrolled in this study. In the first 20 patients, neuromuscular block was evaluated subjectively. After induction of anesthesia with fentanyl and propofol, both the left masseter and ulnar nerves were stimulated in 2-Hz train-of-four (TOF) mode using peripheral nerve stimulators. Contractions of the MM were felt with an anesthesiologist's left hand holding an anesthesia facemask; those of the adductor pollicis (APM) were visually observed. All the patients received a bolus of rocuronium, 0.6 mg/kg. Onset times after rocuronium were defined as the duration until the contractions became impalpable at the MM or invisible at the APM. At the time contraction of the MM had not been felt, intubating conditions were assessed. In the next 20 patients, contractions of the MM and the APM were concurrently quantified using acceleromyography after induction of anesthesia and laryngeal mask insertion. Following 0.6 mg/kg rocuronium, onset of the action was recorded.
Results Onset of the action of rocuronium at the MM evaluated subjectively [mean (SD), 70.3 (17.7) s] was similar to that monitored acceleromyographically [73.3 (27.6) s, $P > 0.05$], and significantly shorter than that at the APM acceleromyographically [111.0 (34.8) s, $P = 0.016$]. Intubating conditions of 20 patients were graded either excellent or good.
Conclusion Subjective evaluation of contractions of the MM by an anesthesiologist's hand may be reliable to determine faster timing for safe tracheal intubation.

Keywords Masseter muscle · Rocuronium · Neuromuscular block · Tracheal intubation

Introduction

The time course of neuromuscular block is generally evaluated at the adductor pollicis muscle (APM). However, the onset of neuromuscular block is much slower at the APM than at the larynx [1], diaphragm [2], and masseter muscle (MM) [3–5]. It is therefore suggested that neuromuscular block at the APM cannot ensure faster timing of tracheal intubation during rapid sequence induction. Intubating conditions should be evaluated by relaxation of the respiratory muscles, specifically by ease of laryngoscopy, vocal cord position, and patient's reaction to intubation [6]. However, direct measurements of neuromuscular block in the larynx and diaphragm are not easy in clinical anesthesia. We previously reported that disappearance of contractions of the MM could be felt subjectively and easily with an anesthesiologist's hand following an injection of vecuronium and could ensure safe and faster timing of tracheal intubation [5]. However, because the MM contractions were only sensed by an anesthesiologist's hand, it was undeniable that the results of the previous study might include some evaluator bias. A further objective study was warranted to establish reliability of the previous results. The main purpose of this study was to compare onset times

O. Kitajima · T. Suzuki (✉) · N. Fukano · S. Saeki · S. Ogawa
Department of Anesthesiology, Surugadai Nihon University Hospital, 1-8-13 Kanda-Surugadai, Chiyoda-Ku, Tokyo 101-8309, Japan
e-mail: suzukit@cd5.so-net.ne.jp

Y. Noda
Department of Anesthesia, Social Insurance Sagamino Hospital, 1-2-30 Futinobe, Sagamihara, Kanagawa 229-0006, Japan

Table 1 Evaluation of intubating conditions [7]

Variable assessed	Excellent	Good	Poor
Laryngoscopy	Easy	Fair	Difficult
Vocal cord position	Abducted	Intermediate/moving	Closed
Diaphragmatic movement or cough after tracheal intubation	None	Slight	Vigorous/sustained

Excellent all qualities are excellent, *good* all qualities are either excellent or good, *poor* the presence of a single quality listed under poor

of rocuronium at the MM evaluated by tactile means and acceleromyography and to determine whether subjective monitoring was useful to determine onset of rocuronium-induced neuromuscular block and allow faster tracheal intubation.

Materials and methods

After approval of the protocol by the Hospital Ethics Committee on Human Rights in Research, 40 adult female patients consented to participate in this study. Patients were ASA physical status I or II, 23–47 years of age, undergoing elective gynecological surgery. None of the patients had neuromuscular, hepatic, or renal disorders or were taking any drug known to interact with neuromuscular blocking agents. Patients whose body mass index (BMI) was $\geq$25 or <18.5 were also excluded from the study. Premedication consisted of orally administered ranitidine 150 mg before going to bed on the day before surgery and in the morning of the day of surgery. On arrival at the operating room, all patients were monitored with ECG, noninvasive blood pressure, and pulse oximetry. The first 20 patients were assigned to evaluate the onset of rocuronium-induced neuromuscular block at the MM and APM subjectively using peripheral nerve stimulators. Surface-stimulating electrodes were attached percutaneously on the left ulnar nerve at the wrist and the left masseter nerve at the space formed by the zygomatic arch superiorly the mandibular notch inferiorly, and two peripheral nerve stimulators (Innervator NS-252; Fisher & Paykel Electronics, Auckland, New Zealand) were used to separately stimulate the ulnar and masseter nerves [5]. General anesthesia was induced with fentanyl 2 μg/kg and propofol 2 mg/kg while patients received 100% oxygen through an anesthesia facemask. After loss of consciousness, the nerves were concurrently stimulated with square-wave stimuli of 0.2-ms duration, delivered in a train-of-four (TOF) mode at 2 Hz every 12 s. For the ulnar nerve, output current of 50 mA was applied; however, 30 mA was used to stimulate the masseter nerve to avoid stimulation of other facial muscles and direct stimulation of the MM [6]. Contractions of the MM were palpated with an anesthesiologist's left palm lifting the patient's jaw and holding an anesthesia facemask [5], and contractions of the APM was visually observed by another evaluator. Then, the patients received an i.v. bolus dose of rocuronium, 0.6 mg/kg. The onset time at the MM was defined as the duration until the contracting response of the MM was become impalpable, and that at the APM was defined as the duration until adduction of the thumb could not be visually observed. Immediately after the onset at the MM was confirmed, the patient's trachea was intubated with a 7.0-mm-ID endotracheal tube (Portex Tracheal Tube; Smiths Medical International, Kent, UK) and the intubating conditions (Table 1) [7] were assessed.

The next 20 patients were allocated to monitor rocuronium-induced neuromuscular block acceleromyographically. Anesthesia was induced with fentanyl 2 μg/kg and propofol 2 mg/kg, and laryngeal mask insertion was accomplished without aid of neuromuscular blocking agents. Anesthesia was maintained by a continuous infusion of propofol 4–5 mg/kg/h and intermittent administrations of fentanyl as required. After a stable depth of anesthesia was obtained, the left ulnar and masseter nerves were stimulated with square-wave stimuli of 0.2-ms duration, which was delivered in a TOF mode at 2 Hz every 15 s. The left ulnar nerve was stimulated at the supramaximal current (range, 40–50 mA); the unilateral facial nerve was stimulated at a current of 30 mA. Contraction of the ipsilateral MM (Fig. 1) or APM was measured using an acceleromyograph (TOF-Watch SX; Organon, Dublin, Ireland). A transducer was attached percutaneously on the masseter adherent to the mandible and the volar aspect of the thumb at the interpharyngeal joint. After the control TOF stimuli were administered for a minimum of 10 min to stabilize the TOF responses [8], all the patients received rocuronium 0.6 mg/kg i.v., and onset of the action was recorded. Onset time was defined from the administration of rocuronium to maximum depression of the first twitch (T_1) of the TOF. Times from administration of rocuronium to spontaneous recovery of T_1 to 10% of the control value were observed.

The sample size was calculated based on the preliminary data on an averaged onset time of rocuronium 0.6 mg/kg observed at the MM (75 $\pm$ 12 s). We considered a 20% difference (>15 s) in the onset times measured by tactile and acceleromyographical means at the MM to be clinically different. To obtain statistically significant results with $\alpha = 0.05$ and a power of 0.9, it was necessary that

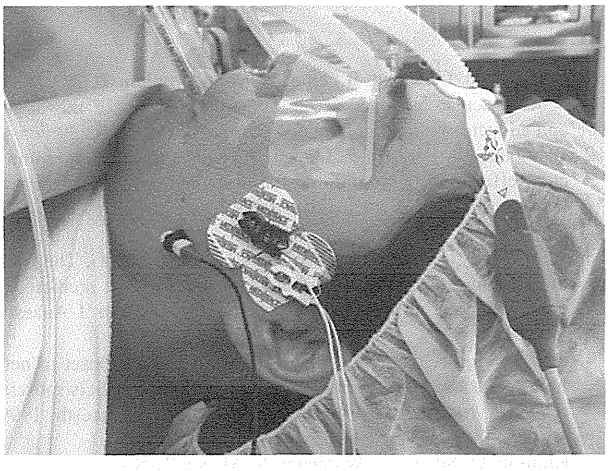

Fig. 1 Placement of surface electrodes stimulating the masseter nerve and an acceleration transducer measuring the contraction of the masseter muscle

15 patients should be included in this study. Allowing for dropouts from the study, we finally enrolled 20 patients. Data are presented as mean (SD). Statistical analysis was performed using StatView software for Windows (SAS Institute, Cary, NC, USA). The unpaired Student *t* test was used for two group comparisons. A P value <0.05 was considered statistically significant.

