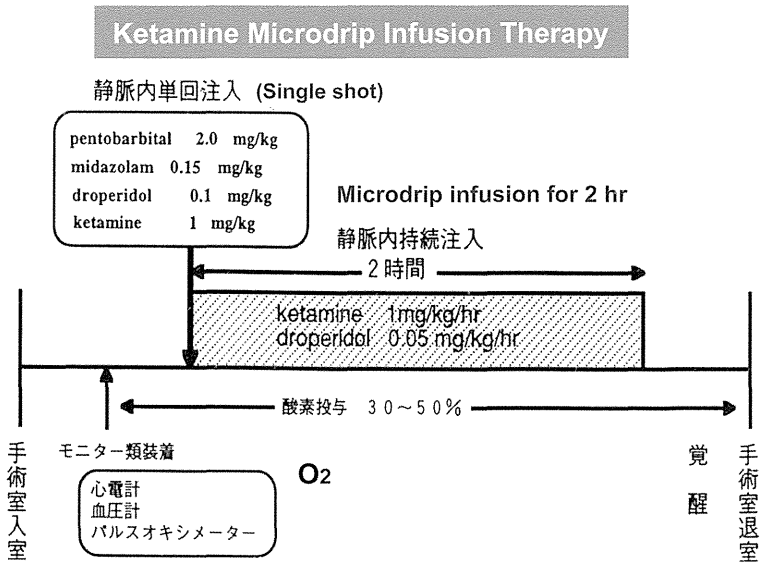

図5 われわれの行っているケタミン持続点滴療法

握において他の診断法と併用して試みるべき試験と考えられる。

神経障害性疼痛の治療[2,9]

神経障害性疼痛の機序がさまざまなので治療法もその機序に見合ったものが必要となる。病態によって適応される治療法は異なるが，現在行われている治療法は以下の通りと思われる。すなわち，① 薬物療法，② 神経ブロック療法，③ 神経刺激療法，④ 電気痙攣療法，⑤ 手術療法，⑥ ガンマナイフ治療，⑦ レーザー治療，⑧ リハビリテーション，⑨ そのほか，がある。

① 薬物療法

基本的な治療薬としては，三環系抗うつ薬とオピオイド系鎮痛薬が挙げられ国際的に認められてる。さらに抗けいれん薬，SSRI，抗不整脈薬，局所麻酔薬，そしてNMDA受容体拮抗薬が用いられている。

神経障害性疼痛の発生にはNMDA受容体を介した脊髄や中枢神経の過敏化が関与している場合があるので，この受容体拮抗薬による治療が行われる（図5）。静脈麻酔薬であるケタミンはこの受容体の非特異的拮抗薬であり，主に点滴静注，内服として用いられている。帯状疱疹後神経痛の患者さんにケタミン静注前後の脳のSPECT検査を行うと痛みの中継点とされる視床の血流が上昇し，痛みの緩和に寄与していると考えられている。

鎮咳剤のデキストロメトルファンもケタミンと同様な作用を持ち，経口投与ができるが，通常量では鎮痛効果はやや弱い。

その他の療法としては外用薬としてP物質枯渇薬のカプサイシンクリーム，高濃度リドカインゲルが用いられている。漢方薬や，循環改善を目的としたカルシウム拮抗薬なども用いられることがある。

図6にはFinnerupら[9]の示した神経障害性疼痛の薬物療法のアルゴリズムを示した。

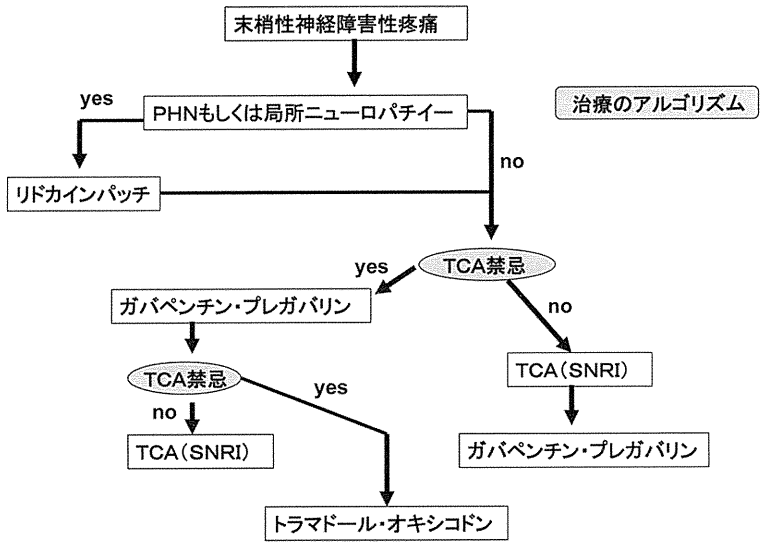

図6　Finnerup らによる神経障害性疼痛の薬物治療アルゴリズム（文献 9 より，著者作成）

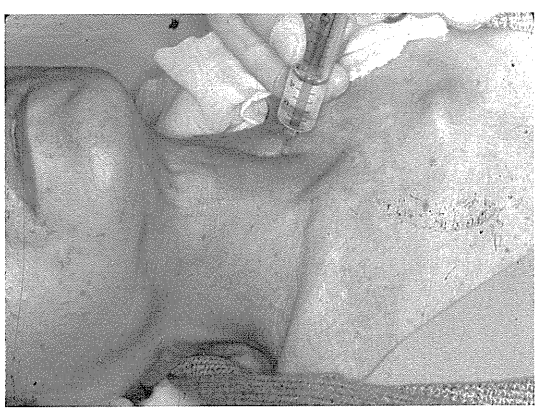

図7　星状神経節ブロック

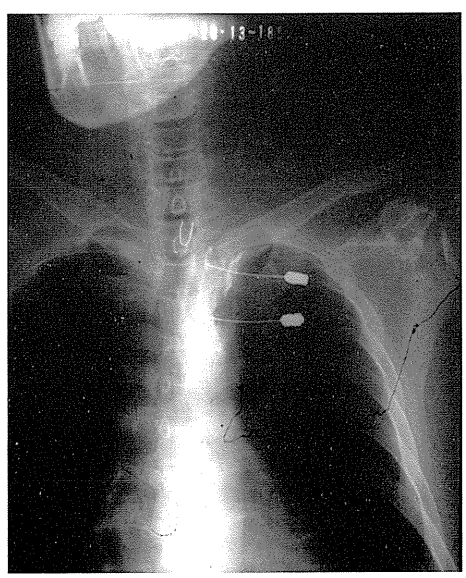

図8　胸部交感神経節ブロック

② 神経ブロック療法 [10)]

すべての神経障害性疼痛症例に交感神経が関与しているわけではないが，交感神経活動が関与しているような例，いわゆる交感神経依存性疼痛（sympathetically maintained pain: SMP）では交感神経ブロックが適応となる。SMP かどうかの診断には，局所麻酔薬を用いた試験的交感神経ブロックの効果をみるか，あるいは交感神経遮断薬のフェントラミンを少量静注して痛みが消えることを確認するテストで判別する。

頭・頸部，上肢の痛みには星状神経節ブロック（図7）か，あるいは胸部交感神経節ブロック（図8）が適応となる。最近では内視鏡的胸部交

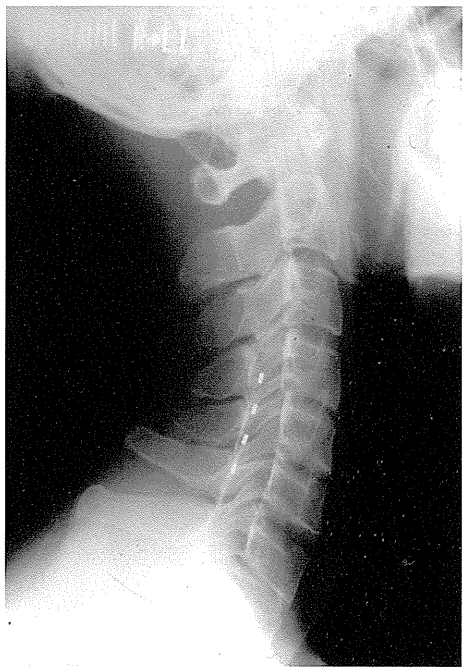

図9　上肢神経障害性疼痛に対する脊髄電気刺激療法

感神経幹焼灼術が行われている。躯幹では胸部交感神経ブロックを，下肢では腰部交感神経(節)ブロックを行う。

罹患神経が限局している場合には，局所麻酔薬を用いた神経根ブロックも奏効することがある。しかし，神経根ブロックに神経破壊薬を用いることは，新たな神経障害性疼痛の発生を起こす可能性があるため慎重でなければならない。

