Cardiovascular effects of epinephrine under sedation with nitrous oxide, propofol, or midazolam

Hitoshi Niwa, DDS, PhD,[a] Ai Tanimoto, DDS, PhD,[b] Mitsutaka Sugimura, DDS, PhD,[c] Yoshinari Morimoto, DDS, PhD,[d] and Hiroshi Hanamoto, DDS, PhD,[e] Osaka and Kyoto, Japan
OSAKA UNIVERSITY GRADUATE SCHOOL OF DENTISTRY AND OTOWA HOSPITAL

Objective. During implant surgery, a large amount of local anesthetics containing epinephrine are often required, and the resulting cardiovascular effects of administered epinephrine are not negligible. On the other hand, sedation has wide applications in implant surgery. Nitrous oxide, propofol, or midazolam are commonly used as sedative drugs, and each has also its own cardiovascular effects. The objective of this study was to investigate the cardiovascular effects of epinephrine on patients under sedation with nitrous oxide, propofol, or midazolam.
Study design. We studied 9 healthy volunteers. They received epinephrine infusion at a nominal rate of 10, 25, or 50 ng/kg per minute under sedation with 30% nitrous oxide inhalation, 4 mg/kg per hour intravenous propofol or 0.2 mg/kg per hour intravenous midazolam. For each, hemodynamic response and blood pressure and heart rate variability were measured.
Results. When epinephrine was infused alone at 50 ng/kg per minute, heart rate (HR) and cardiac index (CI) increased by 19.5% and 40.7%, respectively. Propofol suppressed the epinephrine-induced increase in CI. During midazolam infusion, the highest dose of epinephrine caused a 37.5% increase in HR, which was significantly higher than for epinephrine infusion alone. This response was accompanied by the reduction in high-frequency power of heart rate variability, suggesting decreased parasympathetic activity. Nitrous oxide had no influence on the cardiovascular response to epinephrine.
Conclusion. Increased cardiovascular activity due to epinephrine can be alleviated by propofol. However, midazolam and nitrous oxide are of no advantage for stabilizing the hemodynamic status of the patient. Intravenous sedation with propofol is useful during oral surgical procedures in which a large amount of epinephrine is required. **(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006;102:e1-e9)**

The administration of a vasoconstrictor in combination with a local anesthetic has evolved as a method for decreasing systemic toxicity, increasing the duration of anesthesia, and providing hemostasis during oral surgical procedures. The importance of vasoconstrictor agents is undisputed. Lidocaine with epinephrine is most commonly used in dental practices throughout the world. There have been many studies of the hemodynamic effects of dental anesthesia with epinephrine-containing local anesthetic solution. Tolas et al.[1] reported no significant cardiovascular changes following injection of a single cartridge of an anesthetic containing 18 μg of epinephrine, despite a twofold increase in plasma epinephrine. Knoll-Kohler et al.[2] and Chernow et al.[3] also found only a small reduction in mean arterial blood pressure and a small increase in heart rate after the injection of low-dose epinephrine. Consequently, the hemodynamic effects of epinephrine-containing local anesthetics are small.

Recently, there have been increasing cases of implant surgery, which often requires large amounts of local anesthetics for pain control and hemostasis.[4] Therefore, if a large amount of local anesthetic containing epinephrine is given to a patient, the cardiovascular effects of epinephrine may not be negligible. These effects may cause serious complications such as cardiac ischemia, dysrhythmia, and hypertension in patients with underlying cardiovascular disease.[5-7]

On the other hand, it is generally accepted that most dental patients who undergo implant surgery require sedation. Although intravenous sedation is commonly applied for anxious patients, it is also a well-adapted form of systemic management for implant surgery.[8-10] Some oral surgeons have stated that sedation is essential for reducing the stress of the implant surgery. Intravenous sedation with benzodiazepine derivatives

[a]Professor, Department of Dental Anesthesiology, Osaka University Graduate School of Dentistry.
[b]Staff Dental Anesthesiologist, Department of Oral Surgery, Rakuwa-kai, Otowa Hospital.
[c]Associate Professor, Department of Dental Anesthesiology, Osaka University Graduate School of Dentistry.
[d]Assistant Professor, Department of Dental Anesthesiology, Osaka University Graduate School of Dentistry.
[e]Resident, Department of Dental Anesthesiology, Osaka University Graduate School of Dentistry.
Received for publication Oct 11, 2005; returned for revision Feb 15, 2006; accepted for publication Mar 17, 2006.
1079-2104/$ - see front matter

doi:10.1016/j.tripleo.2006.03.014

or propofol has been used, as well as inhalation sedation with nitrous oxide. However, these drugs have their own effects on the cardiovascular system. The administration of propofol results in a decrease in blood pressure in a dose-dependent manner,[11] and midazolam leads to a smaller decrease in blood pressure than does propofol.[12] Even nitrous oxide has a slight sympathomimetic effect on the cardiovascular system.[13] Therefore, attention should be paid to the interaction between epinephrine and these sedative drugs.

