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Effect of fentanyl on heart rate variability during mechanical ventilation

Kei Kohno[1], Junken Koh[1], and Yoshihiro Kosaka[2]

[1] Department of Anesthesia, Kure National Hospital, 3-1 Aoyama-cho, Kure, Hiroshima 737, Japan
[2] Department of Anesthesiology, Shimane Medical University, 89-1 Enya-cho, Izumo, Shimane 693, Japan

Abstract

Purpose. This study was performed to investigate the effect of fentanyl alone on heart rate variability (HRV) during mechanical ventilation using power spectral analysis. Arterial baroreceptor reflex was also tested with pharmacological manipulation to assess the contribution of vagal baroreceptor reflex modulation of HRV during fentanyl anesthesia.

Method. Ten patients participated in this study. Electrocardiograms and arterial pressure were recorded prior to and during fentanyl ($10\,\mu g \cdot kg^{-1}$) and vecuronium ($0.2\,mg \cdot kg^{-1}$) anesthesia, with respiratory rate and tidal volume controlled ventilation. R–R intervals were analyzed by fast Fourier transformation, and changes in low-frequency (LF) and high-frequency (HF) power were compared. Arterial baroreceptor reflex regulation was also tested with administration of nitroglycerin ($250\,\mu g$) or phenylephrine ($250\,\mu g$).

Results. HF power was significantly reduced during anesthesia from 3.20 ± 2.93 to $0.46 \pm 0.48\,ms^2 \cdot Hz^{-1} \cdot 10^3$ (mean ± SD, $P < 0.05$). However, LF power did not change despite increases in plasma catecholamine concentrations. The response to phenylephrine was reduced during fentanyl anesthesia from 16.6 ± 5.7 to $9.5 \pm 5.4\,ms \cdot mmHg^{-1}$ ($P < 0.05$), whereas the response to nitroglycerin was not affected.

Conclusion. Our data indicate that fentanyl modulates the respiratory frequency fluctuation of HRV. This is partly caused by the effects of fentanyl on arterial baroreflex sensitivity.

Key words: Fentanyl, Heart rate variability, Baroreceptor reflex, Mechanical ventilation

Introduction

Since the introduction of frequency domain analysis of heart rate variability (HRV), the effects of anesthetics on HRV have been extensively studied. Kato et al. [1] reported that isoflurane decreases both the high-frequency (HF) and low-frequency (LF) components of HRV in a concentration-dependent manner. Galletly et al. [2] found a diminution of both components during inhalation anesthesia with the addition of intravenous fentanyl. However, the effect of fentanyl alone on HRV has not been examined closely. Because HRV is affected by respiration, the comparison of HRV prior to and during anesthesia is difficult. In this study, we examined the effect of fentanyl on HRV using spectral analysis, while controlling both respiratory rate and tidal volume prior to and during anesthesia. We also tested arterial baroreceptor reflex regulation by changing systolic arterial pressure with bolus injections of either nitroglycerin or phenylephrine, to assess the contribution of arterial baroreceptor modulation of HRV during fentanyl anesthesia.

Address correspondence to: J. Koh
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Methods

Patients

Ten patients (6 men and 4 women, aged 20 to 35 years, ASA Physical Status 1), scheduled for elective orthopedic surgical procedures, were studied. The patients had no relevant medical history except for accidental trauma. This study was approved by the Committee on Human Investigation of Kure National Hospital. Each patient gave written, informed consent prior to participating in the study.

Measurements

Patients were studied in the supine position. A 22-gauge catheter was inserted into the left radial artery for direct measurement of arterial pressure (Lifescope 12, Nihon Koden, Tokyo, Japan) and for blood sampling. Blood

samples (7 ml) were centrifuged immediately following withdrawal, and the resulting plasma samples were stored at −40°C until assayed for catecholamines (Special Reference Laboratory (SRL), Tokyo, Japan).

Another catheter was placed in the right antecubital vein for fluid and drug administration. Electrocardiograms (ECG) were recorded using standard chest leads. Tidal volumes were measured through a mouthpiece connected to a spirometer (Respiromonitor RM-300, Minato Medical Science, Osaka, Japan). The value of each tidal volume was exported to a personal computer through an RS-232C port, and the data were stored on a hard disk. The arterial partial pressures of carbon dioxide ($Paco_2$) and oxygen (Pao_2) were measured with a blood gas analysis system (CIBA Corning 288 Blood Gas System, CIBA Corning Diagnostics, Medfield, MA, USA). All physiological measurements were archived using either FM tape or electrostatic paper recorders.