Results

Data from all 40 patients could be included in the analyses. No differences were found in patient characteristics between the groups (Table 2). There was no difference between the onset times of rocuronium observed subjectively and acceleromyographically at both MM and APM (Table 3). Onset of the action of rocuronium obtained at the MM was significantly faster than those at the APM (Table 3). When evaluating the rocuronium-induced neuromuscular block subjectively, the intubating condition was graded excellent in 12 patients and good in 8 patients; none of the patients had poor intubating condition. In the group AMG, the time from an administration of rocuronium to spontaneously recover to 10% of control of T_1 was

Table 2 Patient characteristics

Characteristic	Subjective evaluation	Acceleromyography
Age (years)	39.2 (7.1)	41.1 (8.4)
Weight (kg)	51.0 (7.3)	53.4 (6.0)
Height (cm)	156.0 (4.7)	156.9 (5.4)

Data are presented as mean (SD); no significant differences were seen between the groups

Table 3 Onset of the action of rocuronium 0.6 mg/kg

Location	Subjective evaluation	Acceleromyography
Masseter	70.3 (17.7)*	73.3 (27.6)#
Adductor pollicis	143.3 (29.5)	111.0 (34.8)

Data are presented as mean (SD); no significant differences were seen between the groups

* $P < 0.0001$ when compared between the muscles

$P = 0.016$ when compared between the muscles

significantly shorter in the MM [25.4 (8.2) min, $P = 0.045$] than the APM [34.6 (10.8)].

Discussion

This study demonstrated that the onset time of rocuronium-induced neuromuscular block evaluated subjectively did not differ from that monitored acceleromyographically at the MM. Intubating conditions when contractions of the MM had not been felt by an evaluator's hand were all graded as clinically acceptable conditions. Based on the results of this study, it is likely that subjective evaluation of contractions of the MM during the masseter nerve stimulation is a reliable method to know the onset of rocuronium-induced neuromuscular block and enable faster and safe tracheal intubation. Particularly in a patient with a full stomach, monitoring of the MM contraction during rapid sequence induction may be useful to hasten the timing of tracheal intubation and decrease the risk of pulmonary aspiration.

Previous studies [3, 4] revealed that the onset of rocuronium-induced neuromuscular block occurred significantly faster at the MM than at the APM. Unfortunately, the acceleromyographic monitoring was performed in such studies during a steady state of general anesthesia after laryngeal mask insertion [3] or tracheal intubation [4]. It was true that the results of the previous studies could provide some meaningful information about pharmacodynamic differences of rocuronium between the MM and APM. However, the studies were not really sufficient to apply the acceleromyography at the MM in the clinical setting. The important characteristic of rapid onset of paralysis at the MM should be utilized during induction of general anesthesia to assess the optimal timing for tracheal intubation; however, it is hard to monitor the MM objectively because an acceleration transducer cannot correctly assess the jaw movement during mask-to-face ventilation. Consequently, to perform MM monitoring in the clinical setting, we palpated contractions of the MM evoked by a simple peripheral nerve stimulator during mask ventilation, and subjectively assessed the onset of paralysis based on the disappearance of contractions [5]. Concern was greatest

for some bias of the evaluator in the previous study, but it is deniable because the onset times of rocuronium evaluated subjectively and acceleromyographically were similar. This procedure was proven to be of clinical use for determining the earliest suitable time at which laryngoscopy and tracheal intubation could be performed.

Our study has a limitation that must be acknowledged. Ideally, the TOF stimuli should be delivered in the same stimulation frequency when the onset times of neuromuscular block would be compared because a faster stimulation frequency greatly increases blood flow to the monitored muscle and should produce a shorter equilibration of rocuronium [9]. Therefore, the onset of the action of rocuronium observed subjectively might cause minor delays if the nerves were stimulated every 15 s.

Paralysis of the MM was significantly faster than that of the APM. The faster onset of the action of rocuronium at the MM may be caused by the large volume of blood flow to the centrally located muscles [3] and the faster transfer rate of neuromuscular blocking drugs between the plasma and the neuromuscular junction [10]. The shorter duration of action of rocuronium measured at the MM may also result from greater perfusion and more rapid washout of rocuronium, when compared to the APM [11].

In the present study, we did not assign the patients randomly, and at first evaluated the onset time of rocuronium subjectively. If the acceleromyographical study were to be done first, it is likely that the results might be prejudicial for an evaluator and influence the onset time subjectively evaluated from diminishing contractions of the MM.

In conclusion, tactile assessment of muscle paralysis of the MM after administration of rocuronium enables faster tracheal intubation and may improve patient safety.

Acknowledgments This study was funded by the Department of Anesthesiology, Surugadai Nihon University Hospital, Tokyo, Japan.

Conflict of interest There are no relationships between authors and any company or organization with a vested interest in the outcome of the study.

References

1. Meistelman C, Plaud B, Donati F. Rocuronium (ORG 9426) neuromuscular blockade at the adductor muscles of the larynx and adductor pollicis in humans. Can J Anaesth. 1992;39:665–9.
2. Cantineau JP, Porte F, d'Honneur G, Duvaldestin P. Neuromuscular effects of rocuronium on the diaphragm and adductor pollicis muscles in anesthetized patients. Anesthesiology. 1994;81:585–90.
3. De Mey JC, De Baerdemaeker L, De Latt M, Rolly G. The onset of neuromuscular block at the masseter muscle as a predictor of optimal intubating conditions with rocuronium. Eur J Anaesth. 1999;16:387–9.
4. de Rossi L, Preußler NP, Pühringer FK, Klein U. Onset of neuromuscular block at the masseter and adductor pollicis muscles following rocuronium or succinylcholine. Can J Anaesth. 1999;46:1133–7.
5. Kitajima O, Suzuki T, Watanabe N, Maeda T, Noda Y, Saeki S, Ogawa S. Monitoring masseter muscle evoked responses enables faster tracheal intubation. J Anesth. 2010;24:173–6.
6. Hemmerling TM, Donati F. Neuromuscular blockade at the larynx, the diaphragm and the corrugator supercilli muscle: a review. Can J Anaesth. 2003;50:779–94.
7. Fuchs-Buder T, Claudius C, Skovgaard LT, Eriksson LI, Mirakhur RK, Viby-Mogensen J. Good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents II: the Stockholm revision. Acta Anaesthesiol Scand. 2007;51:789–808.
8. Suzuki T, Fukano N, Kitajima O, Saeki S, Ogawa S. Normalization of acceleromyographic train-of-four ratio by baseline value for detecting residual neuromuscular block. Br J Anaesth. 2006;96:44–7.
9. Meretoja OA, Taivainen T, Brandom BW, Wirtavuori K. Frequency of train-of-four stimulation influences neuromuscular responses. Br J Anaesth. 1994;72:686–7.
10. Plaud B, Proost JH, Wierda MKH, Barre J, Debaene B, Meistelman C. Pharmacokinetics and pharmacodynamics of rocuronium at the vocal cords and the adductor pollicis in humans. Clin Pharmacol Ther. 1995;58:185–91.
11. Bragg P, Fisher DM, Shi J, Donati F, Meistelman C, Lau M, Sheiner LB. Comparison of twitch depression of the adductor pollicis and the respiratory muscles. Pharmacodynamic modeling without plasma concentrations. Anesthesiology. 1994;80:310–9.