The objective of this study was to investigate the hemodynamic and autonomic responses to epinephrine under sedation with nitrous oxide, propofol, or midazolam and to determine which sedatives alleviate the effects of epinephrine. We used the epinephrine infusion method[14-16] instead of the injection of epinephrine-containing local anesthesia into the gingiva. To define the cardiovascular effects of these drugs, we measured the stroke volume (SV), cardiac index (CI), and total peripheral resistance (TPR) by impedance cardiography, as well as the blood pressure and heart rate. In addition, variability in the arterial blood pressure and heart rate was also analyzed. Spectral analysis of this variability is widely used as a noninvasive technique to assess autonomic function.[17-18]

MATERIAL AND METHODS

Volunteers

With approval from the Ethics Committee on Human Research at Osaka University and after obtaining written informed consent, we studied 9 volunteers. No history of cardiovascular disease, hypertension, and dysautonomia was present, and the physical examinations and electrocardiograms were all normal. The ages of the subjects ranged from 25 to 45 years, with a mean of 30.3 years; their body weights ranged from 48 to 72 kg, with a mean of 59.7 kg. The volunteers were asked not to consume alcohol or caffeinated beverages 24 hours before each study day. Each study was scheduled to start at 4:00 PM. That way, all interventions were made at similar times each day to minimize the effects of circadian fluctuations.

Measurements

The subjects rested in the supine position for 30 minutes, after which baseline measurements were obtained. Intermittent brachial blood pressure was measured by using an automated cuff sphygmomanometer throughout the study. The subjects underwent continuous electrocardiographic monitoring by using lead II. Arterial oxygen saturation (SpO_2) was continuously monitored with pulse oximetry. When the signs of upper airway obstruction—such as low SpO_2 below 95% or snoring—were observed during sedation, a small pillow was employed to maintain flexion in the lower cervical spine. The subject was placed in a so-called "sniffing position" to improve airway patency.

To evaluate left ventricular function during the study, noninvasive impedance cardiograms (CIC-1000, Sorba Medical Systems, Milwaukee, WI) were recorded. Cardiac output was measured every 20 seconds with a computer-interfaced impedance device. CI, TPR, and rate pressure product (RPP) were calculated by using a CIC-1000. The validity and reproducibility of this method have been described in detail elsewhere.[19]

Radial artery pressure waveforms were continuously measured by a tonometric system sphygmomanometer (BP-508, Cholin Co. Ltd., Tokyo, Japan). Electrocardiogram and blood pressure waveforms were digitized at 1000 Hz for analysis by the software, and the artifact-free, digitized signals were stored on a personal computer for later analysis. The fast peaks of R waves on the electrocardiograms were detected and then R-R intervals were measured. The peak values of systolic blood pressure for each cardiac cycle were also obtained. Data on R-R interval and systolic blood pressure were analyzed with commercially available software (Fraclet, Dainippon, Osaka, Japan), where 2 frequency bands were automatically separated: a low frequency band (LF between 0.04-0.15 Hz) and a high frequency band (HF between 0.15-0.4 Hz). The LF band of systolic blood pressure (SBP-LF) is a good marker of sympathetic activity in peripheral vessles.[17,20,2] On the other hand, the HF band of heart rate variability (HR-HF) coincides with the respiratory frequency and primarily reflects respiration-linked variations in the heart rate resulting from centrally mediated cardiac vagus control.[17,18,22] The ratio of LF to HF power of the heart rate variability (HR-LF/HF) reflects the sympathetic-parasympathetic balance. From this theory, an increased HR-LF/HF ratio suggests sympathetic dominance resulting from increased sympathetic outflow, decreased parasympathetic outflow, or both.

Although the effect of the respiratory rate on HR-HF power is relatively small at normal respiration rates, extremely fast or slow respiration rates significantly alter it.[23,24] Thus, the respiratory rate was also recorded.

Treatment protocol

Each subject underwent 4 treatments: (1) epinephrine was infused alone (E group), (2) epinephrine was infused in addition to propofol (P + E group), (3) epinephrine was infused in addition to midazolam (M + E group), and (4) epinephrine was infused in addition to nitrous oxide inhalation (N + E group). Each of these treatments was given to each subject in randomized order at an interval of at least 1 week.

E group. Two intravenous catheters were inserted into a forearm vein of each arm, one for the administration of epinephrine and the other for blood sampling. We used the epinephrine infusion method[14-16] instead of injecting epinephrine-containing local anesthesia into the gingiva. The epinephrine solutions were prepared by diluting 1 mg of epinephrine (Bosmin, Daiichi-Seiyaku, Tokyo, Japan) in 0.9% saline solution. Epinephrine was incrementally infused at 10, 25, or 50 ng/kg per minute for 12 minutes. Hemodynamic measurements were collected during the last 2 minutes of each infusion period. A 5-mL sample of venous blood was drawn to analyze plasma epinephrine and norepinephrine concentrations in the E group.

P + E group. Two intravenous catheters were inserted into the right forearm vein, one for the administration of epinephrine and the other for propofol. Propofol was infused at 4 mg/kg per hour throughout the study. After a 35-minute propofol infusion, hemodynamic measurements were taken to obtain the value during sedation alone. Then, epinephrine was also given and variables were determined in the same way as for the E group.

M + E group. In this group, midazolam was infused at 0.2 mg/kg per hour throughout the study. Thirty-five minutes after the beginning of midazolam, epinephrine was simultaneously infused. Hemodynamic and autonomic variables were then determined.

N + E group. An intravenous catheter was inserted into the right forearm vein for the administration of epinephrine. Each subject inhaled a gas mixture of nitrous oxide and oxygen by using a face mask at 10 L/min. The end-tidal concentration of nitrous oxide was monitored by an anesthetic gas analyzer (BP-508; Nihon Colin, Tokyo, Japan) and adjusted to between 20% to 25%. Thirty-five minutes after the inhalation of nitrous oxide, epinephrine infusion was started. During the study, the end-tidal concentration of carbon dioxide and respiratory rate were measured.