Experimental protocol

The experiment began after a 15-min rest period. Five-minute recordings were obtained prior to the induction of anesthesia as control data. During this period, patients were prompted to breathe at a rate of 15 breaths·min^{-1} with a timed auditory signal. Anesthesia was induced with fentanyl (bolus of 10 μg·kg^{-1} followed by a continuous infusion of 15 μg·kg^{-1}·h^{-1}), and tracheal intubation was performed following the administration of vecuronium (0.2 mg·kg^{-1}). Five-minute recordings were again obtained after the patient was stabilized. During the period in which measurements were performed under anesthesia, patients were ventilated mechanically at a rate of 15 breaths·min^{-1}, and the tidal volume was adjusted to match the tidal volume values obtained during the control period. To that end, the personal computer controlled each tidal volume of the ventilator (MERA/ADV-1000MK II, Senko Medical Instrument, Tokyo, Japan) using the data stored on the hard disk with the same time course as the control period. The I/E ratio of this ventilator was fixed at 1:1.5. The differences between the tidal volume during the control period and during anesthesia were between 5% and 10% in all patients.

Following the 5-min recording of ECG and arterial pressure, arterial baroreceptor reflex testing was performed by bolus injections of nitroglycerin (250 μg) and phenylephrine (250 μg). The order of drug administration was random, and determined by a coin toss. Three of the patients received phenylephrine first. There was at least a 10-min interval between each drug administration to allow heart rate and arterial pressure to return to values obtained just prior to drug administration. During the measurement of arterial baroreflex sensitivity, the respiratory rate and tidal volumes were controlled by the method described above. The fraction of inspired oxygen was 1.0 during all measurements.

Data analysis

The method used for data analysis has been described previously [3,4]. Briefly, ECG and beat-to-beat arterial pressure wave forms were digitized at 250 Hz using signal acquisition hardware and software (CODAS, Dataq Instruments, Akron, OH, USA). R–R intervals and systolic and diastolic pressures were subsequently analyzed using custom programs developed for DADiSP software (DSP Development, Cambridge, MA, USA). The R–R interval and systolic arterial pressure power spectra were derived by a periodogram method based on the Welch algorithm. The procedure involves analysis of 256 s of consecutive R–R intervals and systolic arterial pressure measurements. The time series were interpolated linearly at 8 Hz to obtain equidistant time intervals that were divided into seven equal overlapping segments. Each segment was zero filled, detrended, and Hanning window-filtered. Fast Fourier transformation was performed, and the modified periodograms were averaged to produce the power spectrum. The frequency resolution of this procedure was 0.0039 Hz. The areas under power spectra were integrated in low- and high-frequency ranges (defined as 0.05 to 0.15 Hz and 0.15 to 0.50 Hz, respectively).

With respect to determination of arterial baroreflex sensitivity, a beat-to-beat analysis was performed for all beats after the first noticeable change in systolic arterial pressure. Each R–R interval value was then plotted as a function of the preceding systolic arterial pressure value. A least-square fit regression line was obtained in each subject, and baroreflex regulation of heart rate was expressed as the slope of the regression line. Data points beyond the linear portion of the curve were discarded; only those lines with correlation coefficients >0.85 were analyzed [5].

Statistical analysis

Data are presented as means ± SD. The paired Wilcoxon test was used to determine if differences were significant. Differences were considered significant at $P < 0.05$.

Results

Values for key parameters obtained prior to and during fentanyl anesthesia are shown in Table 1. Mean heart rate, mean systolic and diastolic pressures, and $Paco_2$ did not change with the administration of fentanyl.

