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Effects of midazolam and diazepam as premedication on heart rate variability in surgical patients

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Summary

We have examined the effects of midazolam 0.06 mg kg^{-1} i.m. and diazepam 0.2 mg kg^{-1} orally as premedication on the spectral components of heart rate (HR) variability in 24 elderly patients aged 65–87 yr and 24 young patients aged 18–35 yr undergoing elective surgery. The low-frequency/high-frequency (LF/HF) ratio of HR variability increased after arrival in the operating room in elderly patients who received no premedication, but not in young patients. In elderly patients who received midazolam or diazepam, the LF/HF ratio did not increase. However, diazepam increased the low-frequency component and the total power of HR variability in both young and elderly patients. We conclude that cardiac sympathetic nerve activity increased after arrival in the operating room in the elderly, that midazolam or diazepam reduced this increase and that diazepam caused an increase in the total power of HR variability that has not been observed for other agents. (*Br. J. Anaesth.* 1994; **43**: 479–483)

Key words

Age factors. Premedication, midazolam. Premedication, diazepam. Heart, heart rate.

Spectral analysis of heart rate (HR) variability permits non-invasive assessment of cardiac sympathetic and parasympathetic nerve activity [1, 2]. Two major components are seen within a typical HR variability spectrum [1, 2]: a high-frequency (HF) component (0.15–0.5 Hz) mediated by the parasympathetic nervous system and attributable to respiratory sinus arrhythmia [3], and a low-frequency (LF) component (0.04–0.15 Hz) mediated by both the sympathetic and parasympathetic nervous systems and related to the so-called 10-s waves in arterial pressure mediated by the baroreflex [1, 2]. The low-frequency/high-frequency (LF/HF) ratio is considered to be a useful index of cardiac sympathetic nerve activity [4, 5].

It has been suggested that resting plasma concentrations of noradrenaline in the elderly are significantly higher than those in the young [6]. However, the sympathetic response to postural changes declines with age [7] and a significant age-related decline in resting parasympathetic function has been noted [8]. Thus elderly patients may show altered sympathetic and parasympathetic responses before surgery.

The objective of this study was to examine the effects of i.m. midazolam and oral diazepam as premedication on spectral components of HR variability in elderly compared with young patients.

Patients and methods

We studied 24 elderly patients aged 65–87 yr and 24 young patients aged 18–35 yr, ASA I or II, who were undergoing elective surgery. The study was approved by the institutional Human Research Committee and all patients gave informed consent. Patients with cardiovascular, pulmonary or neurological disease were excluded and no patients were receiving medications before surgery. Elderly and young patients were allocated randomly to one of three groups: no premedication group (elderly $n = 8$, young $n = 8$), in which no premedication was given; midazolam group (elderly $n = 8$, young $n = 8$), in which midazolam 0.06 mg kg^{-1} i.m. was given as premedication; and diazepam group (elderly $n = 8$, young $n = 8$), in which diazepam 0.2 mg kg^{-1} orally was given as premedication.

MEASUREMENTS

The surface electrocardiogram (ECG) was monitored from lead II with an electrocardiograph (model 78342A, Hewlett–Packard, USA). The output of the ECG monitor was recorded using a digital audio tape (DAT) recorder (PC-108M, Sony, Japan) for longer than 256 s to obtain sufficient frequency resolution. Offline analysis was performed on a personal computer (PC486, EPSON, Japan). ECG data were played back from the DAT and analogue data were transferred via an analogue–digital converter into the computer memory with a sampling rate of 1/840 s. The computer first discriminated noise as power supply interferences, high frequency of it or baseline drifting, using digital band-pass filters, and second,

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Table 1 Patient characteristics (mean (range or SEM)) in elderly and young patients after premedication with midazolam or diazepam and in those who did not receive premedication