In the preliminary study, we simulated the concentration time profile with the computer software package PKSIM[25,26] when 4mg/kg per hour of propofol or 0.2mg/kg/min of midazolam was given intravenously. That study showed that it would take 35 minutes before the plasma concentration of the drug reached a plateau level. So, we studied the effects of epinephrine 35 minutes after the beginning of each sedation.

Statistical analysis

Measurement values obtained before the drug treatment were regarded as baseline values. Hemodynamic data during the testing was expressed as the percentage change from baseline. Absolute values for the plasma catecholamine concentration were used. The distributions of the LF and HF power and the HR-LF/HF ratio were skewed, so a logarithmic transformation was applied. After transformation, they took on a normal distribution. The data was reported as means ± SD.

Statistical analysis was performed with the SPSS software package (SPSS Inc., Chicago, IL). The obtained results were statistically analyzed using 1-way analysis of variance (ANOVA) for repeated measures, followed by Tukey's test to adjust for multiple comparisons. Statistical comparisons between groups were assessed using Dunnett's test. A P value $< .05$ was considered to indicate statistical significance.

RESULTS

Hemodynamic effects

The cardiovascular responses in each group are shown in Table I. In the E group, epinephrine infusion resulted in a significant increase in HR, SV, and CI in a dose-dependent fashion. During epinephrine infusion at 50 ng/kg per minute, HR, SV, and CI increased by 19.5%, 18.2%, and 40.7%, respectively. However, mean arterial pressure (MAP) did not show any significant changes because the increased cardiac output was reversed with reduced TPR. At the highest infusion rate of epinephrine, a 28.4% reduction in TPR occurred. Rate pressure product, an index of myocardial oxygen consumption, increased by 24.0% at the highest rate of epinephrine.

The plasma catecholamine concentrations before and after the infusion of epinephrine are listed in Table II. The plasma epinephrine concentration was 24.6 ± 3.5 pg/mL at baseline and increased to 592.3 ± 62.8 pg/mL during epinephrine infusion at 50 ng/kg per minute. No significant changes were noted in the plasma norepinephrine concentration.

After the 35-minute infusion of propofol, MAP decreased by 12.4% of baseline, while HR did not show any significant change. SV and CI decreased by 15.9% and 18.6%, respectively. Consequently, propofol caused a 14.4% reduction in RPP. When epinephrine was infused with propofol, HR increased in a dose-dependent fashion, but the fall in MAP was maintained. During epinephrine infusion at 50 ng/kg per minute, HR increased by 16.0%, and there was no significant difference between E and P + E groups. The reduced SV and CI due to propofol were reversed with epinephrine, so there were no significant differences compared with the baseline value. However, CI in the P + E group was significantly lower than that in the E group during epinephrine infusion at 50 ng/kg per minute.

After the 35-minute midazolam infusion, HR increased by 7.4%, while SV decreased by 14.9%. Midazolam infusion did not induce any significant changes in the other variables. After the administration

Table I. Percentage changes in hemodynamic parameters after sedation and during epinephrine infusion

	Postsedation	*10 ng/kg/min*	*25 ng/kg/min*	*50 ng/kg/min*
HR (%)				
E		+1.0 ± 3.9[‡]	+9.7 ± 7.3*[‡]	+19.5 ± 8.7*[‡]
P + E	−3.4 ± 5.6[§]	+4.9 ± 8.3[§]	+8.8 ± 6.3*[§]	+16.0 ± 10.8*[§]
M + E	+7.4 ± 4.9*[#]	+16.8 ± 7.1*[#]	+27.3 ± 6.2*[#]	+37.5 ± 10.3*[#]
N + E	−7.9 ± 4.7	+0.4 ± 5.3	+7.8 ± 6.0	+20.2 ± 12.6*
SBP (%)				
E		−3.0 ± 2.9	−1.8 ± 4.2	+3.7 ± 2.3
P + E	−11.1 ± 6.1*	−13.3 ± 6.0*	−9.1 ± 8.8	−5.1 ± 9.2
M + E	−5.5 ± 5.6	−6.8 ± 6.9	−5.1 ± 9.6	+2.0 ± 10.4
N + E	+4.0 ± 6.6	−1.8 ± 8.1	+0.3 ± 4.9	+4.2 ± 1.2
DBP (%)				
E		−4.8 ± 5.7	−5.6 ± 3.8	−5.0 ± 4.5
P + E	−13.2 ± 8.8*	−23.4 ± 9.0*	−20.4 ± 11.6*	−15.1 ± 13.3*
M + E	−8.9 ± 7.9	−11.6 ± 10.4*	−13.6 ± 15.5*	−15.4 ± 12.2*
N + E	+5.9 ± 2.9	+3.1 ± 8.2	−2.0 ± 6.8	+0.0 ± 8.9
MAP (%)				
E		−4.0 ± 4.4	−3.8 ± 3.6	−0.9 ± 2.4
P + E	−12.4 ± 7.0*[¶]	−18.7 ± 6.9*[¶]	−15.0 ± 9.9*	−10.3 ± 11.0
M + E	−7.1 ± 6.6	−9.3 ± 8.6	−9.7 ± 13.0	−7.3 ± 10.6
N + E	+4.8 ± 4.7	+2.6 ± 8.2	−1.0 ± 5.0	+1.8 ± 5.2
SV (%)				
E		+1.9 ± 9.9	+16.4 ± 15.6*	+18.2 ± 19.2*
P + E	−15.9 ± 11.1*	−16.1 ± 14.3*	−8.6 ± 20.3	−5.4 ± 19.6
M + E	−14.9 ± 9.1*	−13.6 ± 8.1*	−1.2 ± 17.4	+2.1 ± 20.2
N + E	−8.1 ± 13.6	−9.9 ± 11.2	−1.6 ± 16.8	−2.2 ± 22.9
CI (%)				
E		+3.1 ± 9.7	+27.3 ± 16.8*	+40.7 ± 21.2*[†]
P + E	−18.6 ± 11.8*	−12.3 ± 14.8	−0.8 ± 20.7	+8.9 ± 20.8[§]
M + E	−8.8 ± 7.3	+0.9 ± 9.7	+25.5 ± 21.8*	+39.5 ± 24.7*
N + E	−17.4 ± 13.9*	−11.4 ± 11.0	+3.4 ± 16.9	+13.2 ± 22.3*
TPR (%)				
E		−5.8 ± 13.2	−24.5 ± 9.0*	−28.4 ± 9.9*[†]
P + E	+10.5 ± 19.0	−5.1 ± 19.1	−10.5 ± 26.5	−16.1 ± 17.2
M + E	+2.2 ± 10.7[#]	−7.8 ± 9.4	−23.8 ± 16.8*	−29.3 ± 16.8*
N + E	+29.3 ± 18.2*	+17.1 ± 16.5	−2.6 ± 19.5	−6.3 ± 22.3
RPP (%)				
E		−2.0 ± 4.7	+7.8 ± 10.2	+24.0 ± 10.6*
P + E	−14.4 ± 4.8*[§]	−9.1 ± 9.1	−1.2 ± 10.8	+10.1 ± 15.2[¶§]
M + E	+1.5 ± 8.8	+9.0 ± 12.4	+21.5 ± 16.0*	+40.6 ± 22.5*
N + E	−6.2 ± 9.1	+0.1 ± 11.5	+5.8 ± 7.3	+21.8 ± 14.5*