③ 神経刺激療法[11,12]

経皮神経刺激法（TENS）や，脊髄電気刺激法(図9)，脳深部刺激法が行われている。脊髄電気刺激法は，保険適応となっている。神経を破壊する他の方法を適応する前に試みてしかるべき方法と考えられる。

④ 電気痙攣療法[13]

電気痙攣療法は従来うつ病の治療に用いられてきたが，近年，求心路遮断性疼痛に有効であることが報告されてきた。本療法は視床機能を改善することで鎮痛効果を表すことが明らかになっている。

⑤ 手術療法[14]

古典的な方法の神経縫合術，神経剥離術，神経移行術，神経腫切除術，などのほか，脊髄後根進入部破壊術や生体内神経再生療法などが限られた症例に行われている。

⑥ ガンマナイフ療法[15]

ガンマナイフ療法は三叉神経痛に適応されてきた低侵襲な脳外科手術であるが，最近では視床症候群などの治療に用いられ，良好な効果をあげている。

⑦ 光線照射療法[16]

低反応レベルレーザーや，直線偏光近赤外線照射を患部や，星状神経近傍へ照射する方法が用いられている。低反応レベルレーザーの作用機序としては，血管拡張・血流増加作用，小口径神経線維における脱分極遮断作用，抗炎症作用，光生体刺激作用などが知られている。

⑧ 理学療法[17]

神経因性疼痛の治療の目的は身体機能の回復にあるので，理学療法は欠かすことができない。運動療法，温熱療法，マッサージなど，積極的に施行すべきである。ただ，疼痛部位を無理に動かすことが痛みをさらに悪化することがあるので，疼痛部位から離れた関節の可動性を

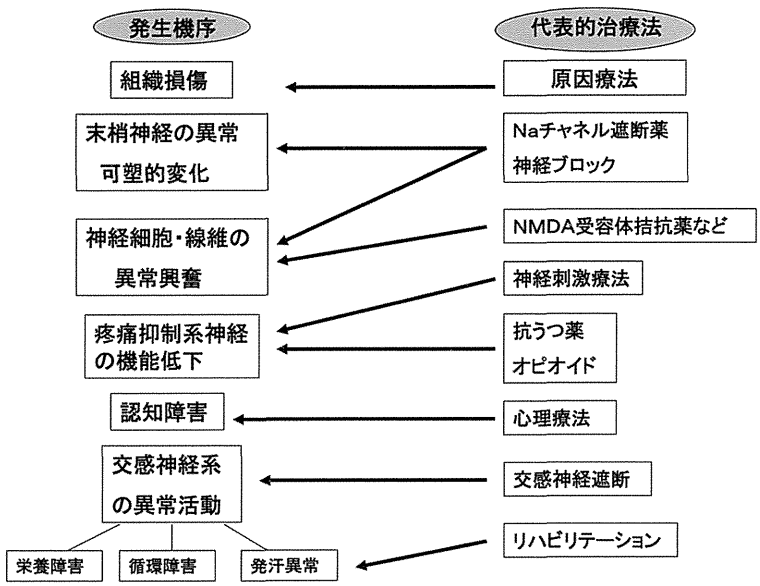

図10

修復するような方法が勧められている。

⑨ 鏡を用いた身体イメージの再形成 [18,19]

さて，「身体がそこにある」というイメージは，体性感覚と視覚を中心に，各種の感覚からの入力が脳内で統合されて形成されているが，この身体イメージが障害されると病的な痛みが出現することが知られている。

神経障害性疼痛の発生機序とそれに適応した代表的治療法を図10に示した。

以上，ペインクリニック診療における神経障害性疼痛の考え方，対処法につき俯瞰的に述べた。神経障害性疼痛へのグリア細胞の関与など基礎的研究が進められている。それらの研究結果が臨床に適応されて本症の治療がより進むことが念じられる。

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Pulse oximetric thresholds for tonsillectomy and adenotomy in children: significance of 1–2% decline in oxyhemoglobin saturation

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Summary

Objectives: We aimed to establish optimal overnight pulse oximetric thresholds for determining the indication of tonsillectomy and adenotomy (TA) in children by revising the definition of 'desaturation'.

Methods: One hundred and thirty four children scheduled for TA (TA group, 5.3 ± 1.4 years old) and 112 otherwise healthy children scheduled for elective minor surgery (control group, 5.4 ± 1.5 years old) were enrolled into this prospective study. Data were recorded and stored every 10 s using Nellcor N-395. Desaturation•resaturation events were defined as x% change (x = 1–4) of SpO_2 (oxyhemoglobin saturation by pulse oximetry) in 10 s. The desaturation•resaturation indices were calculated as events per hour of total sleeping time. For each index, a wide range of temporary thresholds was set. The optimal thresholds for TA were the ones that maximized the weighted average for sensitivity, specificity (based on whether the index improved or not after TA), and the percentage of the control children whose indices were below the threshold.

Results: For all the indices, the optimal thresholds that fulfilled the above condition were determined. Compared with the x = 3–4% results, the application of x = 1–2% approximately doubled the TA patients whose preoperative 'positive' indices improved after TA, with the weighted averages of 84.3–92.3% as described above.

Conclusions: By defining desaturation•resaturation as a 1–2% change in SpO_2 from the preceding value, children with adenotonsillar hypertrophy whose pulse oximetric indices are expected to improve after TA can be detected by pulse oximetry with relatively high sensitivity and specificity.

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Keywords: sleep-disordered breathing; children; adenotonsillectomy; pulse oximetry

Introduction

Sleep-disordered breathing (SDB) is a serious problem in children as well as in adults. The most common cause of childhood SDB is adenotonsillar hypertrophy. Although a gold standard test for SDB is polysomnography, overnight pulse oximetry is an attractive alternate as a single abbreviated diagnostic test for SDB because of its low cost and simplicity. A number of investigators have tried to establish pulse oximetric thresholds to diagnose SDB and adopted 2% (1–3), 3% (1,3–6), or 4% (1,3,4,7–12) change of SpO_2 (oxyhemoglobin saturation by pulse oximetry) as the desaturation criteria. But the thresholds set by those investigators have been found to have relatively low sensitivity•specificity in diagnosing mild SDB such as upper airway resistance syndrome (13,14), which is known to occur without a large decline in SpO_2 (14–16). As younger children are more likely to exhibit a SpO_2 decline over the same duration of apnea•hypopnea than older children and adults (16–18), we thought that slight SpO_2 decline during sleep might be detected more easily in young children with mild SDB.

In this study, we aimed to establish pulse oximetric criteria that could identify children with SDB whose sleep indices are expected to improve after TA, and also evaluated a progress of improvement of these indices shortly after TA. We configured various 'desaturation•resaturation' indices (1–4% SpO_2 decline•restoration in 10 s) and determined the optimal threshold for each index to maximize the weighted average for sensitivity (correct prediction of SDB), specificity (correct prediction of non-SDB), and the percentage of the control children whose indices were below the threshold.

Patients and methods

This study was approved by the ethical committee of the Osaka Medical Center and Research Institute for Maternal and Child Health. Informed written consent was obtained from the parents of all patients.

Patient recruitment

One hundred and thirty four otherwise healthy children (3–8 years old) scheduled for TA were enrolled in the TA group. A preoperative diagnosis of SDB was established by clinical signs such as snoring or apnea and the presence of adenotonsillar enlargement confirmed by direct and fiberoptic visual inspection. Parents were asked about the patients' snoring (habitual loud breathing during sleep) and apnea (cessation of breathing lasting two or more breath cycles) at the preoperative and postoperative out-patient clinic of otorhinolaryngology. None of them underwent polysomnograms to diagnose SDB, as our institute does not have a sleep laboratory.