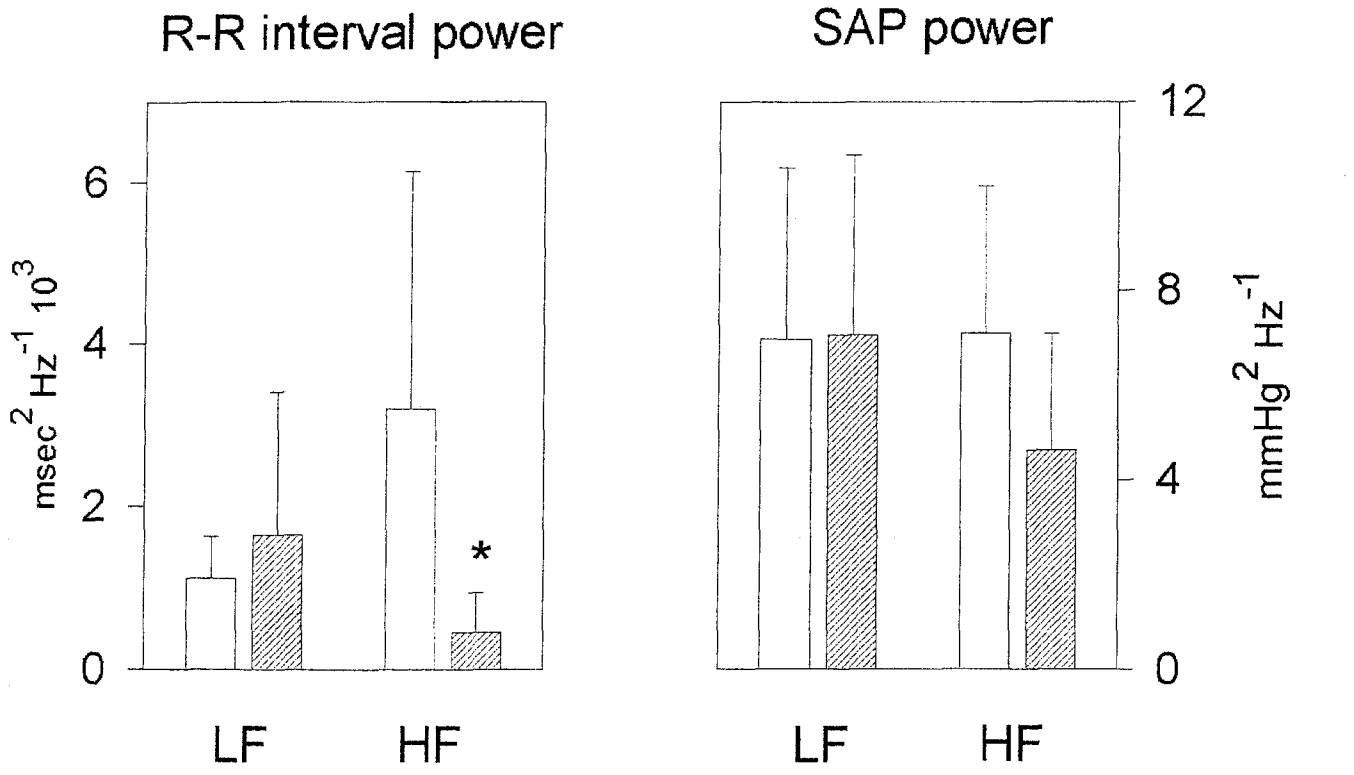

Fig. 1. Statistical analyses of the R–R interval and the systolic arterial pressure (*SAP*) power spectra. Data are expressed as mean ± SD. *LF*, low frequency, HF, high frequency. *open bars*, control; *hatched bars*, fentanyl. *$P < 0.05$ *vs* control

Table 1. Parameter values prior to and during fentanyl anesthesia

Parameter	Control	Fentanyl
mR–R (ms)	890 ± 196	972 ± 164
mSAP (mmHg)	138 ± 19	148 ± 28
mDAP (mmHg)	66 ± 9	69 ± 9
Nor (pg·ml^{-1})	162 ± 63	265 ± 111*
Epi (pg·ml^{-1})	81 ± 60	335 ± 338*
$Paco_2$ (mmHg)	39 ± 6	37 ± 3
Pao_2 (mmHg)	462 ± 76	568 ± 47*

mR–R, mean R–R interval; mSAP, mean systolic arterial pressure; mDAP, mean diastolic arterial pressure; Nor, norepinephrine; Epi, epinephrine.
Values are mean ± SD. *$P < 0.05$ *vs* control.