Acta Anaesthesiol Scand 2012; **56:** 236–239
Printed in Singapore. All rights reserved

ACTA ANAESTHESIOLOGICA SCANDINAVICA
doi: 10.1111/j.1399-6576.2011.02605.x

The effects of age on maintenance of intense neuromuscular block with rocuronium

T. Furuya, T. Suzuki, A. Kashiwai, J. Konishi, M. Aono, N. Hirose, J. Kato and S. Ogawa
Department of Anaesthesiology, Nihon University School of Medicine, Tokyo, Japan

Background: Increasing age is associated with a longer duration of action of neuromuscular block. The aim of this study was to determine the influence of ageing on the recovery of the post-tetanic count (PTC) from rocuronium-induced neuromuscular block.

Methods: Twenty-two younger (20–60 years) and 22 older (> 70 years) patients were enrolled in this study. After induction of anaesthesia with fentanyl and propofol, all patients initially received 1 mg/kg rocuronium and neuromuscular block were evaluated by contractions of the adductor pollicis muscle to ulnar nerve train-of-four stimulation using an acceleromyograph. Subsequently, intense rocuronium-induced block was determined every 6 min using the PTC during 1.0–1.5% sevoflurane and remifentanil anaesthesia. When the first response to the PTC stimulus was detected, 0.2 mg/kg rocuronium was additionally administered, and again, spontaneous recovery of neuromuscular function was monitored until the first response to the PTC reappeared.

Results: Median values (range) of the times from the administration of 1 mg/kg and 0.2 mg/kg rocuronium until recovery of the first detectable PTC were significantly longer in the older [51.0 (27–100) min, $P < 0.0001$ and 30.0 (12–66) min, $P = 0.0036$, respectively] than the younger patients [31.5 (21–45) min and 18.0 (12–36) min, respectively].

Conclusion: The times from rocuronium injection to reappearance of the first response to PTC stimulation are approximately twofold longer and more variable in older than younger patients. Hence, the dosing interval of rocuronium should be adjusted using neuromuscular monitoring when maintaining intense neuromuscular block, especially in older patients.

Accepted for publication 28 October 2011

Ageing is accompanied by decreases in hepatorenal blood flow and function. Because steroidal non-depolarizing neuromuscular blocking agents are eliminated through some combination of these means, alteration in pharmacokinetics and duration of action are to be expected. Actually, rates of plasma clearance for rocuronium decrease with increasing age and are inversely proportional to the duration of neuromuscular blockade produced by rocuronium.[1] It is therefore recommended that subsequent doses should be administered only after reappearance of some train-of-four (TOF) responses in the elderly surgical patients. However, even in older patients, maintenance of intense neuromuscular block is required to prevent unintentional coughs, hiccups, muscle stiffness and body movement that seriously disturb the surgical procedure, especially in patients undergoing thoracoabdominal surgery or microscopically controlled endoscopic surgery. To achieve this, a post-tetanic count (PTC) of zero at the adductor pollicis muscle[2] accurately indicate intense neuromuscular block. The time from administration of rocuronium to the first response of the adductor pollicis to PTC stimulation was expected to be longer with advancing age, although there is so far no report in the literature to support our assumption. Therefore, the present study was designed to determine the effects of age on the duration of rocuronium-induced intense neuromuscular block between older and younger adult patients.

Financial support: *Departmental funding.*

Methods

After approval of the protocol by the Hospital Ethics Committee on Human Rights in Research, 44 patients consented to participate in this study. Patients were American Society of Anesthesiologists

physical status I–II, aged between 20–60 years or 70 years of age or older, and undergoing elective surgery under general anaesthesia. None of the patients had neuromuscular, hepatic or renal disorders, nor were they taking any drug known to interact with neuromuscular blocking agents. Patients whose body mass index was ≥ 25 or < 18.5 kg/m^2 were excluded from the study. Premedication consisted of 150 mg ranitidine administered orally before going to bed on the night before surgery and on the morning of surgery. On arrival at the operating room, all patients were monitored with electrocardiogram and non-invasive blood pressure and pulse oximetry. Acetated Ringer's solution (8–10 ml/kg/h) was intravenously infused in the left forearm of the patients via a cannula. General anaesthesia was induced with 2 μg/kg fentanyl and 1–2 mg/kg propofol intravenously (i.v.) while patients received 100% oxygen through an anaesthesia face mask. Patients' tracheae were intubated after rocuronium-induced complete neuromuscular block, and anaesthesia was maintained with 1.0–1.5% end-tidal sevoflurane and a continuous infusion of 0.1–0.3 μg/kg/min remifentanil and fentanyl as required. Ventilation was adjusted to maintain end-tidal carbon dioxide between 4.3 and 5.1 kPa using a BP-608EV (Omron Colin Inc., Tokyo, Japan). The rectal temperature of the patients was maintained at > 36°C using a warming mattress blanket (Bair Hugger model 750, Arizant Healthcare Inc., Eden Prairie, MN, USA). Using a surface probe equipped in the acceleromyographic device, skin temperature over the adductor pollicis muscle was recorded every 15 s throughout the experiment and maintained at > 32°C.

Rocuronium regimen and neuromuscular monitoring

After induction of anaesthesia, neuromuscular monitoring was started using an acceleromyograph (TOF-Watch SX, Organon Ltd, Dublin, Ireland). Stabilization and calibration of the monitoring were performed according to good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents.[3] The acceleration transducer was placed in the Hand Adaptor (Organon Ltd) to increase the precision of acceleromyography,[4] and the fingers were fixed to the arm board. To enhance stabilization, a 50 Hz tetanic stimulus was applied over 5 s on the ulnar nerve at the wrist. Thereafter, the nerve was stimulated with square-wave stimuli of 0.2 ms duration, which were delivered in a TOF mode at 2 Hz every 15 s, and contraction of the ipsilateral adductor pollicis was measured using an acceleromyograph. When the response to TOF was stabilized, calibration and supramaximal stimulation was ensured by the built-in calibration function (CAL2) of the acceleromyograph. After obtaining stable baseline in at least 2 min, all patients received 1 mg/kg rocuronium i.v. A PTC mode was initially applied 5 min after obtaining complete neuromuscular block and repeated every 6 min.[5] When the first response to PTC stimulation was detected, 0.2 mg/kg rocuronium was administered. The times from initial and second administration of rocuronium to the first detectable response to PTC stimulation were recorded. The times were compared between elderly and younger adult patients.

Statistics

The sample size was calculated based on previous data on the average interval between administration of 1 mg/kg rocuronium and the first response to PTC in younger adult patients (35.2 ± 9.5 min).[6] We considered a 25% increase in the time interval as being clinically relevant. To obtain statistically significant results with $\alpha = 0.05$ and a power of 0.80, it was necessary that 20 patients be included in each group. To compensate for any dropouts, we enrolled 22 patients in each group. Data are presented as median value (range) or mean (standard deviation). Statistical analysis was performed using the StatView software for Windows (SAS Institute, Cary, NC, USA). The Mann–Whitney test or unpaired Student's *t*-test was used for comparing data between the two groups. A *P*-value of < 0.05 was considered statistically significant.

Results

Data from two patients in the younger group were excluded from analysis because of repeated system errors of the PTC mode. Except for age, patient characteristics did not differ between the two groups (Table 1). Median values (range) of the times from

Table 1

The characteristics of the patients.

	Younger patients	Older patients
Age (year)	39.6 (11.7) (19–58)	76.2 (6.4) (70–91)*
Gender (M : F)	14 : 6	16 : 6
Height (cm)	165.4 (12.5)	159.8 (9.5)
Weight (kg)	63.8 (12.0)	57.8 (7.4)

*$P < 0.05$ vs. younger patients. Data are presented as mean (standard deviation) (range).