As normal controls, 112 otherwise healthy 3–8 year old children scheduled for elective minor surgery were enrolled excluding those with snoring, palatine tonsils larger than grade I (19), or other potential factors of SDB (6,7). All the children were recruited consecutively.

Perioperative management for TA

In all the children, oral midazolam (0.5 mg•kg^{-1}, 10 mg at maximum) and famotidine (1 mg•kg^{-1}, 20 mg at maximum) were given 30 min before induction of anesthesia. Anesthesia was induced by inhalation of sevoflurane 5 to 7% and nitrous oxide 67% in oxygen, and maintained with 1.5 to 2.5% sevoflurane with nitrous oxide 67% in oxygen. Prior to incision, fentanyl 4 μg•kg^{-1} was administerd intravenously, and peritonsillar tissue was infiltrated with 0.5% lidocaine with 1:200000 epinephrine. The surgical method was a conventional method of adenotomy by using a Beckman adenotome followed by a conventional method of tonsillectomy by using a tonsillar stainless snare dissector. No opioids were administered in the postoperative course. For postoperative pain relief, rectal acetaminophen was administered. TA patients were usually discharged on five postoperative days, if they met the following discharge criteria: no bleeding, good oral intake, and no pain at rest.

Overnight pulse oximetry

Overnight measurement of SpO_2 with a pulse oximeter (N-395; Nellcor Puritan Benett, St Louis, MO, USA) was performed on the preoperative night in all patients and on the following 3 to 5 postoperative nights in TA patients. The moving averaging time of the oximeter was 5–7 s. The recording time was approximately from 9:00 PM to 6:00 AM. A probe was attached to a patient's toe, and ward nurses or accompanying parents recorded the time while the patient was asleep and the time while the patient was obviously awake. All signals including SpO_2, heart rate, and the patient's movement were stored in the oximeter every 10 s and downloaded to a personal computer using SCORE software 1.1a (Nellcor Puritan Benett).

Desaturation•resaturation events were defined as the changes in SpO_2 by x% (x = 1–4) from the preceding SpO_2 value. Excluding the data while the patients were awake, the following indices were calculated: desaturation index (DI); number of desaturation events per hour of total sleeping time, resaturation index (RI); number of resaturation events per hour of total sleeping time. Motion alerts were marked in the 'status' column of the SCORE data. For the calculation of the above indices, all the data with motion alerts were included.

Statistical analysis

In TA patients, improvement of the indices was assessed by comparing the frequency of desaturation•resaturation events on the preoperative night with those from an aggregate of the postoperative nights using chi-squared test (Microsoft Excel®; Microsoft Corporation, Redmond, WA, USA). If the minimum number of desaturation•resaturation events for comparison was less than 6, Fisher's exact test was employed instead using StatView® version 5.0 (SAS Institute Inc.; Cary, NC, USA). $P < 0.01$ was considered significant. All other statistical analyses including Mann–Whitney U-test, unpaired t-test and one-way ANOVA were carried out using StatView®.

Simulations to set the optimal thresholds for the indication of TA

For each DI and RI, the optimal threshold to determine the TA indication was established as described below. A temporary threshold was arbitrarily set at a certain point near zero, and the corresponding Se, Sp, Cc and the weighted average of Se, Sp and Cc were calculated as defined in Table 1. Then the next temporary threshold was set at the point which was a little higher than the previous threshold, and the corresponding Se, Sp, Cc and the weighted average of Se, Sp and Cc were calculated. This simulation was repeated to obtain the optimal threshold giving the maximum of the weighted average of Se, Sp and Cc for x%. If more than one optimal thresholds were found, the least threshold was chosen as the optimal.

Tonsillectomy and adenotomy patients whose preoperative DI or RI were higher than the optimal threshold determined as above were judged as SDB positive, and those whose preoperative DI and RI were lower than the threshold were judged as SDB negative. For each DI and RI, 'correctly predicted patients' were defined as the TA patients whose indices were judged as SDB positive preoperatively

Table 1
Definitions of the parameters

Se (sensitivity)	Percentage of patients whose indices improved after TA among the TA patients with preoperative indices above the threshold
Sp (specificity)	Percentage of patients whose indices did not improve after TA among the TA patients with preoperative indices below the threshold
Cc (specificity of control group)	Percentage of children whose indices were below the threshold in the control group
Weighted average of Se, Sp, and Cc	Se • (number of TA patients with preoperative indices above the threshold) + Sp • (number of TA patients with preoperative indices below the threshold) + Cc • (number of children in the control group)•total number of children in the TA group and the control group

TA, tonsillectomy and adenotomy.

and improved after TA, and the proportion of 'correctly predicted patients' were compared among each DI and RI.

Results

The control group consisted of 61 males and 51 females (5.4 ± 1.5 years old, mean ± SD). TA group consisted of 102 males and 32 females (5.3 ± 1.4 years old, mean ± SD). There was no statistical difference in age between the two groups ($P > 0.05$, Mann–Whitney U-test). The most common indication for TA was suspected SDB (n = 111). Ninety one out of the 111 children were observed to have apnea and 110 children had snoring. Another indication for TA was recurrent tonsillitis (n = 23), but we could not deny the possible mild SDB in these children. No oxygen was administered in the postoperative period, and no children experienced any respiratory morbidity in the postoperative period.

Data points with motion alerts accounted for 9.67 ± 5.60% (mean ± SD) of total sleeping time. The demographics of the patients along with the relevant pulse oximetric indices are summarized in Table 2.

As for DI and RI (x = 1–4%), preoperative data in the control group and the pre- and postoperative data of DI and RI in the TA group were depicted in Figure 1. For all the indices, TA preoperative value was higher than the control value and improved after TA. DI_1 and RI_1 gradually decreased day by day, whereas the other indices (DI_{2-4} and RI_{2-4}) decreased immediately after TA. The results of the simulations to set the optimal thresholds for DI and RI are shown in Figure 2.

Table 3 summarizes the set optimal thresholds, the corresponding Se, Sp, Cc values and the proportion of 'correctly predicted' patients. Though the weighted averages of Se, Sp and Cc at x = 1 were relatively low (84.3–85.1%) compared to x = 2–4 (91.9–97.2%), the proportion of 'correctly predicted' patients was the highest at x = 1 and gradually decreased as x increased. While 45 out of 134 patients (33.6%) were 'correctly predicted' by a threshold of $DI_1 = 40\ h^{-1}$, only 16 out of 134 patients (11.9%) were 'correctly predicted' by a threshold of $DI_4 = 1.1\ h^{-1}$.

Table 2
Demographics of the patients

Group	Control	TA (recurrent tonsillitis)	TA (SDB)
n	112	23	111
4% desaturation events (h^{-1})	0.07 ± 0.13	0.37 ± 0.80	1.56 ± 5.05
SpO_2 nadir (%)	93.9 ± 2.1	92.8 ± 3.9	90.0 ± 7.1
SpO_2 <95% time (%)	0.12 ± 0.29	0.56 ± 1.77	4.67 ± 13.34
SpO_2 <90% time (%)	0.00 ± 0.01	0.06 ± 0.19	0.95 ± 4.04

TA, tonsillectomy and adenotomy; SDB, sleep-disordered breathing.

The relationship between clinical signs (witnessed apnea and snoring) before TA and the judgment of the preoperative index by the set thresholds are shown in Figure 3. The concordance rate was calculated by: number of patients with preoperative positive SDB signs and positive pulse oximetric judgment + number of patients with preoperative negative SDB signs and negative pulse oximetric judgment •total number of TA group patients.

Discussion

In this study, we found that the overnight pulse oximetry is useful to predict whether an SDB-suspected child with adenotonsillar hypertrophy will benefit from TA or not by using DI and RI (x = 1–4%). The application of x = 1–2% to DI and RI detects more patients who will benefit from TA in the immediate postoperative period, while the application of x = 3–4% to DI and RI detects less patients who will benefit from TA.