However, during fentanyl anesthesia, Pao_2 and plasma catecholamines increased.

In the power spectra of R–R intervals and systolic pressures, statistical analysis revealed that the LF power of R–R interval, LF, and HF power of systolic arterial pressure were not significantly affected by fentanyl anesthesia. However, there was a significant decrease in the HF power of R–R interval during fentanyl anesthesia from 3.20 ± 2.93 to 0.46 ± 0.48 ms^2·Hz^{-1}·10^3 ($P < 0.05$) (Fig. 1).

Regarding the relationship between HRV and catecholamines, there was a weak correlation between plasma norepinephrine levels and LF/HF ratio; however, no relationship was found between plasma epinephrine concentrations and LF/HF ratio (Fig. 2).

Figure 3 shows typical systolic arterial pressure, and R–R interval responses to nitroglycerin and phenylephrine administration in one patient. For statistical analysis, one patient's data sets were eliminated because the correlation coefficients were <0.85 during the measurements under anesthesia.

Treatment with either drug caused significant changes in arterial pressure. However, the slope of the regression line was greater for the data obtained from phenylephrine administration. The slope of the regression line correlating increases in the R–R interval with increases in systolic arterial pressure induced by phenylephrine decreased significantly during fentanyl anesthesia (9.5 ± 5.4 ms·mmHg^{-1}) when compared to the data obtained prior to anesthesia (16.6 ± 5.7 ms·mmHg^{-1}). In contrast, baroreflex response to nitroglycerin injection was not different when comparing the periods prior to and during anesthesia (5.6 ± 3.8 *vs* 5.8 ± 4.1 ms·mmHg^{-1}) (Fig. 4).

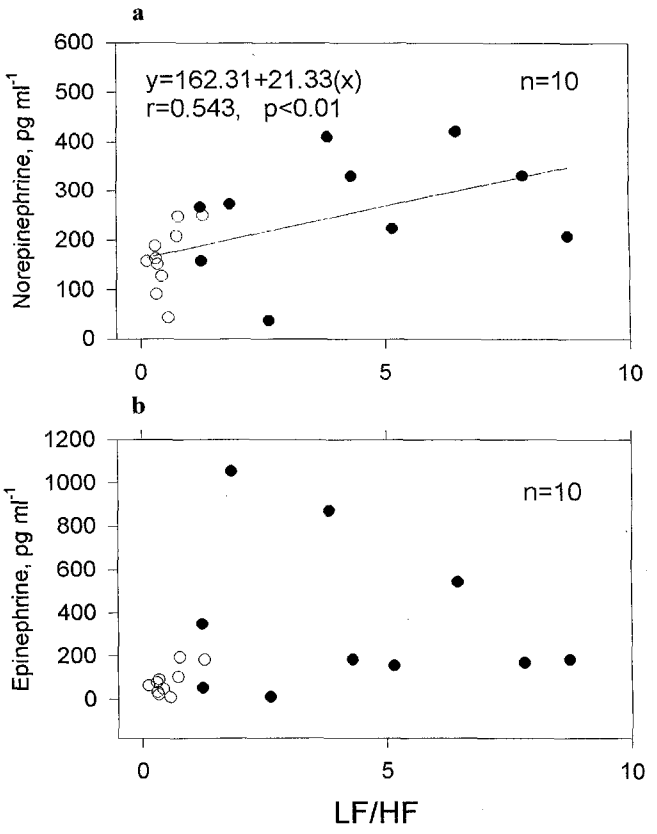

Fig. 2a,b. Relationships between the low frequency/high frequency (*LF/HF*) ratio and norepinephrine (**a**), and epinephrine (**b**), concentrations. Open circles: control period: filled circles, during fentanyl anesthesia. There is no significant correlation between the LF/HF ratio and epinephrine concentration