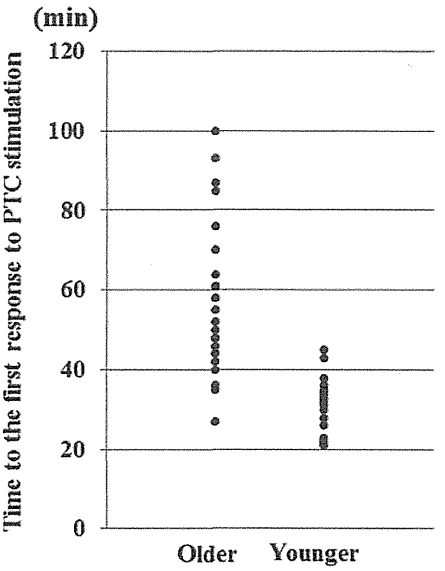

Fig. 1. The times from the administration of 1 mg/kg rocuronium to the first detectable response to the post-tetanic count (PTC) stimulation in older and younger patients.

the administration of 1 mg/kg and 0.2 mg/kg of rocuronium to the first response to PTC stimulation were significantly longer in the older [51.0 (27–100) min, $P < 0.0001$ and 30.0 (12–66) min, $P = 0.0036$, respectively] than younger patients [31.5 (21–45) min and 18.0 (12–36) min, respectively]. More than twofold greater variability of the times from the administration of 1 mg/kg rocuronium to the first detectable PTC was shown in older patients when compared with younger patients (Fig. 1).

Discussion

This study shows that a median value of the time interval between rocuronium injection and reappearance of the first response to PTC stimulation is significantly age-related and approximately twofold longer in older patients than younger adults. In addition, a more intriguing result we showed is a wider variability of duration of the action of rocuronium-induced intense neuromuscular block until detection of the first PTC. Even in healthy elderly patients, the pharmacokinetic changes impact on duration of the action of rocuronium are unpredictable, and therefore, the dosing interval of rocuronium should be adjusted according to the patient's inter-individual variation, and neuromuscular monitoring should be used to maintain an intense neuromuscular block.

The results of previous studies have indicated that recovery from rocuronium-induced neuromuscular block to reappearance of TOF responses, i.e. duration to moderate neuromuscular block, is prolonged in older patients when compared with younger adults because the elimination of rocuronium from the patient's body decreases in relation to age-dependent decreases in hepatic and renal blood flow.[1] In addition, the dose of rocuronium, calculated on the basis of actual body weight, may actually be overdosing for the elderly because of the decreased muscle mass and increased fat mass and a lower volume of distribution of rocuronium in older patients, which may result in a higher plasma concentration of rocuronium even when the same dose of rocuronium was administered.[1] However, a difference in the duration of rocuronium-induced intense neuromuscular block between older and younger adults has not been reported. Baykara and colleagues reported that the first response to PTC stimulation appeared earlier in children than adults following rocuronium injection,[7] while the time from administration of 1 mg/kg rocuronium until detection of the first PTC did not differ between elderly and younger adult patients (38.5 vs. 35.2 min).[6] The interval between onset of rocuronium action and the first detectable response to PTC stimulation monitored in elderly patients of this study was much longer (57.4 min) than that of Baykara study. It is reasonable to assume that age-associated decline in the clearance of rocuronium is related to a decline in physiological function, which explains the significantly slower recovery of the PTC from rocuronium-induced neuromuscular block in elderly patients. The study by Baykara and colleagues was done during intravenous anaesthesia using propofol and opioid,[6] while our present results were obtained during sevoflurane anaesthesia. It is therefore likely that sevoflurane may contribute to the longer duration of action of rocuronium in elderly patients of this study. Sevoflurane pharmacodynamically potentiates neuromuscular blockade,[8] and especially in older patients, decreases peripheral blood flow[9] and may reduce the elimination of rocuronium from the neuromuscular junction.

The result of the present study regarding wide variability of duration of the action of rocuronium shown in elderly patients can be supported by the previous result[10] reported by Arain and colleagues. The study demonstrated that there was a greater variability of each time range of the duration of neuromuscular blockade by 0.6 mg/kg rocuronium

(33–119 min) and 0.1 mg/kg vecuronium (35–137) for the recovery of T1 in the TOF responses to 25% of control in elderly patients. In contrast to the steroidal neuromuscular blocking agents primarily eliminated in the bile, the action of atracurium and cisatracurium eliminated by Hofmann elimination is independent of ageing and predictable even in elderly patients.[10–12] It is anticipated that the duration of intense neuromuscular block produced by atracurium and cisatracurium unresponsive to the PTC stimulation should also be unaffected by advanced age, however, further studies will be needed to verify the prediction.

PTC stimulation has previously been investigated and clinically used to estimate the approximate interval to reappearance of the first twitch in response to TOF stimulation during deep neuromuscular blockade.[5] However, the PTC mode is also useful for maintaining intense or deep neuromuscular block to prevent unintentional patient's movement during clinical anaesthesia. A previous study demonstrated that a PTC level of zero observed at the adductor pollicis muscle was necessary to achieve total diaphragmatic paralysis.[2] Therefore, to ensure an intense neuromuscular block and to prevent unexpected bucking or coughing during physical and autonomic surgical stress, the PTC stimulation mode is very informative.

In conclusion, the duration of rocuronium-induced intense neuromuscular block is markedly prolonged in older patients. It is, therefore, recommended to monitor neuromuscular function and adjust the dosing interval of rocuronium accordingly, particularly in elderly patients.

Acknowledgement

Conflict of interest: Takahiro Suzuki has received speaker fees from MSD Inc., JAPAN.

References

1. Matteo RS, Ornstein F, Schwartz AE, Ostapkovich N, Stone JG. Pharmacokinetics and pharmacodynamics of rocuronium (Org9426) in elderly surgical patients. Anesth Analg 1993; 77: 1193–7.
2. Fernando PU, Viby-Mogensen J, Bonsu AK, Tamilarasan A, Muchhal KK, Lambourne A. Relationship between posttetanic count and response to carinal stimulation during vecuronium-induced neuromuscular blockade. Acta Anaesthesiol Scand 1987; 31: 593–6.
3. Fuchs-Buder T, Claudius C, Skovgaard LT, Eriksson LI, Mirakhur RK, Viby-Mogensen J. Good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents II: the Stockholm revision. Acta Anaesthesiol Scand 2007; 51: 789–808.
4. Claudius C, Skovqaard LT, Viby-Mogensen J. Is the performance of acceleromyography improved with preload and normalization? A comparison with mechanomyography. Anesthesiology 2009; 110: 1261–70.
5. Viby-Mogensen J, Howardy-Hansen P, Chraemmer-Jørgensen B, Ording H, Engbaek J, Nielsen A. Posttetanic count (PTC): a new method of evaluating an intense nondepolarizing neuromuscular blockade. Anesthesiology 1981; 55: 458–61.
6. Baykara N, Solak M, Toker K. Predicting recovery from deep neuromuscular block by rocuronium in the elderly. J Clin Anesth 2003; 15: 328–33.
7. Baykara N, Woelfel S, Fine GF, Solak M, Toker K, Brandom BW. Predicting recovery from deep neuromuscular block by rocuronium in children and adults. J Clin Anesth 2002; 14: 214–7.
8. Suzuki T, Munakata K, Watanabe N, Katsumata N, Saeki S, Ogawa S. Augmentation of vecuronium-induced neuromuscular block during sevoflurane anaesthesia: comparison with balanced anaesthesia using propofol or midazolam. Br J Anaesth 1999; 83: 485–7.
9. Dwyer R, Howe J. Peripheral blood flow in the elderly during inhalational anaesthesia. Acta Anaesthesiol Scand 1995; 39: 939–44.
10. Arain SR, Kern S, Ficke DJ, Ebert TJ. Variability of duration of action of neuromuscular-blocking drugs in elderly patients. Acta Anaesthesiol Scand 2005; 49: 312–5.
11. D'Hollander AA, Luyckx C, Barvais L, De Ville A. Clinical evaluation of atracurium besylate requirements for a stable muscle relaxation during surgery: lack of age-related effects. Anesthesiology 1983; 59: 237–40.
12. Ornstein E, Lien CA, Matteo RS, Ostapkovich ND, Diaz J, Wolf KB. Pharmacodynamics and pharmacokinetics of cisatracurium in geriatric surgical patients. Anesthesiology 1996; 84: 520–5.