Values are expressed as percentage of hemodynamic change from baseline (mean ± SD).
HR, heart rate; *SBP,* systolic blood pressure; *DBP,* diastolic blood pressure; *MAP,* mean arterial pressure; *SV,* stroke volume; *CI,* cardiac index; *TPR,* total peripheral resistance; *RPP,* rate pressure product;
*□ < .05 vs. baseline;
[†]□ < .05 E vs. P + E, [‡]□ < .05 E vs. M + E, [§] < .05 P + E vs. P + M,
[¶]□ < .05 P + E vs. N + E,
[#]□ < .05 M + E vs. N + E.

of epinephrine, there was a dose-dependent increase in HR. A 37.5% increase was seen at the highest dose of epinephrine and was significantly higher than that in the other groups. Consequently, CI and RPP were remarkably increased by epinephrine. The increased CI and RPP in the M + E group were significantly higher than those in the P + E group.

In the N + E group, data for 2 volunteers was excluded from analysis because they became restless and exited with the prescribed nitrous oxide inhalation. Inhalation of nitrous oxide resulted in a 17.4% reduction in CI and a 29.3% increase in TPR, so there was no significant change in MAP. During the highest infusion rate of epinephrine, HR increased by 20.2%. As the infusion rate of epinephrine rose, the reduction of CI was reversed and eventually CI increased by 13.2%. Rate pressure product also increased by 21.8% with 50 ng/kg per minute of epinephrine. The elevation in TPR

Table II. Changes in plasma epinephrine and norepinephrine concentration in E group

	Baseline	*Postsedation*	*10 ng/kg/min*	*25 ng/kg/min*	*50 ng/kg/min*
Epinephrine (pg/ml)	24.6 ± 3.5		151.5 ± 17.8*	304.6 ± 34.9*	592.3 ± 62.8*
Norepinephrine (pg/ml)	224.0 ± 18.4		250.0 ± 17.1	247.7 ± 18.4	258.5 ± 18.7

Data are mean ± SD.
*$P < .05$ vs. baseline.

due to nitrous oxide inhalation disappeared by administration of epinephrine. However, hemodynamic responses to epinephrine infusion were not influenced by nitrous oxide because there were no significant differences during epinephrine infusion between the E and the N + E groups.

Autonomic effects

The autonomic effects in each group are shown in Table III. All autonomic measurements remained unchanged compared with the baseline value during epinephrine infusion in E group. SBP-LF was slightly reduced by epinephrine at 50 ng/kg per minute, but this change was not significant.

During propofol infusion, HR-HF was reduced when epinephrine was given at 10 ng/kg per minute. However, the hemodynamic and autonomic effects of 10 ng/kg per minute epinephrine were so small, as shown in the E group, that the reduction of HR-HF was more likely to have been caused by propofol. Thus, this change suggested decreased parasympathetic activity with propofol. Midazolam infusion caused a decrease in HR-HF power, and this reduction was maintained during epinephrine infusion. This finding reflects decreased parasympathetic activity. SBP-LF power showed no significant change with midazolam, while it slightly increased during inhalation of nitrous oxide. However this response was not significant ($P = .08$), suggesting increased sympathetic nervous activity.

We could not detect any differences in autonomic measurements between any of the groups.

Respiratory effects

Although SpO_2 decreased occasionally below 95% during the propofol or midazolam sedation, due to upper airway obstruction, it was easily improved by placing the head of the subject in the sniffing position. Therefore, the effect of hypoxia on the hemodynamic and autonomic systems seemed to be small. Changes in the respiratory rate may cause substantial bias in estimating HR and blood pressure variability. The respiratory rates fluctuated between 10-18 breaths per minute, and there were no significant differences between the 4 groups for any study period. So, the effect of the respiratory rate on HR and blood pressure variability was also small.