One to two % desaturation •resaturation criteria are useful in determining the indication of TA in children

Many investigators have tried to set an overnight pulse oximetric threshold to diagnose SDB in children as well as in adults for abbreviated testing (9,10). Consistent with adult polysomnographic criterion, many investigators had adopted 3 or 4% as desaturation (1,3,5–12). This was partly because the optimal agreement with polysomnography was found to be 3% oxygen desaturation level (20). It was also partly because the error ranges of new generation pulse oximeters were ±2–3%, leading desaturation criterion to be set above 2–3% (21). Some reports had adopted 'a 2% decline from the baseline' as a criterion for desaturation (1–3). Olson et al. (22) had adopted 1%, 2%, and 3% as desaturation criteria for calculating oxygen desaturation

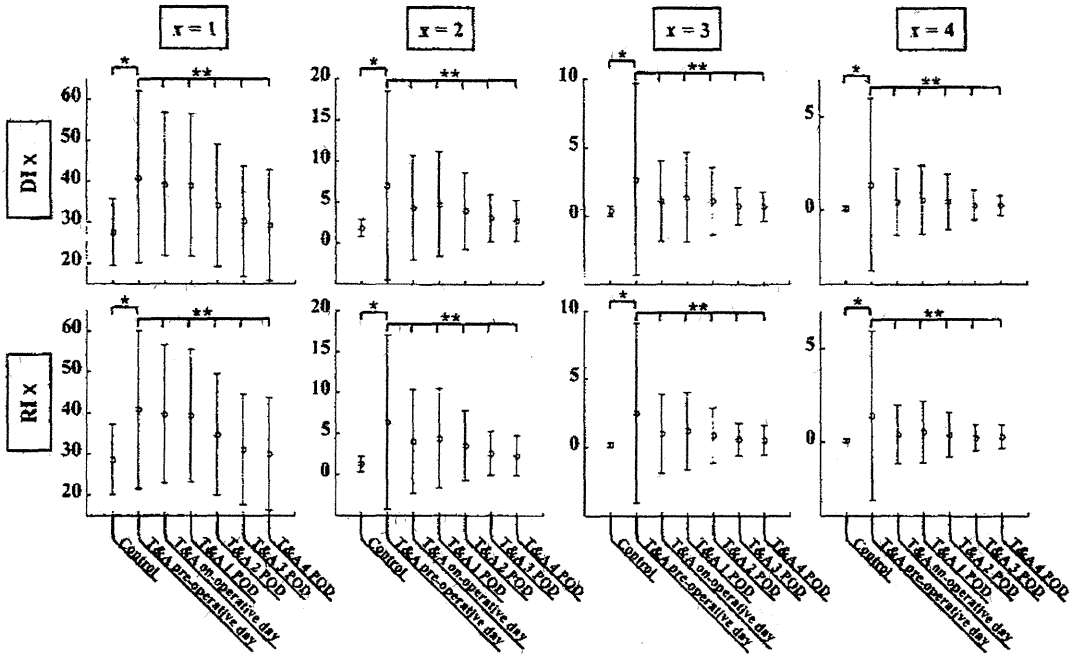

Figure 1
Preoperative desaturation index (DI) and resaturation index (RI) in the control group and the pre- and postoperative DI and RI in the tonsillectomy and adenotomy (TA) group. Data were depicted as mean (open circles) ±SD (bars). For all the indices, TA preoperative value was higher than the control value ($P < 0.01$, unpaired t-test) and all the indices of TA group improved after TA ($P < 0.01$, one-way ANOVA). DI_1 and RI_1 gradually decreased day by day, whereas the other indices decreased immediately after TA. *$P < 0.01$ (unpaired t-test), **$P < 0.01$ (one-way ANOVA), POD; postoperative day

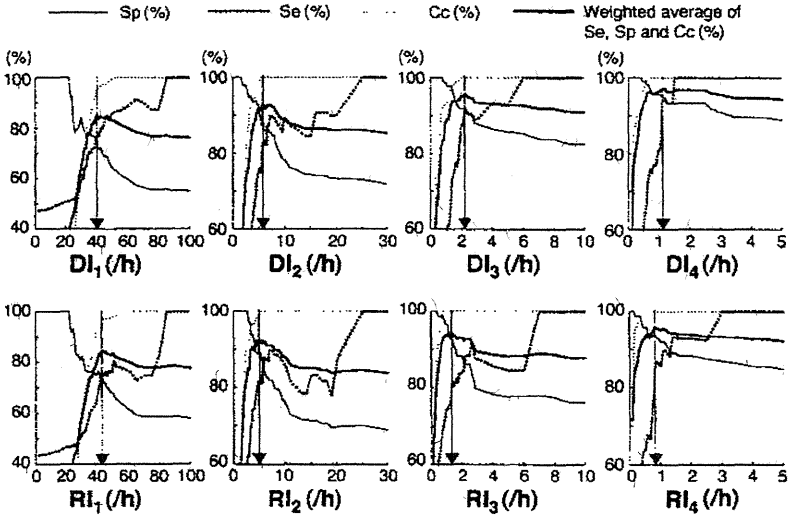

Figure 2
Se, Sp, and Cc and the weighted average of Se, Sp, and Cc at various consecutive temporary thresholds of DI and RI. The optimal thresholds are indicated by vertical arrows. Se, sensitivity; Sp, specificity; Cc, specificity of control group; DI, desaturation index; RI, resaturation index.

indices, but they established no criteria for detecting SDB.

We argue that although the absolute error of the oximeter may be ±2–3%, relative changes of 1–2% in continuous SpO_2 measurement with 5–7 s of moving averaging time may reflect real changes in arterial oxyhemoglobin saturation, as long as the probe is appropriately attached and the oximeter is functioning properly. In the current study, we investigated if subtle (1–2%) changes in SpO_2 could be employed as

Table 3
Result of the simulation to determine the optimal pulse oximetric thresholds for the indication of tonsillectomy and adenotomy in children

Index	DI1	RI1	DI2	RI2	DI3	RI3	DI4	RI4
Set threshold (h^{-1})	40	43	6	5	2.2	1.4	1.1	0.85
Se (%)	78.9	76.6	83.3	81.4	91.3	81.6	94.1	87
Sp (%)	74.7	73	87	88.2	92	92.9	95	93.8
Cc (%)	95.5	96.4	100	99.1	100	100	100	100
Weighted average of Se, Sp, and Cc (%)	85.1	84.3	92.3	91.9	95.6	94.4	97.2	96
Proportion of 'correctly predicted patients' (%)	33.6	26.9	22.4	26.1	15.7	23.1	11.9	14.9

Se, sensitivity; Sp, specificity; Cc, specificity of control group.

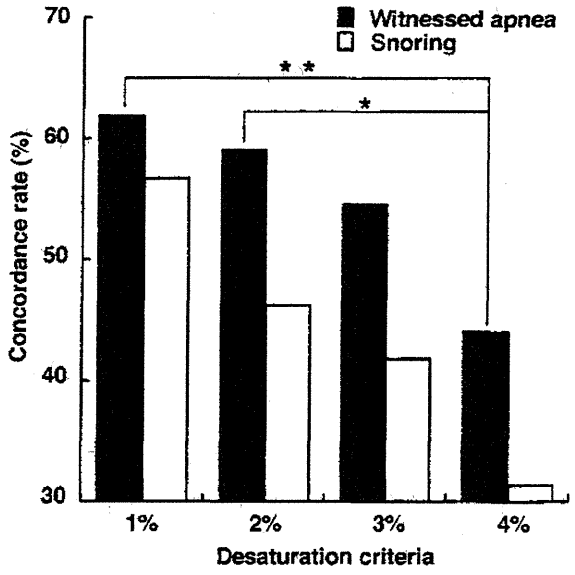

Figure 3
The concordance rates between preoperative signs and the preoperative pulse oximetric judgment. Preoperative pulse oximetric data were judged as positive if either desaturation index or resaturation index exceeded the set threshold. The concordance rate was calculated as: number of patients with preoperative positive signs and positive pulse oximetric judgment + number of patients with preoperative negative signs and negative pulse oximetric judgment ÷ total number of TA group patients. *P < 0.05, **P < 0.01 (chi-squared test).

desaturation ·resaturation criteria, and found that 1–2% desaturation ·resaturation criteria were useful to identify the patients whose pulse oximetric indices improved in the immediate post-TA period.