Address:
Takahiro Suzuki
Department of Anaesthesiology
Nihon University School of Medicine
30-1 Oyaguchi Kamimachi
Itabashi-Ku, Tokyo 173-8610
Japan
e-mail: suzukit@cd5.so-net.ne.jp

J Anesth
DOI 10.1007/s00540-012-1363-0

ORIGINAL ARTICLE

The effect of dexmedetomidine on arterial-cardiac baroreflex function assessed by spectral and transfer function analysis

Toru Ehara · Yojiro Ogawa · Jitsu Kato · Ken Aoki · Setsuro Ogawa · Ken-ichi Iwasaki

Received: 11 October 2011 / Accepted: 14 February 2012

Abstract
Purpose The α_2-adrenergic receptor agonist dexmedetomidine reportedly weakens heart rate (HR) responses to 'rapid' (during a few seconds) reduction in arterial pressure, but does not affect HR responses to 'gradual' (during 60 s) reduction in arterial pressure. As the speed of neurotransmission along the parasympathetic nerve is relatively rapid, alteration of parasympathetic-mediated arterial-cardiac baroreflex function plays a more important role in HR responses to 'rapid' changes in arterial pressure. We therefore hypothesized that dexmedetomidine attenuates parasympathetic-mediated arterial-cardiac baroreflex function.
Methods Twelve healthy men received placebo, low-dose (loading, 3 μg/kg/h for 10 min; maintenance, 0.2 μg/kg/h for 60 min) (low-DEX), or moderate-dose (loading, 6 μg/kg/h for 10 min; maintenance, 0.4 μg/kg/h for 60 min) (moderate-DEX) dexmedetomidine infusions in a randomized, double-blind, crossover study. Before and after 70 min of infusion, arterial-cardiac baroreflex function was assessed by spectral and transfer function analysis between arterial pressure variability and HR variability.
Results The high-frequency power of systolic arterial pressure (SAP) variability increased significantly with low-DEX and moderate-DEX infusions (significant interaction effects, $P = 0.005$), whereas the high-frequency power of R-wave–R-wave interval (RRI) variability (as an index of cardiac parasympathetic activity) did not change significantly at any dose infusions. Then, transfer function gain in the high-frequency range (as an index of parasympathetic arterial-cardiac baroreflex) decreased significantly with low-DEX and moderate-DEX infusions (significant interaction effects, $P = 0.007$).
Conclusions The present results suggest that dexmedetomidine attenuates parasympathetic-mediated arterial-cardiac baroreflex function, implying weakened HR response to 'rapid' reduction in arterial pressure.

Keywords Dexmedetomidine · Autonomic baroreflex regulation · Autonomic nerve activity · Spectral analysis · Transfer function analysis

Introduction

Dexmedetomidine, a highly selective α_2-adrenergic receptor agonist, is often used for sedation in the operating theater and intensive care unit [1–3]. Many studies have reported various effects of dexmedetomidine on the autonomic nervous system or cardiovascular system [4–9]. Thus, the effects of dexmedetomidine on heart rate (HR) responses to reduction in arterial pressure are controversial [4, 6, 9]. A few studies have examined HR responses to a 'gradual' (during 60 s) decrease in arterial pressure by nitroprusside administration during dexmedetomidine infusion [4, 6]. These previous studies concluded that dexmedetomidine has no effect on baroreflex sensitivity. Conversely, our previous study evaluated cardiovascular reflex responses to 'rapid' (during a few seconds) reduction in arterial pressure after thigh cuff deflation during dexmedetomidine infusion [9]. Our previous research

T. Ehara · J. Kato · S. Ogawa
Division of Anesthesiology, Department of Anesthesiology, Nihon University School of Medicine, Tokyo, Japan

Y. Ogawa (✉) · K. Aoki · K. Iwasaki
Division of Hygiene, Department of Social Medicine, Nihon University School of Medicine, 30-1 Oyaguchi-Kamicho, Itabashi-Ku, Tokyo 173-8610, Japan
e-mail: ogawa.yojiro@nihon-u.ac.jp

Published online: 02 March 2012

demonstrated that dexmedetomidine weakens HR responses to temporal reduction in arterial pressure, implying attenuated baroreflex function. The discrepancy between our study and other previous studies may be explained by the difference in the speed of neurotransmission between sympathetic and parasympathetic regulatory mechanisms [10] responding to different speeds of reduction in arterial pressure. Because the parasympathetic nerve with fast neurotransmission can modulate HR more rapidly than the sympathetic nerve [10], alteration of parasympathetic arterial-cardiac baroreflex function would probably play a more important role in HR responses to 'rapid' changes in arterial pressure during dexmedetomidine sedation.

We therefore hypothesized that dexmedetomidine attenuates parasympathetic arterial-cardiac baroreflex function. Spectral and transfer function analysis between arterial pressure variability and HR variability can distinguish parasympathetic arterial-cardiac baroreflex function from other functions [11–14]. By using these analyses, arterial-cardiac baroreflex function was estimated in the same subjects as in our previous study [9].

Methods

The institutional review board of Nihon University School of Medicine approved this study. All study volunteers provided written informed consent as well as a medical history and were screened by a physical examination including electrocardiography (ECG) and arterial pressure measurements. We investigated 12 healthy, normotensive males with a mean age of 21 years (range, 18–23 years), a mean height of 173 cm (163–182 cm), and a mean weight of 66 kg (57–79 kg). The present study is a follow-up on two earlier articles on dexmedetomidine research [9, 15] and is based on reanalysis of the data obtained from the same subjects in a previous study on cardiovascular reflexes during dexmedetomidine infusion [9].

The present experiment protocol was the same as the description provided in our previous reports [9, 15]. Briefly, an analog ECG and continuous arterial pressure waveforms obtained from a 3-lead ECG (Life scope BSM-5132; Nihon Kohden, Tokyo, Japan) and tonometry (JENTOW 7700; Colin, Aichi, Japan) were recorded at a sampling rate of 1 kHz using commercial software (Notocord-hem 3.3; Notocord, Paris, France) throughout the experiment. A pulse oximeter, nasal cannula (Life scope BSM-5132; Nihon Kohden), and bispectral index monitor (BIS XP; Aspect Medical Systems, Norwood, MA, USA) were applied. All participants received placebo (normal saline), low-dose dexmedetomidine (low-DEX; loading dose of 3 μg/kg/h for 10 min; maintenance dose of 0.2 μg/kg/h for 60 min), or moderate-dose dexmedetomidine (moderate-DEX; loading dose of 6 μg/kg/h for 10 min; maintenance dose of 0.4 μg/kg/h for 60 min) infusions in a randomized, double-blind, crossover study. These doses and periods of infusion were chosen to obtain dexmedetomidine plasma concentrations of approximately 0.6 and 0.3 ng/ml, respectively, as described in the manufacturer's material (Hospira Japan, Osaka, Japan). Moreover, these infusion regimens were similar to those used in previous studies [16, 17], including dexmedetomidine plasma concentrations [18]. At least 7 days were allowed between experiments. Drugs were administered after recording baseline data for 6 min after at least 30 min of rest. Seventy minutes after commencement of infusion of dexmedetomidine or placebo (loading, 10 min; maintenance, 60 min), 6-min data of ECG and continuous arterial pressure waveforms were analyzed for spectral and transfer function analyses. Before each 6-min data acquisition, sedation depths were assessed by the modified Observer's Assessment of Alertness/Sedation (OAA/S) scale [19]. Bispectral index (BIS) was used to confirm the stability of sedation depth during data acquisition. Steady-state values of HR, systolic arterial pressure (SAP), and diastolic arterial pressure (DAP) were obtained by averaging the 6 min of data. Steady-state values of arterial oxygen saturation (SpO_2), respiratory rate, and BIS that were manually recorded every minute were averaged over this 6-min time interval. After the data measurements, infusion of the drugs was discontinued.