Table III. Autonomic parameters after sedation and during epinephrine infusion

	Baseline	*Postsedation*	*10 ng/kg/min*	*25 ng/kg/min*	*50 ng/kg/min*
In SBP-LF					
E	0.37 ± 0.24		0.32 ± 0.20	0.30 ± 0.15	0.20 ± 0.13
P + E	0.31 ± 0.26	0.23 ± 0.18	0.20 ± 0.13	0.29 ± 0.19	0.30 ± 0.31
M + E	0.28 ± 0.25	0.28 ± 0.20	0.27 ± 0.10	0.27 ± 0.17	0.23 ± 0.18
N + E	0.26 ± 0.11	0.40 ± 0.21	0.23 ± 0.14	0.33 ± 0.21	0.21 ± 0.23
In HR-HF					
E	2.00 ± 0.26		2.10 ± 0.39	1.82 ± 0.33	1.79 ± 0.42
P + E	2.04 ± 0.37	1.88 ± 0.35	1.64 ± 0.60*	1.70 ± 0.62	1.69 ± 0.58
M + E	2.10 ± 0.42	1.53 ± 0.55*	1.34 ± 0.57*	1.39 ± 0.63*	1.09 ± 0.61*
N + E	1.92 ± 0.74	1.95 ± 0.79	2.16 ± 0.81	1.89 ± 0.71	1.77 ± 0.80
In LF/HF ratio					
E	0.30 ± 0.24		0.23 ± 0.11	0.32 ± 0.11	0.24 ± 0.19
P + E	0.31 ± 0.24	0.23 ± 0.26	0.36 ± 0.51	0.44 ± 0.56	0.41 ± 0.36
M + E	0.30 ± 0.23	0.19 ± 0.22	0.31 ± 0.29	0.30 ± 0.32	0.40 ± 0.42
N + E	0.42 ± 0.41	0.53 ± 0.70	0.33 ± 0.44	0.37 ± 0.36	0.40 ± 0.33

Data are mean ± SD.
In SBP-LF, logarithm of low-frequency power of systolic blood pressure; *In HR-HF,* logarithm of high-frequency power of heart rate; *In LF/HF ratio,* logarithm of the ratio of low to high-frequency power of heart rate.
*$P < 0.05$ vs. baseline.

DISCUSSION

In this study of healthy volunteers, we compared their hemodynamic and autonomic responses when epinephrine was given alone with those when it was given under sedation with propofol, midazolam, or nitrous oxide. The major findings of this study are that propofol suppresses the increase in CI and RPP induced by epinephrine infusion, midazolam increases the HR due to the suppression of parasympathetic nervous activity and this response is accelerated by epinephrine infusion, and that nitrous oxide has no effect on the cardiovascular response to epinephrine.

Hemodynamics during infiltration anesthesia are greatly affected not only by the agent, especially for vasoconstrictors, but also by the pain and anxiety associated with the injection.[27-29] Pain and anxiety cause the release of endogenous catecholamine, and the effect of these stressors on hemodynamics can be greater than of the drug. Therefore, it is necessary to eliminate such effects as much as possible when attempting to evaluate the effects of the agent alone. Epinephrine infusion is the best way to carry this out and has some definitive advantages. First, the effects of pain and anxiety associated with injection can be avoided. Secondly, infusion of epinephrine at a fixed rate can be ensured, and repeated doses of epinephrine at different rates enable the reduction of the number of tests that need to be performed.

The rate of epinephrine infusion that causes cardiovascular responses similar to those caused by infiltration anesthesia into the oral region was determined in a previous study.[15] There, cardiovascular responses to infiltration anesthesia with 1 cartridge of 2% lidocaine containing 22.5 μg of epinephrine were almost equivalent to those produced by epinephrine infusion at 10 ng/kg per minute. Furthermore, hemodynamic changes caused by epinephrine infusion at 50 ng/kg per minute could be equivalent to those induced by injection of 5 cartridges. We compared the effects of 3 sedatives on the hemodynamic response to epinephrine. Although each sedative drug might not have provided the same level of sedation, all subjects fell asleep but exhibited purposeful reaction to verbal or mild physical stimulation after induction. Therefore, the sedation level was thought to be similar in each group. Wilson et al.[30] reported that mean infusion rates of 3.63 mg/kg per hour propofol and 0.26 mg/kg per hour midazolam sedated patients who receive spinal anesthesia, while Mackenzie and Grant[31] found that sedation with propofol was maintained at 4.1mg/kg per hour in patients less than 65 years of age. Runes and Strom[32] used intravenous sedation with midazolam in oral surgical procedure and stated that the mean dose of midazolam was 0.15mg/kg per hour. On the basis of those studies, we administered propofol at 3.0 mg/kg per hour and midazolam at 0.20 mg/hg per hour. In dental practice, about 30% nitrous oxide is usually given to a patient to cause sedation. When 30% nitrous oxide is given with a nasal mask, the end-tidal concentration of nitrous oxide corresponds with about 20% to 25%, according to our previous study.[33] However, because we had to maintain a stable end-tidal concentration of nitrous oxide, we used a face mask instead of a nasal mask to respond to respiration through the mouth and reduce gas leakage from the mask. Although nitrous oxide sedation was successfully performed in 7 of 9 subjects, the remaining 2 subjects became restless and excited by inhaling the nitrous oxide, and so they were excluded from the N + E group. The sedation level produced by 20% to 25% of nitrous oxide was too deep for them.