Setting the thresholds for the indication of TA

There are few criteria to determine whether children with SDB because of adenotonsillar hypertrophy resolve their parameters after TA (4,13). In this study, we determined the optimal pulse oximetric threshold that maximized the weighted average of sensitivity, specificity (based on whether the index statistically improved or not after TA) and the percentage of the control children whose indices were below the threshold.

As shown in Table 3, the proportion of 'correctly predicted' patients were only 11.9–23.1% at x = 3 and x = 4, whereas 22.4–33.6% of the patients were 'correctly predicted' at x = 1 and x = 2. And as shown in Figure 3, the concordance rate between the preoperative parent-notified apneic events with abnormal preoperative pulse-oximetric judgment was the highest at x = 1. These results may suggest that the thresholds at x = 1–2 predict more patients who will benefit from TA.

Desaturation ·resaturation indices at x = 1% gradually decreased day by day after TA

By using our method of overnight pulse oximetry, the effect of the operation can be tracked conveniently and objectively. We have shown that an objective index of SDB gradually decreased day by day after TA (Figure 1). After TA, it may take several days for the surgery-induced edema of the upper airway to subside, and it may also take several days for the child to adapt to the spacial change of the upper airway, probably explaining why DI_1 and RI_1 gradually decreased day by day after TA.

Limitation of the current study

We acknowledge that there are some limitations in our current study. First, we did not perform full polysomnography, therefore we cannot validate each desaturation event as a real apneic ·hypopneic episode. Second, different oximeters, different

averaging times, and different sampling intervals may record different values during a single desaturation event (11,23). As our study utilized Nellcor N-395 with an averaging time of 5–7 s and sampling interval of 10 s, our indices along with its thresholds can be applied only to this condition. A different threshold may be set with different brand oximeters and different sampling conditions (11).

Conclusion

This is the first reported overnight pulse oximetric study which determined the thresholds for the indication of TA in children based on whether the patients' indices improved or not after TA in the immediate postoperative period. Our 1–2% desaturation•resaturation criteria can conveniently detect more children whose pulse oximetric indices are expected to improve after TA than traditional 3–4% desaturation•resaturation criteria.

Acknowledgements

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A Comparison of the Effects on Respiratory Carbon Dioxide Response, Arterial Blood Pressure, and Heart Rate of Dexmedetomidine, Propofol, and Midazolam in Sevoflurane-Anesthetized Rabbits

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BACKGROUND: Dexmedetomidine, propofol, and midazolam are commonly used sedative-hypnotic drugs. Using a steady-state method, we examined the CO_2 ventilatory response, mean arterial blood pressure (MAP) and heart rate (HR) effects of these three drugs in sevoflurane-anesthetized rabbits.

METHODS: New Zealand white rabbits weighing 2.9 ± 0.2 kg (mean ± SD) were used. After anesthetic induction and tracheostomy, the animals inhaled 2% sevoflurane to ensure a stable level of sedation throughout the experiment. After preparation, the rabbits were randomly assigned to four groups ($n = 10 \times 4$) and received the following drugs: Group C, control; Group D, dexmedetomidine infused at 2 $\mu g \cdot kg^{-1} \cdot h^{-1}$; Group P, propofol with the plasma concentration maintained at 15 $\mu g/mL$; Group M, midazolam initial IV 0.3 mg/kg bolus dose, followed by infusion at 1.86 $mg \cdot kg^{-1} \cdot h^{-1}$. At 15 minutes after the start of infusion, for 20 min periods, in random sequences, gas including 0%, 1%, 2%, 3%, 4%, or 5% of CO_2 was delivered to each animal. Fraction of inspired oxygen was maintained at 0.9. We did intergroup comparisons of minute ventilation (MV), respiratory rate, MAP, and HR during the final minute of each inspiratory carbon dioxide concentration ($FiCO_2$) period.

RESULTS: For Groups P and M, the rightward shift of plots for MV against $FiCO_2$ indicated significant respiratory depression compared with Group C. There was also significantly more depression than in Group D. We found no significant differences between Groups P and M or between Groups C and D in the plots of MV against $FiCO_2$. No significant differences among the four groups were apparent for respiratory rate. $Paco_2$-MV response plots were derived from linear regression analysis of data for mean MV and mean $Paco_2$ at each $FiCO_2$ to compute apneic CO_2 thresholds and CO_2 sensitivities. The apneic CO_2 thresholds of Groups P and M were larger than those of Groups C and D. The CO_2 sensitivities of Group D were slightly lower than in Group C. No similar significant difference between the CO_2 sensitivities of other group pairs was apparent. MAP in Group D was lower than in Groups C and M. In Group D, HR was lower than in Groups C, P, and M.

CONCLUSIONS: The major finding is that, during sevoflurane anesthesia in rabbits, dexmedetomidine slightly altered the ventilatory response to CO_2. It decreased MAP more than propofol and midazolam, which both significantly depressed the ventilatory response to CO_2.

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Propofol, midazolam, and dexmedetomidine are often used to achieve satisfactory sedation for critically ill intensive care unit patients.[1] Although several human and animal studies have presented evidence that each of the three commonly used sedatives cause respiratory depression,[2–8] no direct comparison of the respiratory depression associated with dexmedetomidine, propofol, and midazolam had previously been performed.

Knowing that CO_2 ventilatory response is affected by many factors, such as hypoxia, exercise, state of wakefulness, sleep, or anesthesia,[9] in the groups under comparison, we aimed to maintain a uniform level of anesthesia, which has varied in previous reports for dexmedetomidine.[7,8,10] To clarify the depressive effects on respiration, we designed a steady-state protocol using a sevoflurane-anesthetized rabbit model to examine and the different effects of dexmedetomidine,

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propofol, and midazolam on mean arterial blood pressure (MAP) and heart rate (HR) and how each drug affects ventilatory responses to CO_2.

METHODS

The Laboratory Investigation Committee of Osaka University Medical School approved this study. Animals were cared for in accordance with the University's standards for care and use of laboratory animals.

Animal Preparation

Forty adult New Zealand white rabbits weighing 2.9 ± 0.2 kg (mean ± SD) were used. After a marginal ear vein was cannulated, anesthesia was induced by administering 3%–5% sevoflurane in 4 L/min of 100% oxygen through a facemask. When the corneal reflex was depressed, the animals were placed in a supine position on a heating pad. After infiltration of 1% lidocaine (1–2 mL), tracheostomy was performed. A 3.5 mm (body weight <3.0 kg) or 4.0 mm (body weight >3.0 kg) inner diameter endotracheal tube was inserted into the trachea. The tube was connected to a heat-moisture exchanger (Pneumoist PMH+N, TKB International, Costa Mesa, CA) and a pneumotachograph (Hans Rudolph, Kansas City, MO) which, to measure respiratory flow, was connected to a differential pressure transducer (TP-602T, ±5 cm H_2O, Nihon Kohden, Tokyo, Japan). To measure inspiratory carbon dioxide concentration ($FiCO_2$), fraction of inspired oxygen, and concentration of sevoflurane, inspiratory gas was sampled with an anesthesia gas monitor (Capnomac Ultima; GE Healthcare, Buckinghamshire, UK). The right internal carotid artery was cannulated with a 20-gauge catheter to measure MAP. Blood samples were later aspirated through this carotid arterial line and measured with a blood gas analyzer (ABL505, Radiometer, Copenhagen, Denmark). Respiratory-flow wave and arterial-pressure wave signals were amplified (AP-641G, AR-601G, Nihon Kohden, Tokyo, Japan) and recorded to a computer at a sampling rate of 100 Hz using an analog-digital converter (DI-220, Dataq Instruments, Akron, OH) and data acquisition software (WinDaq, Dataq Instruments, Akron, OH). Each animal received lactate Ringer's solution at 8 $mL \cdot kg^{-1} \cdot h^{-1}$ through the venous line and a normal saline solution, including 4 U/mL heparin at 2 mL/h through the arterial line. To maintain the animal's body temperature at 39°C, body temperature was monitored rectally (Mon-a-therm/Model 6510, Mallinckrodt Medical, St. Louis, MO) and through the heating pad. Measuring devices were calibrated before each experiment.