Beat-to-beat values of SAP and R-wave–R-wave interval (RRI) were obtained using PC-based Notocord-hem 3.3 software to assess arterial-cardiac baroreflex function. Using previously validated algorithms [13, 20, 21], these data were linearly interpolated and resampled at 2 Hz to create an equidistant time series for spectral and transfer function analysis. The time series of SAP and RRI were first de-trended with third-order polynomial fitting and then subdivided into 256-point segments with a 50% overlap. This process resulted in five segments of data over a 6-min period of data collection. Fast Fourier transform analysis was implemented with each Hanning-windowed data segment and then averaged to calculate the autospectra of SAP and RRI. The minimal resolution of these spectra is ~0.0078 Hz. High-frequency powers of SAP variability and RRI variability in the range of 0.15–0.50 Hz and low-frequency power in the range of 0.04–0.15 Hz were calculated from integration of the autospectra [20, 21]. This data acquisition and processing strategy conforms to the recommendations of international consensus panels for the assessment of cardiovascular variability [21]. Transfer function gain, phase, and coherence (squared coherence function) between SAP and RRI variability were estimated using the cross-spectral method [11–14] as mean values of high and low frequency in the ranges of 0.15–0.35 and 0.04–0.15 Hz, respectively. Transfer function gain between

SAP and RRI variability reflects changes in RRI variability in response to changes in SAP mediated by baroreflex function, whereas the estimated phase reflects the time relationship between these two variables. The assumption of linearity and reliability of the transfer function estimation were evaluated by coherence ≥0.4 [22, 23]. Transfer function estimates in the high-frequency range are predominantly determined by parasympathetic modulation, whereas estimates of transfer function in the low-frequency range are influenced by both sympathetic and parasympathetic modulation [11–14]. Data were analyzed using PC-based software (DADiSP; DSP Development, Cambridge, MA, USA).

Variables were compared using two-way repeated-measures analysis of variance (ANOVA) with stage (baseline and drug administration) × dose (placebo, low-DEX, and moderate-DEX). If the spectral power estimates were not normally distributed, transformation into the square root was performed before the ANOVA. The interaction effect was considered the most relevant for differences occurred. To determine where significant difference occurred, a Student–Newman–Keuls post hoc test was used for all pairwise comparisons. $P < 0.05$ was considered statistically significant. The analyses were performed using PC-based software (SigmaStat; Systat Software, Chicago, IL, USA). Data are presented as mean ± SEM.

Results

Because continuous measurement of BIS at baseline was not stable with the electromyogram in two subjects, these values were excluded from the group-averaged data for statistical analysis. The average values of steady-state hemodynamic and respiratory data with each infusion dose are presented in Table 1. HR decreased significantly with low-DEX and moderate-DEX infusions (significant interaction effects, $P < 0.001$). SAP and DAP decreased significantly with low-DEX and moderate-DEX infusions (significant interaction effects, $P < 0.001$ and $P = 0.005$, respectively). SpO_2 and respiratory rate did not change significantly at any dose infusions. The OAA/S score decreased significantly with moderate-DEX (significant interaction effects, $P = 0.008$), whereas BIS did not change significantly at any dose infusions.

Group-averaged power spectral density and transfer function indices of beat-to-beat changes in SAP and RRI are presented in Fig. 1 and Table 2. The high-frequency power of SAP variability increased significantly with low-DEX and moderate-DEX (significant interaction effects, $P = 0.005$), whereas the high-frequency power of RRI variability (as an index of cardiac parasympathetic activity) did not change significantly. Transfer function gain in the high-frequency range (as an index of parasympathetic arterial-cardiac baroreflex) decreased significantly with low-DEX and moderate-DEX (significant interaction effects, $P = 0.007$). The values of all these indices were not significantly different between low-DEX and moderate-DEX infusions.

The low-frequency powers of SAP variability (as an index of sympathetic vasomotor activity) decreased significantly with low-DEX and moderate-DEX (significant interaction effects, $P < 0.001$). The low-frequency powers of RRI variability (as an index of cardiac sympatho-vagal activity) decreased significantly with moderate-DEX (significant interaction effects, $P = 0.021$). Transfer function gain in the low-frequency range (as an index of sympathetic and parasympathetic baroreflex) increased significantly with moderate-DEX compared with baseline (significant

Table 1 Steady-state hemodynamics and respiratory conditions

	Placebo		Low-DEX		Moderate-DEX	
	Baseline	Drug administration	Baseline	Drug administration	Baseline	Drug administration
HR (beats/min)	59 ± 2	58 ± 2	61 ± 1	53 ± 2*	60 ± 3	53 ± 2*
SAP (mmHg)	114 ± 3	117 ± 4	113 ± 3	98 ± 3*,#	117 ± 3	102 ± 3*,#
DAP (mmHg)	58 ± 1	62 ± 3	56 ± 1	51 ± 1#	61 ± 2	54 ± 2*,#
SpO_2 (%)	98 ± 0	98 ± 0	98 ± 0	97 ± 0	98 ± 0	97 ± 0
Resp-R (breath/min)	13 ± 1	13 ± 1	12 ± 1	13 ± 1	12 ± 1	14 ± 1
OAA/S score	4.8 ± 0.1	4.7 ± 0.2	4.8 ± 0.0	4.3 ± 0.3	4.8 ± 0.1	3.3 ± 0.2*,#,†
BIS	84 ± 2	86 ± 2	88 ± 1	84 ± 2	86 ± 3	78 ± 2

Values are means ± SEM

Low-DEX low-dose dexmedetomidine, *moderate-DEX* moderate-dose dexmedetomidine, *HR* heart rate, *SAP* systolic arterial pressure, *DAP* diastolic arterial pressure, *SpO_2* arterial oxygen saturation, *Resp-R* respiratory rate, *OAA/S* Observer's Assessment of Alertness/Sedation Score (*OAA/S score of 5* responds readily to name spoken in normal tone, *OAA/S score of 4* lethargic response to name spoken in normal tone, *OAA/S score of 3* responds only after name is called loudly and/or repeatedly), *BIS* bispectral index

*$P < 0.05$ (vs. each baseline), #$P < 0.05$ (vs. placebo in drug administration), †$P = 0.052$ (vs. low-DEX in drug administration)

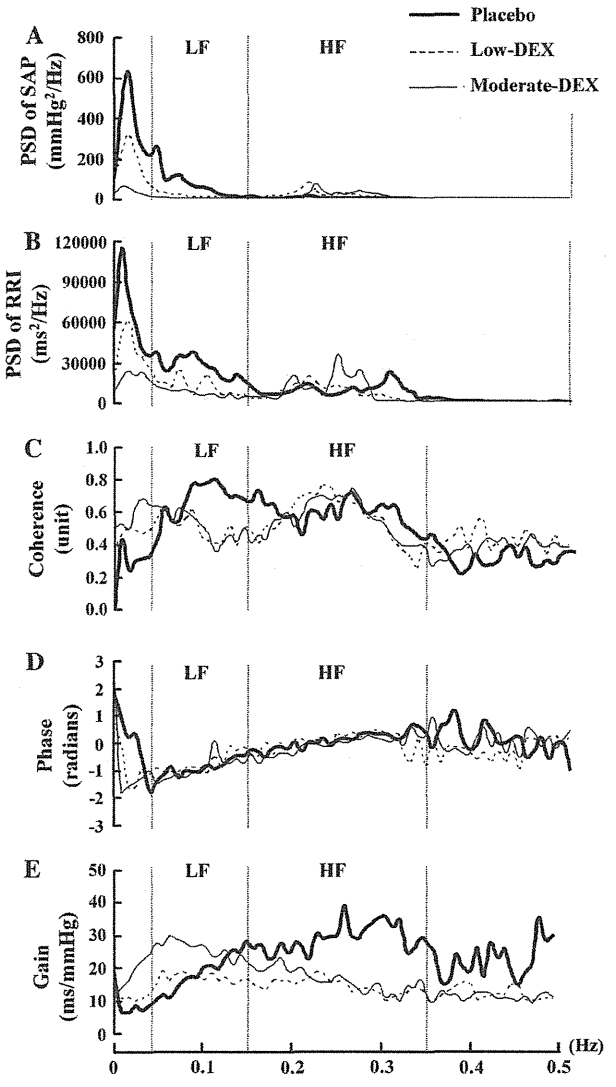

Fig. 1 Group-averaged power spectral density (PSD) and transfer function indices between systolic arterial pressure (SAP) and R-wave–R-wave interval (RRI) during administration of placebo and two doses of dexmedetomidine (DEX). **a** PSD of SAP. **b** PSD of RRI. **c** Coherence function. **d** Phase between SAP and RRI. **e** Transfer function gain between SAP and RRI. *LF* low-frequency range, *HF* high-frequency range. Placebo data (placebo), *thick line*; low-dose dexmedetomidine data (low-DEX), *dotted line*; moderate-dose dexmedetomidine data (moderate-DEX), *thin line*

main effect of time, $P = 0.027$). Coherence in the high- and low-frequency ranges was above 0.5 with all infusions, and phase in these frequency ranges did not change significantly at any dose infusions.