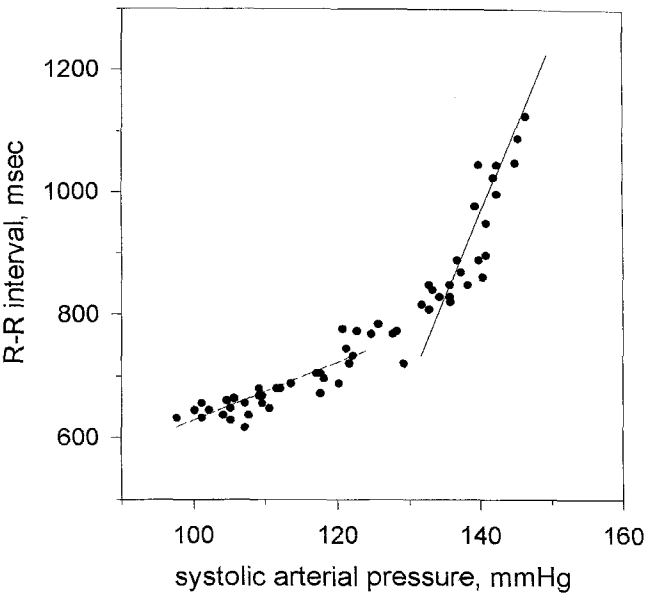

Fig. 3. Correlation between systolic arterial pressures and corresponding R–R intervals during the measurement of arterial baroreflex sensitivity from a representative patient. The *solid line* represents the regression line of the data obtained after injection of phenylephrine, and the *dashed line* represents the regression line of the data obtained after nitroglycerin injection

Discussion

This study demonstrates that the HF component of HRV is significantly reduced by fentanyl anesthesia during mechanical ventilation, while mean heart rate, and mean systolic and diastolic pressures do not change. Furthermore, arterial baroreceptor reflex control of heart rate was significantly reduced in the pressor test but did not change in the depressor test. In addition, the results show that the LF component of HRV does not change during fentanyl anesthesia, despite an increase in plasma catecholamine concentrations.

Three mechanisms may be responsible for the genesis of the HF component [6]: (1) medullary respiratory neurons could regulate vagal cardiovascular motor neurons directly in synchrony with the respiratory cycle; (2) blood pressure changes could indirectly modulate heart rate via arterial baroreceptors; and (3) lung inflation could cause a reflex response mediated by lung stretch receptors. There is general agreement that respiratory variables such as respiratory rate, tidal volume, and inspiratory/expiratory ratio strongly influence the HRV [7]. Therefore, in an effort to control these variables, the respiratory rate and tidal volume were matched during the periods prior to and during anesthesia. We were not able to control the inspiratory/expiratory ratio in this study. However, $Paco_2$ did not change significantly during mechanical ventilation, and the HF power of systolic pressure variability, which is believed to be due to the mechanical work of respiration [8], was not altered by fentanyl anesthesia (Fig. 1). These data strongly suggest that changes in the breathing pattern are not responsible for the decrease in the HF component of HRV.

Concerning arterial baroreceptor sensitivity during fentanyl anesthesia [9,10], there is no report found in such a setting of increased sympathetic and vagal activity (heart rate and arterial pressure remained stable despite high catecholamine concentrations during anesthesia). It is known that the baroreflex slopes for phenylephrine-induced bradycardia are in the range of 12 to 17 ms·mmHg^{-1} in healthy normotensive people [11], which are almost identical to the values we obtained in patients prior to the administration of anesthesia. During fentanyl anesthesia, the phenylephrine-induced baroreflex slope was reduced from 16.6 ± 5.7 to 9.5 ± 5.4 ms·mmHg^{-1} (Fig. 4). Rouby et al. [12] have studied baroreflex sensitivity during conventional mechanical ventilation using the same anesthetic