Spectral analysis of HR and blood pressure variability permits the noninvasive assessment of autonomic nervous activity. The HF component of HR is mediated by the parasympathetic nervous system and attributable to respiratory sinus arrhythmia.[18] The LF/HF ratio of HR variability is a useful index of cardiac sympathetic nervous activity, and the LF component of the SBP variability is a good marker of peripheral sympathetic nervous activity.[17] Therefore, analysis of the HR and blood pressure variability enables permits assessment of the autonomic response produced by sedative drugs and epinephrine.

In this study, the hemodynamic responses to epinephrine were increased HR, CI and RPP, and decreased TPR in a dose-dependent manner. Consequently, there were no significant changes in blood pressure. These findings are consistent with those of previous studies.[15,34] It is difficult to evaluate the effects of epinephrine on the HR and blood pressure variability because the direct effects of circulating epinephrine on the heart and vessels affect the HR and blood pressure variability, and the response of the end-organ in turn affects the central sympathetic nervous system. Published data on the effect of epinephrine on the HR and blood pressure variability are conflicting. Ahmed et al.[35] and Schachinger et al.[36] did not find any significant changes in HR and blood pressure variability during epinephrine infusion. On the other hand, Tulen et al.[37] revealed increased LF power of SBP, but they failed to show any changes in the HR variability. Although we noted significant hemodynamic changes during epinephrine infusion, we could not detect any changes in the HR and blood pressure variability. We speculate that the HR and blood pressure variability mediated by the autonomic nervous system were over-

whelmed by the direct effect of epinephrine on the end-organ.

Thirty-five minutes after beginning the use of propofol, it caused a 12% fall in the MAP, and this response did not return to baseline until epinephrine was given at the highest rate. Propofol produces dose-dependent falls in blood pressure and cardiac output.[38] Monk et al.[39] and Brussel et al.[40] observed a significant decrease in blood pressure, cardiac output, and systemic vascular resistance following propofol administration. Our results were consistent with theirs. The cause of the fall in blood pressure during propofol infusion was most likely to be a decrease in systemic vascular resistance or cardiac output caused by a combination of venous and arterial vasodilatation. Depression of myocardial contractility might not have developed at the small dose of propofol that we used.[41]

Propofol affects the peripheral and central autonomic nervous systems. In a study that measured peripheral sympathetic nervous activity, propofol anesthesia reduced muscle and renal sympathetic nervous activity. Deutschman et al.[42] and Galletly et al.[43] observed a significant reduction in the HR-HF power after administering propofol. In our study, HR-HF was reduced when propofol and the smallest dose of epinephrine were given simultaneously. At this infusion rate of epinephrine, the autonomic and hemodynamic effects of epinephrine were so small that the possible cause of reduced HR-HF was thought to be due to propofol. This finding reflects the reduction of parasympathetic nervous activity, which was mediated by the baroreceptor reflex to the decrease in blood pressure caused by propofol.

When epinephrine was given during propofol administration, the hemodynamic response to epinephrine was blunted by propofol. Thus, changes in CI and RPP in the P + E group were significantly smaller than those in the E group. These findings suggest that propofol can alleviate the hemodynamic effects of epinephrine. However, we could not find any differences in the autonomic variables between the P + E and E groups.

Midazolam has minimal cardiovascular effects 35 minutes after induction, except for a 7% increase in HR and a 15% decrease in SV. The HR response to midazolam remains controversial.[30,44-46] The primary reason underlying conflicting results is the methodological variety of their studies, such as dosing, the route of administration, and the condition of each subject.

However, it has been confirmed in human laboratory studies that benzodiazepines increase HR by suppressing cardiac vagal activity. DiMicco[47] reported that midazolam increased HR and that this effect could be prevented by the cholinergic receptor antagonist atropine. This suggests that midazolam-induced tachycardia is subject to vagal control. Agelink et al.[46] also elucidated that an increase in HR and a significant reduction in the HR-HF power occurred after intravenous midazolam.

We found that an increase in HR and the reduction in HR-HF occurred 35 minutes after the induction of midazolam. An increase in HR combined with a reduction in the HR-HF power after administering midazolam was considered to be evidence for a benzodiazepine-induced vagolytic effect. In our study, we observed the highest HR after the combination of midazolam and epinephrine, which led to significant increases in CI and RPP. If a large amount of epinephrine were to be given under sedation with midazolam, a marked increase in HR could develop due to the midazolam-induced vagolytic effect and the epinephrine-induced sympathomimetic effect. Therefore, when a large dose of epinephrine is required for surgical procedure, intravenous sedation with midazolam might not be called for because of the possible resultant tachycardia.

Nitrous oxide exerts a weak sympathomimetic effect.[48] Eisele and Smith[49] showed that an increase in the TPR occurred after 30 minutes of exposure to 40% nitrous oxide. We observed a 29% increase in TPR, which was consistent with their results.

Sellgren et al.[50] and Ebert and Kampine[51] observed an increase in the efferent activity of sympathetic muscle nerve fibers during exposure to nitrous oxide. In our study, we also observed a slight increase in the SBP-LF power, which reflects the enhanced sympathetic tone in peripheral vessels. Since we could not show significant differences in any variables between the N + E and E groups after the administration of epinephrine, it seems that nitrous oxide sedation has no effect on the hemodynamic and autonomic responses produced by epinephrine.

In conclusion, this study shows that propofol can alleviate the effects of epinephrine and that midazolam and nitrous oxide have no advantage on hemodynamics when a large dose of epinephrine is administered. Intravenous sedation with propofol is useful during oral surgery in which a large amount of epinephrine is required.