Experimental Protocol

Throughout the experiment, to ensure a stable level of anesthesia, the animals inhaled 2% sevoflurane, which suppressed any voluntary movement of the extremities while maintaining stable conditions for respiration and circulation. After inhalation for 1 h to stabilize anesthesia, each rabbit was randomly assigned, according to the drug administered, to one of four groups of 10 animals: control group Group C, distilled water; Group D, dexmedetomidine infused at 2 $\mu g \cdot kg^{-1} \cdot h^{-1}$; Group P, propofol emulsion, which was administered using target-controlled infusion simulation software (Rugloop simulation software, Version 3.28, University Hospital Ghent, Belgium) to control propofol-in-plasma concentration at 15 $\mu g/mL$ (actual administration was bolus 3.4 mg/kg within 30 s followed by infusion at between 30 to 50 $mg \cdot kg^{-1} \cdot h^{-1}$); and Group M, midazolam administered as an initial bolus dose of 0.3 mg/kg IV, followed by infusion at 1.86 $mg \cdot kg^{-1} \cdot h^{-1}$. Throughout the experiment, all animals were allowed to breathe spontaneously. At 15 minutes after the start of the infusion, gas including 0%, 1%, 2%, 3%, 4%, or 5% of CO_2 was delivered to each animal in a random sequence of 20-min periods. Fraction of inspired oxygen was maintained throughout at 0.9. The absence of any further increase of end-tidal CO_2 and respiratory rate (RR) was taken as confirmation of the achievement of steady-state.

Baseline data were recorded just before the beginning of the drug infusion and respiratory-flow waves and arterial-pressure waves were recorded, and arterial blood gases were measured during the final minute of each $FiCO_2$ period. Immediately after sampling, each sample was stored at −70°C for later analysis. For six Group P animals, the plasma concentration of propofol was measured using high performance liquid chromatography. For six Group M animals, the plasma concentration of midazolam was similarly measured using high performance liquid chromatography.

Data Analysis

Wave form analysis software (WinDaq playback, Dataq Instruments, Akron, OH) was used for analyzing the stored data. Minute ventilation (MV) and RR were calculated from the recorded respiratory wave forms. MAP and HR were calculated from the recorded arterial-pressure wave forms. All results are expressed as mean ± SD.

Plotting the $Paco_2$-MV response has proven useful for assessing respiratory depression caused by drugs.[9,11] Linear regression analysis was performed from data for mean MV and mean $Paco_2$ during each $FiCO_2$ period. The relationship between MV and $Paco_2$ is expressed by the following formula[9]:

$$MV = S \times Paco_2 + K$$

Changes in the $Paco_2$-MV response plot are characterized by changes in the X intercept ($-K/S$) and changes in slope (S). The X intercept is derived by extrapolating the $Paco_2$-MV response plot line to zero ventilation and represents the apneic CO_2 threshold of the respiratory center.[9,12] When the X intercept value

increases, there is a means rightward displacement of the $Paco_2$-MV response plot, which indicates respiratory depression. The $Paco_2$-MV response slope indexes the CO_2 sensitivity of the respiratory system: the lower the slope value, the less the CO_2 sensitivity and the greater the respiratory depression.

Statistical analyses were performed using statistical software (SPSS 13.0, SPSS, Chicago, IL). Repeated analysis of variance was applied for group comparisons, followed by a Tukey honestly significant difference test for *post hoc* analysis. Using linear regression analysis data, $Paco_2$-ventilatory response was plotted from the data for mean MV and mean $Paco_2$ during each $FiCO_2$ period. Differences among the regression plots of each drug were checked by analysis of covariance. $P < 0.05$ was considered statistically significant.

RESULTS

We found no statistically significant differences among the four groups in the baseline data of body weight, MV, RR, MAP, HR, and blood gas data (data not shown). $Paco_2$ at the baseline of all the animals was 32.8 ± 5.3 mm Hg. Neither were any statistically significant differences apparent in the measured plasma concentrations of propofol or midazolam at each $FiCO_2$ setting; mean plasma concentrations in the samples from six animals of the relevant groups were propofol 12.6 ± 2.7 μg/mL and midazolam 717.4 ± 115.6 ng/mL.

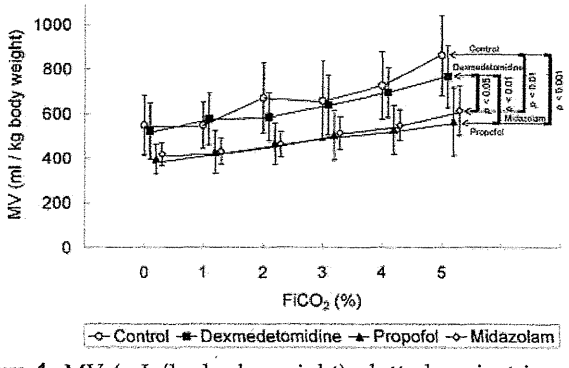

Figure 1. MV (mL/kg body weight) plotted against inspiratory carbon dioxide concentration ($FiCO_2$); MV = minute ventilation.

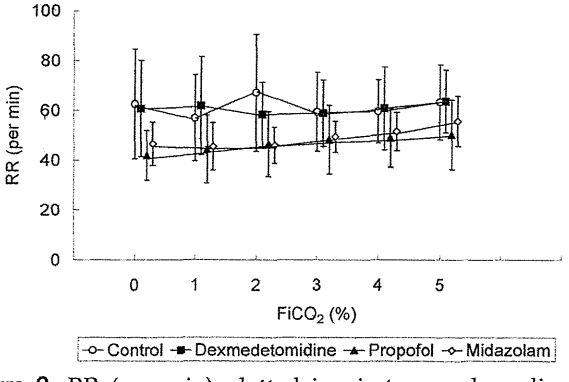

Figure 2. RR (per min) plotted inspiratory carbon dioxide concentration ($FiCO_2$); RR = respiratory rate.

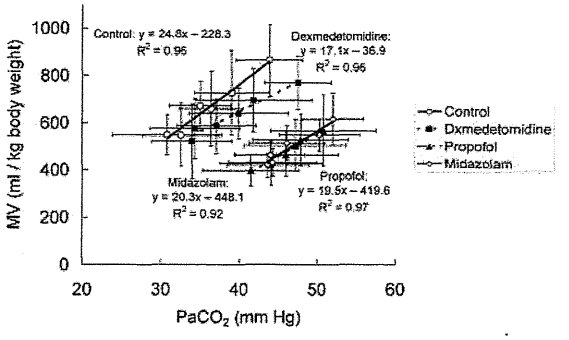

Figure 3. $Paco_2$-MV response curves. Linear regression analysis data were plotted for mean MV and mean $Paco_2$ during each $FiCO_2$ period. MV = minute ventilation.

Plots of MV (mL/kg body weight) against $FiCO_2$ in Groups P and M show that MV was statistically significantly lower than in Groups C and D (Fig. 1). Analyzing MV plotted against $FiCO_2$, we found no statistically significant differences between Groups P and M or between Groups C and D. Figure 2 shows the relationship of RR to $FiCO_2$ for each of the groups. We found no statistically significant differences for RR among any of the four groups.

Plots for $Paco_2$-MV response were derived from linear regression analysis data for mean MV and mean $Paco_2$ during each $FiCO_2$ period (Fig. 3). Table 1 shows the slope (S) and X intercept (K/S) findings of the linear regression lines. The slope values (CO_2 sensitivity) for Group D were statistically significantly lower than that for Group C ($P < 0.05$). No similar statistically significant differences between the slope values of the other group pairs was apparent. The X intercepts (apneic CO_2 threshold) of Groups P and M were larger than those of Groups C and D ($P < 0.001$); our results revealed that greater respiratory depression is associated with propofol and midazolam.

Figure 4 shows MAP plotted against $FiCO_2$. In Group D, MAP was statistically significantly lower than in Groups C and M. As Figure 5 shows, across $FiCO_2$ levels, HR for Group D was statistically significantly lower than for Groups C, P, and M.