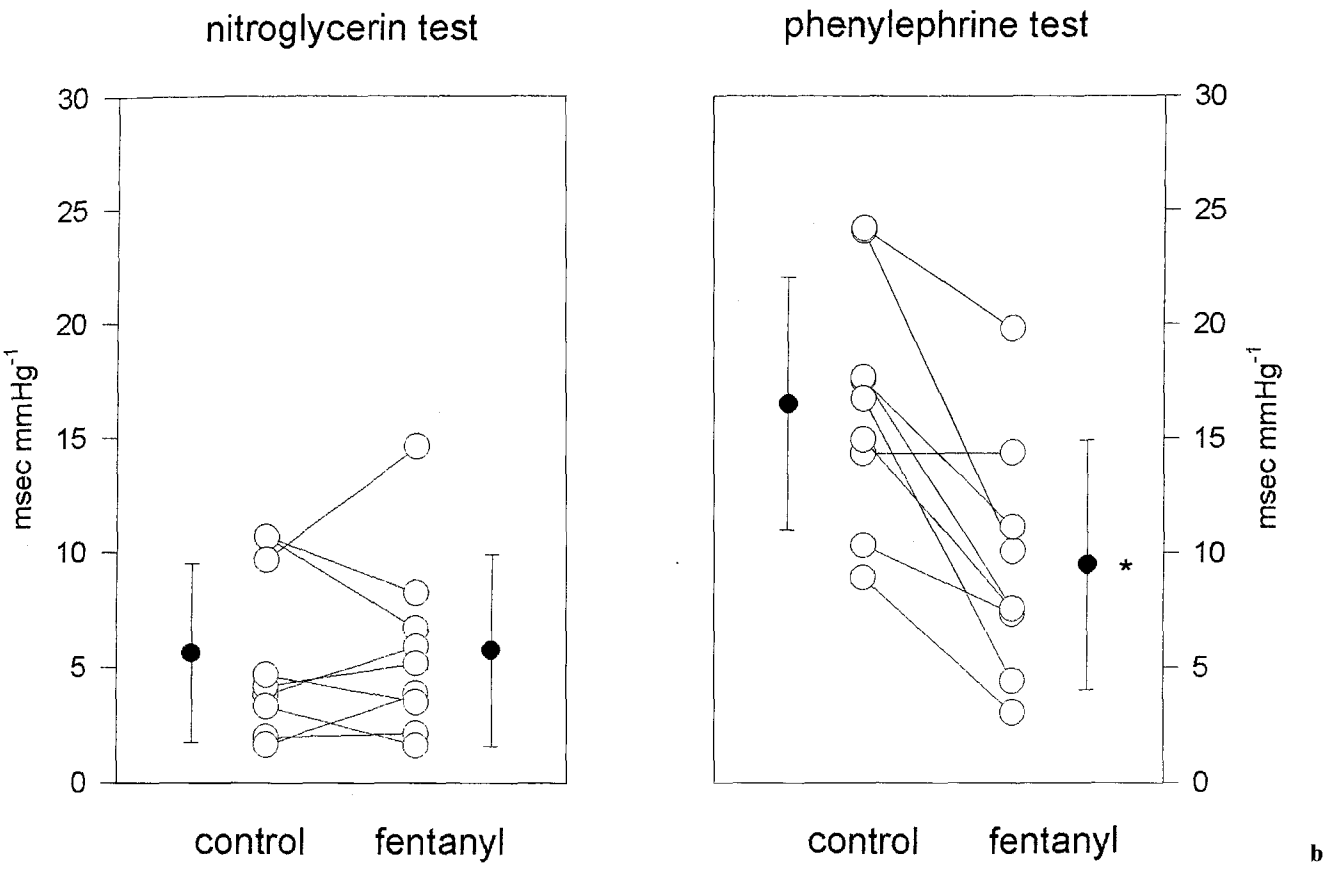

Fig. 4a,b. Effect of fentanyl on the baroreflex regulation of heart rate after nitroglycerin-induced decreases (**a**) and phenylephrine-induced increases (**b**) in systolic arterial pressure in each individual ($n = 9$). The baroreflex slope is significantly lower during fentanyl anesthesia after phenylephrine injection, whereas there is no difference after nitroglycerin injection. $^*P < 0.05$ *vs* control