REFERENCES

1. Tolas AG, Pflug AE, Halter JB. Arterial plasma epinephrine concentrations and hemodynamic responses after dental injection of local anesthetic with epinephrine. J Am Dent Assoc 1982;10:441-3.
2. Knoll-Kohler E, Frie A, Becker J, Ohlendorf D. Changes in plasma epinephrine concentration after dental infiltration anesthesia with different doses of epinephrine. J Dent Res 1989;68:1098-101.
3. Chernow B, Balestrieri F, Ferguson CD, Terezhalmy GT, Fletcher JR, Lake CR. Local dental anesthesia with epinephrine.

Minimal effects on the sympathetic nervous system or on hemodynamic variables. Arch Intern Med 1983;143:2141-3.
4. Nagao H, Munakata M, Tachikawa N, Shiota M, Kasugai S. Clinical study of risk management for dental implant treatment–changes of blood pressure and pulse rate during implant surgery under local anesthesia. Kokubyo Gakkai Zasshi 2002;69:27-33.
5. Massalha R, Valdman S, Farkash P, Merkin L, Herishanu Y. Fatal intracerebral hemorrhage during dental treatment. Isr J Med Sci 1996;32:774-6.
6. Murakawa T, Koh H, Tsubo T, Ishihara H, Matsuki A. Two cases of circulatory failure after local infiltration of epinephrine during tonsillectomy. Masui 1998;47:955-62.
7. Lind LJ, Mushlin PS, Schnitman PA. Monitored anesthesia care for dental implant surgery: analysis of effectiveness and complications. J Oral Implantol 1990;16:106-13.
8. Runes J, Strom C. Midazolam intravenous conscious sedation in oral surgery. A retrospective study of 372 cases. Swed Dent J 1996;20:29-33.
9. Chanavaz M, Ferri J, Donazzan M. Intravenous sedation in implantology. Rev Stomatol Chir Maxillofac 1997;98:57-61.
10. Craig DC, Boyle CA, Fleming GJ, Palmer P. A sedation technique for implant and periodontal surgery. J Clin Periodontol 2000;27:955-9.
11. Hug CC Jr, McLeskey CH, Nahrwold ML, Roizen MF, Stanley TH, Thisted RA, et al. Hemodynamic effects of propofol: data from over 25,000 patients. Anesth Analg 1993;77:S21-9.
12. Reves JG, Glass PSA, Lubarsky DA. Nonbarbiturate intravenous anesthetics. In: Miller RD, editor. Anesthesia. 5th ed. Philadelphia: Churchill Livingstone; 2000. p. 229-37.
13. Ebert TJ. Differential effects of nitrous oxide on baroreflex control of heart rate and peripheral sympathetic nerve activity in humans. Anesthesiology 1990;72:16-22.
14. Johannessen KA, Cerqueira M, Veith RC, Stratton JR. Influence of sympathetic stimulation and parasympathetic withdrawal on Doppler echocardiographic left ventricular diastolic filling velocities in young normal subjects. Am J Cardiol 1991;67:520-6.
15. Niwa H, Satoh Y, Matsuura H. Cardiovascular responses to epinephrine-containing local anesthetics for dental use: a comparison of hemodynamic responses to infiltration anesthesia and ergometer-stress testing. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2000;90:171-81.
16. Niwa H, Shibutani T, Hori T, Kim Y, Akita M, Matsuura H. The interaction between pindolol and epinephrine contained in local anesthetic solution to the left ventricular diastolic filling velocity in normal subjects. Anesth Prog 1996;43:78-84.
17. Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P, et al. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. Circ Res 1986;59:178-93.
18. Pomeranz B, Macaulay RJ, Caudill MA, Kutz I, Adam D, Gordon D, et al. Assessment of autonomic function in humans by heart rate spectral analysis. Am J Physiol 1985;248(1 Pt 2):H151-3.
19. Smith JJ, Muzi M, Barney JA, Ceschi J, Hayes J, Ebert TJ. Impedance-derived cardiac indices in supine and upright exercise. Ann Biomed Eng 1989;17:507-15.
20. Kingwell BA, Thompson JM, Kaye DM, McPherson GA, Jennings GL, Esler MD. Heart rate spectral analysis, cardiac norepinephrine spillover, and muscle sympathetic nerve activity during human sympathetic nervous activation and failure. Circulation 1994;90:234-40.
21. 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.
22. Pagani M, Furlan R, Pizzinelli P, Crivellaro W, Cerutti S, Malliani A. Related Spectral analysis of R-R and arterial pressure variabilities to assess sympatho-vagal interaction during mental stress in humans. J Hypertens Suppl 1989;7:S14-5.
23. Hayano J, Mukai S, Sakakibara M, Okada A, Takata K, Fujinami T. Effects of respiratory interval on vagal modulation of heart rate. Am J Physiol 1994;267(1 Pt 2):H33-40.
24. Hayano J, Sakakibara Y, Yamada A, Yamada M, Mukai S, Fujinami T, et al. Accuracy of assessment of cardiac vagal tone by heart rate variability in normal subjects. Am J Cardiol 1991;67:199-204.
25. Li RC, Wong SL, Chan KK. Expanded version of PKSIM for pharmacokinetic simulations of both metabolite and parent drugs. Am J Ther 1997;4:16-22.
26. Li RC, Wong SL, Chan KK. Microcomputer-based programs for pharmacokinetic simulations. Am J Pharm Educ 1995;59:143-7.
27. Brand HS, Abraham-Inpijn L. Cardiovascular responses induced by dental treatment. Eur J Oral Sci 1996;104:245-52.
28. Meyer FU. Haemodynamic changes under emotional stress following a minor surgical procedure under local anaesthesia. Int J Oral Maxillofac Surg 1987;16:688-94.
29. Goldstein DS, Dionne R, Sweet J, Gracely R, Brewer HB Jr, Gregg R, et al. Circulatory, plasma catecholamine, cortisol, lipid, and psychological responses to a real-life stress (third molar extractions): effects of diazepam sedation and of inclusion of epinephrine with the local anesthetic. Psychosom Med 1982;44:259-72.
30. Wilson E, David A, MacKenzie N, Grant IS. Sedation during spinal anaesthesia: comparison of propofol and midazolam. Br J Anaesth 1990;64:48-52.
31. Mackenzie N, Grant IS. Propofol for intravenous sedation. Anaesthesia 1987;42:3-6.
32. Runes J, Strom C. Midazolam intravenous conscious sedation in oral surgery. A retrospective study of 372 cases. Swed Dent J 1996;20:29-33.
33. Taki K, Sugimura M, Satoh Y, Tanimoto A, Kuki F, Niwa H. Comparison between concentration of nitrous oxide with a nasal cannula and with a nasal mask on the nitrous oxide sedation. J Jpn Dent Soc Anesthesiol 2002;30:584-7.
34. Sugimura M, Hirota Y, Shibutani T, Niwa H, Hori T, Kim Y, et al. An echocardiographic study of interactions between pindolol and epinephrine contained in a local anesthetic solution. Anesth Prog 1995;42:29-35.
35. Ahmed MW, Kadish AH, Parker MA, Goldberger JJ. Effect of physiologic and pharmacologic adrenergic stimulation on heart rate variability. J Am Coll Cardiol 1994;24:1082-90.
36. Schachinger H, Weinbacher M, Kiss A, Ritz R, Langewitz W. Cardiovascular indices of peripheral and central sympathetic activation. Psychosom Med 2001;63:788-96.
37. Tulen JH, Man in t Veld AJ, Van Roon AM, Moleman P, Van Steenis HG, Blankestijn PJ, et al. Spectral analysis of hemodynamics during infusions of epinephrine and norepinephrine in men. J Appl Physiol 1994;76:1914-21.
38. Claeys MA, Gepts E, Camu F. Haemodynamic changes during anaesthesia induced and maintained with propofol. Br J Anaesth 1988;60:3-9.
39. Monk CR, Coates DP, Prys-Roberts C, Turtle MJ, Spelina K. Haemodynamic effects of a prolonged infusion of propofol as a supplement to nitrous oxide anaesthesia. Studies in association with peripheral arterial surgery. Br J Anaesth 1987;59:954-60.
40. Brussel T, Theissen JL, Vigfusson G, Lunkenheimer PP, Van Aken H, Lawin P. Hemodynamic and cardiodynamic effects of propofol and etomidate: negative inotropic properties of propofol. Anesth Analg 1989;69:35-40.
41. Gelissen HP, Epema AH, Henning RH, Krijnen HJ, Hennis PJ,