DISCUSSION

Our major findings are that dexmedetomidine produces less ventilatory depression but more hypotension and reduction of HR than propofol or midazolam in a sevoflurane-anesthesia rabbit model. Although ventilatory depression was greater with propofol and midazolam than with sevoflurane anesthesia alone, there was much less ventilatory depression when dexmedetomidine was added to sevoflurane.

Previous studies have shown that dexmedetomidine produces relatively mild respiratory depression and our results are in line with the findings of those studies.[7,8,10] We found that dexmedetomidine, producing a $Paco_2$-MV response plot with a slope (CO_2

Table 1. Slope (S) and X Intercepts ($-K/S$) of $Paco_2$-MV Response Curves

	Control	Dexmedetomidine	Propofol	Midazolam
Slope (S) (mL · kg BW^{-1} · mm Hg^{-1})	24.8	17.1*	19.5	20.3
X intercept ($-K/S$) (mm Hg)	9.21	2.18	21.52*†	22.07*†

The equation MV (mL/kg body weight) = $S \times Paco_2 + K$ is derived from linear-regression analysis of the results shown in Figure 3. The X intercepts ($-K/S$) are derived by extrapolating the $Paco_2$-MV plot line to zero ventilation and mark the apneic CO_2 threshold of the respiratory center. The slopes of $Paco_2$-MV response curves (S) show the CO_2 sensitivity of the respiratory system.

MV = minute ventilation.

*$P < 0.05$ compared with control.

†$P < 0.05$ compared with dexmedetomidine group.

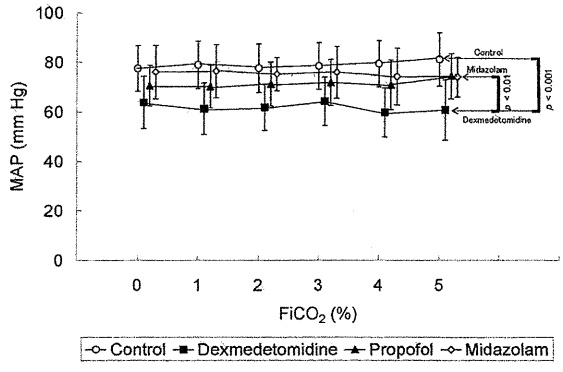

Figure 4. MAP plotted against inspiratory carbon dioxide concentration ($FiCO_2$). MAP = mean arterial blood pressure.

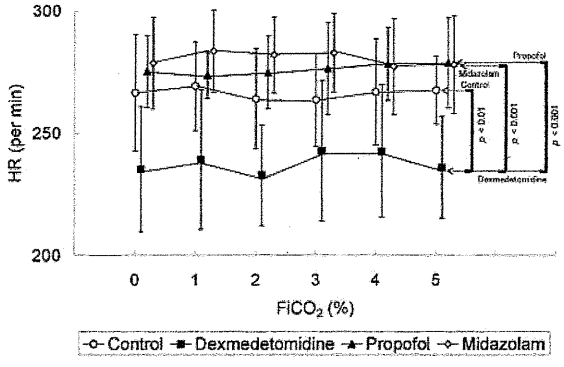

Figure 5. HR plotted against inspiratory carbon dioxide concentration ($FiCO_2$). HR = heart rate.

sensitivity) only slightly different than the control, had little effect on the X intercept (apneic CO_2 threshold). In a rabbit rebreathing model, Nishida et al.[10] found that administration of dexmedetomidine did not change CO_2 sensitivity. Our differing results reflect a different state of wakefulness and different method of measurement. Even in the absence of CO_2 inhalation, the Nishida et al. study showed wide RR variation, ranging from 80 to 200 breaths/min. This variation might have obscured any changes in the character of the CO_2 sensitivity. In addition, there are two methods for estimating the ventilatory response to CO_2: the rebreathing method and the steady-state method. The CO_2 sensitivities obtained with the rebreathing method are generally greater than those obtained with the steady-state method.[13–15] In two studies, one of well-trained dogs[7] and the other of humans,[8] bolus dexmedetomidine had an effect on the CO_2 sensitivity similar to that in the present study. In the human study, dexmedetomidine was also associated with minor increases in the apneic CO_2 threshold, which the authors speculated was affected by variations in sedation and sleep status.[8] In the present study, because we maintained a uniform state of anesthesia through all the settings, the apneic CO_2 threshold may have been little affected by dexmedetomidine.

Because the apneic CO_2 thresholds for Groups P and M were larger than those of Groups C and D, our results revealed that greater respiratory depression is associated with propofol and midazolam. Although previous studies have similarly shown that propofol and midazolam produce respiratory depression, reports of the effects of sedatives on the $Paco_2$-MV response plot are still confusing. For example, administration of diazepam is reported to shift the apneic CO_2 threshold in the same way as our results[16]; however, Power et al.[4] reported that midazolam has little effect on either the CO_2 sensitivity or the apneic CO_2 threshold in humans. Forster et al.[5] presented evidence that midazolam reduces CO_2 sensitivities in humans. Moreover, although Goodman et al.[17] reported that propofol reduces CO_2 sensitivity but does not change the apneic CO_2 threshold in humans, Nieuwenhuijs et al.[18] found, with volunteers, that propofol reduces CO_2 sensitivity and changes apneic CO_2 threshold.

The X intercept marks the apneic CO_2 threshold of the respiratory center.[9,12] Because it is difficult to suppress spontaneous breathing effort in the conscious state, it is difficult to actually measure the apneic CO_2 threshold. Hickey et al.[19] have plotted $Paco_2$-MV response and actually measured apneic CO_2 thresholds in humans inhaling volatile anesthetics. They found the measured apneic CO_2 thresholds, which were higher than the X intercept of $Paco_2$-MV response plots, were 5–9 mm Hg lower than $Paco_2$ at rest.[19] Although the X intercept is not exactly the same as $Paco_2$ at rest, changes in the X intercept may indicate the effects of sedatives on $Paco_2$ at rest. In a resting state, midazolam and propofol are more likely than dexmedetomidine to increase $Paco_2$.

The slope of the $Paco_2$-MV response plot shows the CO_2 sensitivity of peripheral chemoreceptors and the respiratory center. For example, inhaled anesthetics usually cause ventilatory depression, which is indicated by decreased slope values.[11] Our results indicate that the effects of dexmedetomidine are not likely to have much effect on the $Paco_2$-MV response plot.

The pathways through which sedatives affect respiratory depression have yet to be properly clarified. Propofol and midazolam are thought to depress respiration by stimulating central γ-aminobutyric acid (GABA) A receptors.[5,18] This could implicate the caudal ventrolateral medulla, which contains GABAergic neurons that modulate the activity of the rostal ventrolateral medulla which, in turn, is involved in respiratory regulatory within the brainstem.[20] By contrast, several studies have reported that α_2-adrenergic receptors in the brainstem are also involved in respiration. Errchidi et al.[21] reported that the activity of the medullary respiratory rhythm generator is modulated by the neurons of the pontine A5 area via α_2-adrenergic receptors located in the rostal ventrolateral medulla. Oyamada et al.[22] reported that the respiratory-phased inhibition of locus coeruleus neurons depends on activation of an α_2-adrenergic pathway. The present study does not provide any obvious clues why dexmedetomidine, propofol, and midazolam have different respiratory depressive effects. We can only conjecture that the working of GABA A receptors and α_2-adrenergic receptors in the brainstem may explain our results.

In this study, we assume that changes in MV were caused mainly by the change of tidal volume. The RR plot is not significantly different for any of the four groups. Moreover, our findings show that RR changed relatively little as $FiCO_2$ increased. A previous rabbit study found that increasing $FiCO_2$ led to decreasing RR in both nonsedated and dexmedetomidine groups.[10] Why the effect on RR in rabbits studies and humans might be different is unknown.

To compare CO_2 response, it would be ideal to achieve a steady-state of three factors: level of $Paco_2$, blood drug concentration, and level of sedation. In the classical steady-state study,[23] the CO_2 inhalation time was 20 min, so we decided to allow 20 min CO_2 inhalation, which was actually longer than in previous animal studies.[13,24] In addition, the absence of any further increase of end-tidal CO_2 and RR was taken as confirmation of the achievement of a steady state.