method and drug intervention as the present study, and have obtained similar results. Eckberg and Wallin have reported a reduction in the carotid-baroreceptor reflex slope during hand grip exercise or sympathetic activation [13], and have attributed this phenomenon to sympathetic modulation of vagal responses to baroreceptor input. Therefore, it may be predicted that baroreflex-mediated bradycardia is reduced during fentanyl anesthesia with mechanical ventilation because of sympathetic modulation of vagal cardiac outflow during phenylephrine injection. In contrast to phenylephrine-induced bradycardia, the reflex slope for nitroglycerin-induced tachycardia was unchanged in this study. The reflex slope during anesthesia, however, was 5.8 ± 1.3 ms·mmHg^{-1}, which is much higher than the value reported by Rouby et al. (1.96 ± 1.23 ms·mmHg^{-1}). During the measurement of arterial baroreceptor reflex sensitivity using pharmacologic interventions, heart rate acceleration rises with the attenuation of vagal tone [14], and the reflex slope is known to be ~7 ms·mmHg^{-1} [15]. If the vagal cardiac motor nuclei were highly activated by fentanyl, the response of the heart rate to baroreceptor stimuli would be exaggerated [16]. This may explain, to some extent, the greater value for the slope that we obtained compared to data of Rouby's et al. However, enhanced baroreceptor sensitivity is not responsible, because there was no change in the reflex slope for nitroglycerin-induced tachycardia during anesthesia. It is known that drug-induced arterial pressure changes, if they are within the range of spontaneous circadian arterial pressure fluctuations, do not affect the baroreceptor-cardiac reflex slope [17]. Although we could not exclude another cause, e.g., the administration of a muscle relaxant or mechanical ventilation [18], it is likely that fentanyl altered the arterial baroreflex control in this study.

Although no patient could recall the anesthetic procedure on the day following surgery, a 10 μg·kg^{-1} dose of fentanyl might not be sufficient to produce unconsciousness and protect sympathetic response from the

endotracheal intubation [19]. However, the magnitude of respiratory sinus arrhythmia does not decline even in the setting of elevated plasma norepinephrine concentrations [20]. Fentanyl is widely known to induce significant central respiratory depression and increase vagal cardiac tone [21,22]. Furthermore, Goldberger et al. [23] recently demonstrated a decrease in the HF power of HRV during baroreflex vagal stimulation with phenylephrine infusions. In keeping with these findings, reduced baroreflex control and depressed central respiratory control, as well as increased vagal and sympathetic neural activity, might have contributed to the decrease in the HF component of HRV, while the HF of systolic arterial pressure variability remains unchanged in this study.

There is disagreement in the literature concerning the interpretation of the LF component of HRV, which is considered by some [24], as a marker of sympathetic modulation, and by others [25] as a parameter that includes both sympathetic and vagal influences. In the present study, we were not able to demonstrate an increase in the LF component that corresponded with an increase in plasma catecholamine concentrations. However, we did demonstrate a weak correlation between the LH/HF ratio and plasma norepinephrine concentrations (Fig. 2). Pagani et al. [26] have shown that increased sympathetic tone is associated with marked increase in the LF component and a decrease in the HF component. They concluded that the LF/HF ratio is a marker of sympathetic activity. Further, Saul et al. [27] have found a weak relationship between sympathetic activity and the LF/total power ratio during nitroprusside infusion. Our data support the observations of Pagani et al. and Saul et al.; however, further studies are necessary to determine the precise mechanism responsible for the regulation of HRV by sympathetic neural outflow.