Discussion

The main findings of the present study were as follows: RRI variability in the high-frequency range (as an index of cardiac parasympathetic activity) remained unchanged despite increase in SAP variability with dexmedetomidine infusion. Then, transfer function gain in this range, representing the parasympathetic component of autonomic baroreflex regulation, decreased significantly with dexmedetomidine infusion. As expected, the present results suggest that dexmedetomidine attenuates parasympathetic arterial-cardiac baroreflex function.

In the previous studies, dexmedetomidine has been reported to weaken heart rate (HR) responses to 'rapid' reduction in arterial pressure resulting from thigh cuff deflation [9], but does not affect HR responses to 'gradual' reduction in arterial pressure induced by nitroprusside administration [4, 6]. This discrepancy may result from differences in the regulatory mechanisms responding to different speeds of reduction in arterial pressure. We therefore speculated that HR responses to 'rapid' reduction in arterial pressure would consist primarily of parasympathetic baroreflex.

In the present study, we used spectral and transfer function analysis between SAP variability and RRI variability to assess autonomic baroreflex regulation of the heart. RRI variability includes output signals of arterial-cardiac baroreflex [11, 24]. In other words, a change in SAP variability as input would influence estimation of RRI variability as output. In fact, both the low- and high-frequency powers of SAP variability changed significantly with dexmedetomidine infusions in the present study, possibly influencing RRI variability. To further understand the changes in autonomic circulatory control [11, 25], investigation of not only RRI variability but also SAP variability and transfer function between these two variables was applied in the present study. Transfer function analysis estimates the relationship between SAP variability as input and RRI variability as output, and transfer function gain between these two variables represents autonomic baroreflex regulation of the heart [11–14]. Moreover, transfer function analysis would be able to provide detailed information on autonomic baroreflex regulation by considering their frequency region: for example, the estimates of transfer function in the high-frequency range (0.15–0.35 Hz or 3–7 s) are primarily determined by parasympathetic modulation [11–14].

In the present results, RRI variability in the high-frequency range remained unchanged with dexmedetomidine infusion, suggesting unchanged cardiac parasympathetic activity. This result is consistent with previous reports that investigated the effects of dexmedetomidine on autonomic nervous activity assessed by spectral analysis of HR variability [6]. However, SAP variability in the high-frequency range (as input on the baroreflex arc) significantly increased with dexmedetomidine infusion. It is likely that dexmedetomidine induces capacitive vessel dilatation, leading to relative central hypovolemia.

Table 2 Autonomic nerve activity and arterial-cardiac baroreflex function

	Placebo		Low-DEX		Moderate-DEX	
	Baseline	Drug administration	Baseline	Drug administration	Baseline	Drug administration
HF_{SAP} ($mmHg^2$)	1.2 ± 0.2	1.1 ± 0.3	1.6 ± 0.3	3.9 ± 0.7*,#	1.4 ± 0.3	4.0 ± 0.7*,#
HF_{RRI} (ms^2)	1950 ± 813	2055 ± 1023	1235 ± 341	1567 ± 600	1937 ± 646	2088 ± 900
Gain-HF (ms/mmHg)	30.1 ± 5.7	29.2 ± 6.0	21.5 ± 2.7	14.5 ± 2.3*,#	29.0 ± 4.9	16.6 ± 3.8*,#
LF_{SAP} ($mmHg^2$)	6.7 ± 1.0	7.7 ± 1.4	5.5 ± 0.7	1.9 ± 0.7*,#	6.0 ± 1.0	0.6 ± 0.1*,#
LF_{RRI} (ms^2)	1592 ± 491	2856 ± 955*	983 ± 181	1291 ± 786#	1963 ± 508	932 ± 398*,#
Gain-LF (ms/mmHg)	15.3 ± 3.1	17.2 ± 3.1	12.2 ± 0.8	16.5 ± 1.4*	20.1 ± 4.4	26.0 ± 4.7*,†

Values are means ± SEM

Low-DEX low-dose dexmedetomidine, *Moderate-DEX* moderate-dose dexmedetomidine, HF_{SAP} power in high-frequency range of systolic arterial pressure variability, HF_{RRI} power in high-frequency range of R-wave–R-wave interval variability, *Gain-HF* transfer function gain in high-frequency range, LF_{SAP} power in low-frequency range of systolic arterial pressure variability, LF_{RRI} power in low-frequency range of R-wave–R-wave interval variability, *Gain-LF* transfer function gain in low-frequency range

*$P < 0.05$ (vs. each baseline), #$P < 0.05$ (vs. placebo in drug administration), †$P = 0.052$ (vs. low-DEX in drug administration)

Therefore, the increased SAP variability in this range would be caused by augmented effects of pleural pressure by respiration under the relative central hypovolemia. For precise interpretation of autonomic circulatory control as already stated, the present study also evaluated transfer function between these two variables. As expected, transfer function gain in the high-frequency range significantly decreased with dexmedetomidine infusions, suggesting attenuation of parasympathetic arterial-cardiac baroreflex function. Therefore, we consider that the attenuated parasympathetic baroreflex would weaken HR responses to rapid changes in arterial pressure, and this speculation is consistent with our previous report [9].

In the low-frequency range, SAP variability and RRI variability decreased significantly with dexmedetomidine infusions, suggesting diminished sympathetic vasomotor activity and cardiac sympatho-vagal activity. However, transfer function gain in this range, as an index of both sympathetic and parasympathetic arterial-cardiac baroreflex function, remained unchanged with low-dose dexmedetomidine or increased with moderate-dose dexmedetomidine infusions in the present study. This finding may imply augmentation of sympathetic baroreflex function, which has a relatively slow rate of neurotransmission [10], because of attenuation of parasympathetic baroreflex function as already stated. This dissociation between diminution of sympathetic vasomotor activity and maintenance of baroreflex function in the low-frequency range is consistent with the previous study, which reported decreased muscle sympathetic nerve activity and unchanged baroreflex function as estimated by vasoactive drug injection during clonidine administration [26]. Thus, there is a possibility that dexmedetomidine may have different effects on sympathetic and parasympathetic baroreflex regulation. The complex effects may relate to discrepant alterations of baroreflex function between previous studies [4, 6, 9].

Dexmedetomidine reportedly produces complex dose-dependent responses in the systemic circulation at a wide range of plasma concentrations (0.7–14.7 ng/ml) [4]. For example, HR and cardiac output decrease progressively with increasing concentrations of dexmedetomidine. Mean arterial pressure and vascular resistance show a biphasic dose–response relationship. Moreover, plasma levels of norepinephrine and epinephrine decreased substantially after the first dose and remained suppressed until high plasma concentrations of dexmedetomidine. In the present results, transfer function gain in the high-frequency range decreased with low-dose dexmedetomidine and remained at the same low-dose level even with moderate-dose dexmedetomidine. This change may be a similar type of dose-dependent response as plasma levels of catecholamines and does not indicate a simple linear dose-dependent response. Also, transfer function gain in the low-frequency range increased only with moderate-dose dexmedetomidine, implying a possible threshold for this alteration. The present study used low and moderate clinical doses of dexmedetomidine, probably equivalent to plasma concentrations of 0.3 and 0.6 ng/ml [15]. To provide a complete overview of dose-dependent effects of dexmedetomidine on autonomic baroreflex regulation, a wider range of infusion doses should be used in future studies.