Blood concentration of the drugs in each $FiCO_2$ should also be kept at the same level. Stable blood concentration of drugs is best achieved by continuous drug infusion, and a long period of infusion is required to sustain stable concentration. To avoid lengthy infusion, we sought to minimize any differences in drug concentration by randomizing the $FiCO_2$ sequence. Rather than absolute control of drug concentration, given the practical circumstances, we think that this aspect of the protocol was more important for yielding valid data. We administered propofol using target-controlled infusion software control. Midazolam was administered by bolus plus continuous infusion. Bolus administration of dexmedetomidine causes transient circulatory change[6,25] so, to avoid these unpredictable effects, we did not use bolus injection of dexmedetomidine. Plasma concentrations of propofol and midazolam were confirmed to be almost the same at each $FiCO_2$ phase. We did not measure dexmedetomidine plasma concentration, which was assumed to be acceptably similar at each sequence-randomized $FiCO_2$.

The results of this study are limited because they are derived from a model using sevoflurane-inhaling rabbits. When investigating the effects of sedatives on respiration, obviously it would be better if control animals did not receive any drug that affects respiration. In animals without sedatives, however, CO_2 response would be difficult to measure because exercise, state of wakefulness, and incidental stress or pain are likely to stimulate respiration. Consequently, to stabilize basal conditions, we designed a protocol using inhaled sevoflurane to maintain minimal basal anesthesia in each of the groups. In rabbits, the minimum alveolar concentration (MAC) for sevoflurane is 3.7%, so we administered 2% sevoflurane, or about 0.54 MAC,[26] which produces no significant depression of phrenic nerve activity[27] and has little effect on hemodynamics.[6,10,28] Nguyen et al.[7] have reported that, compared with 1.5% isoflurane alone, 3 μg/kg of dexmedetomidine during 1.5% isoflurane (1.15 MAC in dogs) anesthesia caused a small increase in $Paco_2$ at rest and decrease in the $Paco_2$-sensitivity. Inhaled anesthetics are assumed to have synergic effects with propofol, midazolam, or dexmedetomidine. Because the present study compared the effects of sedative drugs used in conjunction with sevoflurane, there is always a possibility that sevoflurane might bias the results, instead of merely minimizing the effects of exercise, state of wakefulness, and any stress or pain. In addition, the results exhibited the relative pharmacological characteristics of the three drugs in rabbits. Our results cannot be directly applied to humans in the intensive care unit.

Because assessment of the sedation level of animals presents practical difficulties, we also cannot be sure whether the doses of the three drugs were comparable in terms of their sedative effects. In the present study, we used three criteria to evaluate target sedation levels: the drugs did not induce any critical problems in respiration and circulation; the animals exhibited minimal voluntary movement; and the animals maintained response to noxious stimuli. Without sedation, because inhalation of CO_2 in itself is stimulating in rabbits, it would be impossible to keep the animals awake and calm. Also, because tests to assess level of sedation would probably affect the response to CO_2, it was not practical to evaluate sedation. Consequently, we can only assume that our drug-administration protocols sedated the animals at adequately similar sedation levels. Throughout each protocol, each animal met the target sedation level criteria.

Compared with control, administration of dexmedetomidine resulted in lower MAP and decreased HR. Our findings in MAP and HR for dexmedetomidine

are consistent with other studies.[6,10,25,29,30] We found no statistically significant differences for MAP and HR data among Groups C, P, and M. We found that dexmedetomidine induced hypotension and reduced HR more than propofol and midazolam.

In conclusion, in a sevoflurane-anesthetized rabbit CO_2 inhalation model, the results for midazolam and propofol were similar but, compared with propofol and midazolam, dexmedetomidine produced less respiratory depression, more hypotension and greater reduction of HR.

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CRPS

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CRPS

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疾患概念

複合性局所疼痛症候群(complex regional pain syndrome, CRPS)は，かつて反射性交感神経性ジストロフィー(reflex sympathetic dystrophy)ないしはカウザルギーと呼ばれた病態で，外傷や神経損傷の後，痛みが遷延し，浮腫，皮膚温の異常，発汗の異常を伴う症候群である．明らかな神経損傷を伴わないものをtype Ⅰ，神経損傷(部分損傷)を伴うものをtype Ⅱに分類する．近年皮膚温の異常や発汗の異常など交感神経の機能異常と考えられる症状は，必ずしも末梢神経の交感神経活動の亢進によるものではないことが明らかとなった[1]．また，かつてこの病態に対する根本的な治療と考えられた交感神経ブロックや交感神経遮断術が必ずしも有効でないことが明らかとなり[2]，病名に「交感神経」という用語を用いることが適切でないと指摘されCRPSという名称で統一されるに至った[3]．歴史的にはアメリカの南北戦争の際に末梢神経に銃弾を受けた兵士の一部に，強い灼熱痛と皮膚温や発汗の異常を伴う症状を呈する者がいることをMichelが報告したのにはじまる．後にドイツの医師Sudeckが骨折後に進行性の骨萎縮をきたす例があることを報告し，Sudeck骨萎縮と呼ばれるようになった．外傷後に一部の症例にだけCRPSが発症する原因については今もなおほとんど解明されておらず，遺伝的素因，外傷機転，心理的影響などが関連していると考えられている．原因が明らかでなく，特異度の高い検査法がないため診断はもっぱら症状によって行われる．症状は1994年に設定された診断基準に含まれている，異常な遷延する痛み，アロディニア，痛覚過敏など痛みに関する症状，皮膚温や皮膚色の異常(皮膚温が健常側に比べて高い場合と低い場合とがある)，発汗の異常(亢進ないしは低下)，浮腫など交感神経と関連すると考えられる症状をもとに行う[3]．また，皮膚，爪，毛などの萎縮性変化，関節可動域制限，筋力低下などを伴う場合もある．検査所見としてはX線検査における骨萎縮，骨シンチグラムでの骨端部における異常集積などがある．CRPSの疾患概念において重要な点は，これら痛み，浮腫，皮膚温の異常，発汗異常，筋力低下，組織の萎縮性変化，X線や骨シンチの異常などCRPSに特徴とされる症状や所見は，痛みがあって四肢の不動化がおこるとおこりうるものであり，病態生理学的に均一なCRPSという症候群の存在を保証するものではなく，疾患概念そのものにあいまいな点があり混乱がみられることである[4]．実際の疫学的解析に基づいて明らかにした報告はないが，多数の診療経験からCRPSにはいくつかの類型があると思われる．第一はMichelが報告した例のような末梢神経の部分損傷後に痛みが遷延する病態で，痛みの領域は損傷された神経の支配領域を超えて広がることが多い．第二はSudeckが報告した骨折後に進行性の骨萎縮を伴う例で，橈骨遠位端骨折などの後にみられる例である[5]．第三は外傷機転に比して症状が進行性で重篤な例である．日常臨床上はこれらの病態をひとまとめにCRPSと呼ぶ習慣となっており混乱の原因となっている．いずれの病態も，古典的な神経科学や整形外科学では説明することは困難であり，外傷後に痛みが遷延しその病態の説明が困難な場合にCRPSという用語をつけているのが現状であろう．type Ⅰとtype Ⅱとは神経損傷の有無で分類されているが，実際には神経損傷の有無を確実に評価する方法がなく明確に分類することはできない．神経伝達速度などの客観性の高い方法で神経損傷の有無を評価する方法が最も確実ではあるが，皮神経など細い神経の損傷を評価することはできない．実際の診療では，受傷機転，他覚所見(知覚低下，筋力低下，ティネルサインなど)などと組み合わせて総合的に判断する．症状を統計学的に分析した研究ではtype Ⅰとtype Ⅱとを分類できなかったことから，分類することそのものに疑問を投げかける意見もあるが[6]，神経損傷後痛と神経損傷のない遷延した痛みとでは病態が異なり，治療に対する反応性も異なると考えられるので，区別する必要はあると思われる．かつてはCRPS type Ⅰも神経障害性疼痛に分類されていたが，現在ではtype Ⅱのみが神経障害性疼痛に分類される．

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