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References

1. Kato M, Komatsu T, Kimura T, Sugiyama F, Nakashima K, Shimada Y (1992) Spectral analysis of heart rate variability during isoflurane anesthesia. Anesthesiology 77:669–674
2. Galletly DC, Westenberg AM, Robinson BJ, Corfiatis T (1994) Effect of halothane, isoflurane and fentanyl on spectral components of heart rate variability. Br J Anaesth 72:177–180
3. Koh J, Brown TE, Beightol LA, Ha CY, Eckberg DL (1994) Human autonomic rhythms: vagal cardiac mechanisms in tetraplegic subjects. J Physiol (Lond) 474:483–495
4. Brown TE, Beightol LA, Koh J, Eckberg DL (1993) Important influence of respiration on human R–R interval power spectra is largely ignored. J Appl Physiol 75:2310–2317
5. Sullebarger JT, Liang CS, Woolf PD, Willick AE, Richeson JF (1990) Comparison of phenylephrine bolus and infusion methods in baroreflex measurements. J Appl Physiol 69:962–967
6. Hirsch JA, Bishop B (1981) Respiratory sinus arrhythmia in humans: how breathing pattern modulates heart rate. Am J Physiol 241:H620–H629
7. Eckberg DL (1983) Human sinus arrhythmia as an index of vagal cardiac outflow. J Appl Physiol 54:961–966
8. Furlan R, Guzzetti S, Crivellaro W, Dassi S, Tinelli M, Baselli G, Cerutti S, Lombardi F, Pagani M, Malliani A (1990) Continuous 24-hour assessment of the neural regulation of systemic arterial pressure and RR variabilities in ambulant subjects. Circulation 81:537–547
9. Kotrly KJ, Ebert TJ, Vucins EJ, Roerig DL, Standricka A, Kampine, JP (1986) Effects of fentanyl-diazepam-nitrous oxide anesthesia on arterial baroreflex control of heart rate in man. Br J Anaesth 58:406–414
10. Ebert TJ, Muzi M (1994) Propofol and autonomic reflex function in humans. Anesth Analg 78;369–375
11. Goldstein DS, Horwitz D, Keiser HR (1982) Comparison of techniques for measuring baroreflex sensitivity in man. Circulation 66:432–439
12. Rouby JJ, Houissa M, Brichant JF, Baron JF, McMillan C, Arthaud M, Amzallag P, Viars P (1987) Effects of high-frequency jet ventilation on arterial baroreflex regulation of heart rate. J Appl Physiol 63:2216–2222
13. Eckberg DL, Wallin BG (1987) Isometric exercise modifies autonomic baroreflex responses in humans. J Appl Physiol 63:2325–2330
14. Thames MD, Kontos HA (1970) Mechanisms of baroreceptor-induced changes in heart rate. Am J Physiol 218:251–256
15. Giudicelli JF, Berdeaux A, Edouard A, Richer C, Jacolot D (1985) The effect of enalapril on baroreceptor mediated reflex function in normotensive subjects. Br J Clin Pharmacol 20:211–218
16. Chen RYZ, Matteo RS, Fan FC, Schuessler GB, Chien S (1982) Resetting of baroreflex sensitivity after induced hypotension. Anesthesiology 56:29–35
17. Fritsch JM, Rea RF, Eckberg DL (1989) Carotid baroreflex resetting during drug-induced arterial pressure changes in humans. Am J Physiol 256:R549–R553
18. Yli-Hankala A, Porkkala T, Kaukinen S, Hakkinen V, Jantti V (1991) Respiratory sinus arrhythmia is reversed during positive pressure ventilation. Acta Physiol Scand 141:399–407
19. Lunn JK, Stanley TH, Eisele J, Webster L, Woodward A (1979) High dose fentanyl anesthesia for coronary artery surgery: plasma fentanyl concentrations and influence of nitrous oxide on cardiovascular response. Anesth Analg 58:390–395
20. Eckberg DL, Rea RF, Andersson OK, Hedner T, Pernow J, Lundberg JM, Wallin BG (1988) Baroreflex modulation of sympathetic activity and sympathetic neurotransmitters in humans. Acta Physiol Scand 133:221–231
21. Reitan JA, Stengert KB, Wymore ML, Martucci RW (1978) Central vagal control of fentanyl-induced bradycardia during halothane anesthesia. Anesth Analg 57:31–36
22. Laubie M, Schmitt H, Drouillat M (1977) Central sites and mechanisms of the hypotensive and bradycardic effects of the narcotic analgesic agent fentanyl. Arch Pharmacol 296:255–261
23. Goldberger JJ, Ahmed MW, Parker MA, Kadish AH (1994) Dissociation of heart rate variability from parasympathetic tone. Am J Physiol 266:H2152–H2157
24. Montano N, Ruscone TG, Porta A, Lombardi F, Pagani M, Malliani A (1994) Power spectrum analysis of heart rate variabil-

ity to assess the changes in sympathovagal balance during graded orthostatic tilt. Circulation 90:1826–1831
25. Appel ML, Berger RD, Saul JP, Smith JM, Cohen RJ (1989) Beat to beat variability in cardiovascular variables: noise or music? J Am Coll Cardiol 14:1139–1148
26. Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P, Sandrone G, Malfatto G, Dell'Orto S, Piccaluga E, Turiel M, Baselli G, Cerrutti S, Malliani A (1986) Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. Circ Res 59:178–193
27. Saul JP, Rea RF, Eckberg DL, Berger RD, Cohen RJ (1990) Heart rate and muscle sympathetic nerve variability during reflex changes of autonomic activity. Am J Physiol 258:H713–H721