den Hertog A. Inotropic effects of propofol, thiopental, midazolam, etomidate, and ketamine on isolated human atrial muscle. Anesthesiology 1996;84:397-403.
42. Deutschman CS, Harris AP, Fleisher LA. Changes in heart rate variability under propofol anesthesia: a possible explanation for propofol-induced bradycardia. Anesth Analg 1994;79:373-7.
43. Galletly DC, Buckley DH, Robinson BJ, Corfiatis T. Heart rate variability during propofol anaesthesia. Br J Anaesth 1994;72:219-20.
44. Weinbroum AA, Halpern P, Rudick V, Sorkine P, Freedman M, Geller E. Midazolam versus propofol for long-term sedation in the ICU: a randomized prospective comparison. Intensive Care Med 1997;23:1258-63.
45. Ronan KP, Gallagher TJ, George B, Hamby B. Comparison of propofol and midazolam for sedation in intensive care unit patients. Crit Care Med 1995;23:286-93.
46. Agelink MW, Majewski TB, Andrich J, Mueck-Weymann M. Short-term effects of intravenous benzodiazepines on autonomic neurocardiac regulation in humans: a comparison between midazolam, diazepam, and lorazepam. Crit Care Med 2002;30:997-1006.
47. DiMicco JA. Evidence for control of cardiac vagal tone by benzodiazepine receptors. Neuropharmacology 1987;26:553-9.
48. Eisele JH. Nitrous oxide administration and hemodynamics. Chest 1977;72:271-2.
49. Eisele JH, Smith NT. Cardiovascular effects of 40 percent nitrous oxide in man. Anesth Analg 1972;51:956-63.
50. Sellgren J, Ponten J, Wallin BG. Percutaneous recording of muscle nerve sympathetic activity during propofol, nitrous oxide, and isoflurane anesthesia in humans. Anesthesiology 1990;73:20-7.
51. Ebert TJ, Kampine JP. Nitrous oxide augments sympathetic outflow: direct evidence from human peroneal nerve recordings. Anesth Analg 1989;69:444-9.

Reprint requests:

Hitoshi Niwa, DDS, PhD
Department of Dental Anesthesiology
Osaka University Graduate School of Dentistry
1-8 Yamadaoka, Suita, Osaka 565-0871, Japan
niwa@dent.osaka-u.ac.jp