The primary limitation of the present study is that autonomic circulatory control was estimated by the variable output of a complex system passing through a target organ, namely, the heart and arterioles. SAP variability and RRI variability are only indirect indices of autonomic nerve activity, being influenced by many other factors such as respiratory condition and reactivity of the heart and arterioles [27], although dexmedetomidine sedation produces little respiratory depression [28]. In addition, the steady-state changes in SAP or HR might affect the spontaneous arterial-cardiac baroreflex function, i.e.,

transfer function gain. Generally, the steady-state changes in SAP or HR lead to movement of the operating point on the static stimulus–response curve of the arterial-cardiac baroreflex, shift of static stimulus–response curve itself, or modification of the shape of the curve. Because SAP and HR in the present study decreased with dexmedetomidine infusions, some alteration of static stimulus–response relationship should occur. However, the present study cannot reveal which alterations of the static stimulus–response relationship occurred. Also, transfer function analysis cannot estimate the buffering capacity of the stimulus–response relationship. On the other hand, the transfer function analysis can show the dynamic properties of baroreflex function around the operating point. The gain (slope) around the operating point is dependent on the speed of changes in SAP, that is, the dynamic properties of baroreflex function. The present study revealed differences in dynamic properties of baroreflex function with speed of changes in SAP (gain-LF vs. gain-HF) during dexmedetomidine infusions.

The present protocol has limitations. In this study, no power analysis for baroreflex function indices was performed before the experiment because the present study was a follow-up analysis on our earlier article that investigated the effects of dexmedetomidine on cerebral circulation [15]. Because the sample size is small, there is a possibility that the present study could not show significant differences between low-DEX and moderate-DEX infusions (type II error).

In conclusion, the present study determined the effects of dexmedetomidine on arterial-cardiac baroreflex function assessed by spectral and transfer function analysis between SAP variability and RRI variability. Dexmedetomidine may have complex effects on autonomic circulatory control, but such effects would lead to simple attenuation of parasympathetic arterial-cardiac baroreflex function at low and moderate doses.

Acknowledgments Financial support for this work was partly provided by Hospira Japan K.K. (Osaka, Japan) and institutional funding.

References

1. Venn M, Newman J, Grounds M. A phase II study to evaluate the efficacy of dexmedetomidine for sedation in the medical intensive care unit. Intensive Care Med. 2003;29:201–7.
2. Kunisawa T, Nagashima M, Hanada S, Suzuki A, Takahata O, Iwasaki H. Awake intubation under sedation using target-controlled infusion of dexmedetomidine: five case reports. J Anesth. 2010;24:789–92.
3. Turan A, Sen H, Sizlan A, Yanarateş O, Ozkan S, Koyuncu O, Dağli G. Dexmedetomidine: an alternation for epidural anesthesia in tension-free vaginal-tape surgery. J Anesth. 2011;25:386–91.
4. Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colinco MD. The effects of increasing plasma concentrations of dexmedetomidine in humans. Anesthesiology. 2000;93:382–94.
5. Drew GM, Whiting SB. Evidence for two distinct types of postsynaptic alpha-adrenoceptor in vascular smooth muscle in vivo. Br J Anaesth. 1979;67:207–15.
6. Hogue CW Jr, Talke P, Stein PK, Richardson C, Domitrovich PP, Sessler DI. Autonomic nervous system responses during sedative infusions of dexmedetomidine. Anesthesiology. 2002;97:592–8.
7. Langer SZ. Presynaptic regulation of the release of catecholamines. Pharmacol Rev. 1981;32:337–61.
8. Unnerstall JR, Kopajtic TA, Kuhar MJ. Distribution of α_2 agonist binding sites in the rat and human central nervous system: analysis of some functional, autonomic correlates of the pharmacologic effects of clonidine and related adrenergic agents. Brain Res Rev. 1984;7:69–101.
9. Kato J, Ogawa Y, Kojima W, Aoki K, Ogawa S, Iwasaki K. Cardiovascular reflex responses to temporal reduction in arterial pressure during dexmedetomidine infusion: a double-blind, randomized and placebo-controlled study. Br J Anaesth. 2009;103:561–5.
10. Persson PB, Di Rienzo M, Castiglioni P, Cerutti C, Pagani M, Honzikova N, Akselrod S, Parati G. Time versus frequency domain techniques for assessing baroreflex sensitivity. J Hypertens. 2001;19:1699–705.
11. Iwasaki K, Zhang R, Perhonen MA, Zuckerman JH, Levine BD. Reduced baroreflex control of heart period after bed rest is normalized by acute plasma volume restoration. Am J Physiol Regul Integr Comp Physiol. 2004;287:R1256–62.
12. Saitoh T, Ogawa Y, Aoki K, Shibata S, Otsubo A, Kato J, Iwasaki K. Bell-shaped relationship between central blood volume and spontaneous baroreflex function. Auton Neurosci. 2008;143:46–52.
13. Saul JP, Berger RD, Albrecht P, Stein SP, Chen MH, Cohen RJ. Transfer function analysis of the circulation: unique insights into cardiovascular regulation. Am J Physiol. 1991;261:H1231–45.
14. Triedman JK, Cohen RJ, Saul JP. Mild hypovolemic stress alters autonomic modulation of heart rate. Hypertension. 1993;21:236–47.
15. Ogawa Y, Iwasaki K, Aoki K, Kojima W, Kato J, Ogawa S. Dexmedetomidine weakens dynamic cerebral autoregulation as assessed by transfer function analysis and the thigh cuff method. Anesthesiology. 2008;109:642–50.
16. Hall JE, Uhrich TD, Barney JA, Arain SR, Ebert TJ. Sedative, amnestic, and analgesic properties of small-dose dexmedetomidine infusions. Anesth Analg. 2000;90:699–705.
17. Arain SR, Ebert TJ. The efficacy, side effects, and recovery characteristics of dexmedetomidine versus propofol when used for intraoperative sedation. Anesth Analg. 2002;95:461–6.
18. Prielipp RC, Wall MH, Tobin JR, Groban L, Cannon MA, Fahey FH, Gage HD, Stump DA, James RL, Bennett J, Butterworth J. Dexmedetomidine-induced sedation in volunteers decreases regional and global cerebral blood flow. Anesth Analg. 2002;95:1052–9.
19. Chernik DA, Gillings D, Laine H, Hendler J, Silver JM, Davidson AB, Schwam EM, Siegel JL. Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: study with intravenous midazolam. J Clin Psychopharmacol. 1990;10:244–51.
20. Parati G, Saul JP, Di Rienzo M, Mancia G. Spectral analysis of blood pressure and heart rate variability in evaluating cardiovascular regulation. A critical appraisal. Hypertension. 1995;25:1276–86.
21. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate

variability: standards of measurement, physiological interpretation and clinical use. Circulation. 1996; 93:1043–65.
22. Dietrich A, Riese H, van Roon AM, van Engelen K, Ormel J, Neeleman J, Rosmalen JGM. Spontaneous baroreflex sensitivity in (pre)adolescents. J Hypertens. 2006;24:345–52.
23. Pinna GD, Maestri R. New criteria for estimating baroreflex sensitivity using the transfer function method. Med Biol Eng Comput. 2002;40:79–84.
24. Ogawa Y, Iwasaki K, Shibata S, Kato J, Ogawa S, Oi Y. Different effects on circulatory control during volatile induction and maintenance of anesthesia and total intravenous anesthesia: autonomic nervous activity and arterial cardiac baroreflex function evaluated by blood pressure and heart rate variability analysis. J Clin Anesth. 2006;18:87–95.
25. Introna R, Blair J, Martin DC. Measurement of the low-frequency component of blood pressure variability can assist the interpretation of heart rate variability data. Anesthesiology. 2003;99:237.
26. Muzi M, Goff DR, Kampine JP, Roerig DL, Ebert TJ. Clonidine reduces sympathetic activity but maintains baroreflex responses in normotensive humans. Anesthesiology. 1992;77:864–71.
27. Parati G, Di Rienzo M, Castiglioni P, Mancia G, Taylor JA, Studinger P. Point: counterpoint: cardiovascular variability is/is not an index of autonomic control of circulation. J Appl Physiol. 2006;101:676–82.
28. Belleville JP, Ward DS, Bloor BC, Maze M. Effects of intravenous dexmedetomidine in humans. I. Sedation, ventilation, and metabolic rate. Anesthesiology. 1992;77:1125–33.

20111801IB（資料）

第3次対がん総合戦略研究事業
「がん性疼痛患者のQOL向上のための橋渡し研究連携拠点の構築」

総合研究報告書（平成21～23年度）
(資料)

a) 試験実施計画書
b) 統計解析報告書
c) 付録－関連解析結果
d) 質問回答書
e) 翻訳