	Young			Elderly		
	Midazolam	Diazepam	None	Midazolam	Diazepam	None
Age (yr)	26 (18–32)	30 (22–35)	24 (18–32)	69 (65–77)	75 (68–84)	75 (65–87)
Height (cm)	165 (2)	159 (3)	163 (3)	160 (3)	150 (3)	152 (3)
Weight (kg)	59 (4)	53 (4)	58 (7)	54 (4)	51 (3)	56 (5)
Sex (F/M)	3/5	1/7	4/4	2/6	4/4	4/4

it detected the peak of the R wave of the ECG to calculate consecutive R-R intervals with a resolution of 1.19 ms using the peak detection algorithm. As fast Fourier transform requires equally distributed points, linear interpolation techniques were used between the calculated instantaneous heart rate points which were distributed irregularly. Spectral power distribution was calculated by fast Fourier transform with 512 sampling points of 0.5-Hz interval and the power spectrum of HR variability was divided into two zones; an LF (0.04–0.15 Hz) and HF component (0.15–0.5 Hz). We examined the LF component power, the HF component power, total (LF+HF) power and the LF/HF ratio of HR variability.

EXPERIMENTAL PROCEDURE

On the day before surgery, baseline ECG recordings and ventilatory frequency measurements were obtained while the patient rested in the supine position in a quiet room. On the day of surgery, premedication was administered by i.m. injection in the deltoid muscle (midazolam) or orally (diazepam), 20 min before the patient was transferred to the operating room. After arrival in the operating room, post-premedication ECG recordings and ventilatory frequency measurements were obtained at the same times for all groups in the operating room.

DATA ANALAYSIS

Statistical analysis was carried out using the paired t test. Differences were considered significant when $P < 0.05$. All values are presented as mean (SEM).

Results

There were no differences in age, height, weight or sex between the young or elderly patients in the three groups (table 1). A representative baseline HR trace and spectral analysis of HR variability from one elderly patient are shown in figure 1.

EFFECTS OF AGE ON BASELINE HR VARIABILITY

There were no significant differences in HR between young and elderly patients (table 2). However, marked differences were observed in HF variability: the LF component power, HF component power and total power of HR variability were significantly lower in the elderly than in the young patients. The

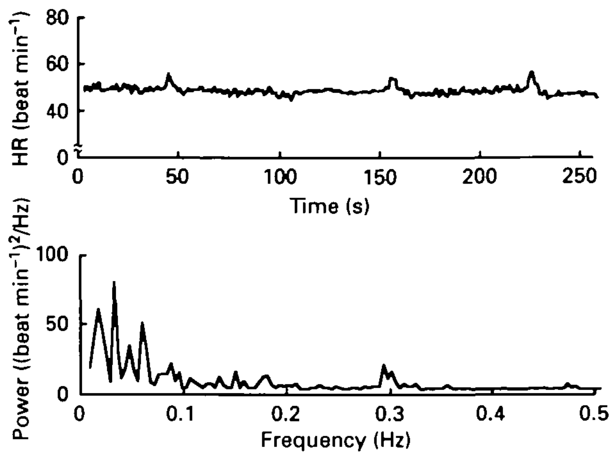

Figure 1 Instantaneous heart rate (HR) calculated from R-R intervals. Linear interpolation techniques were used between the calculated instantaneous HR points. Spectral analysis of HR variability was calculated by fast Fourier transform. Two major components are seen within a typical HR variability spectrum: a high-frequency (HF) component (0.15–0.5 Hz) medicated by the parasympathetic nervous system and a low-frequency (LF) component (0.04–0.15 Hz) mediated by the sympathetic and parasympathetic nervous systems.

Table 2 Mean (SEM) baseline values for heart rate (HR) and HR variability (LF, HF = low, high frequency, respectively). * $P < 0.05$ compared with young patients

	Young (n = 24)	Elderly (n = 24)
HR (beat min^{-1})	69.3 (1.9)	72.6 (3.0)
LF component ((beat min^{-1})^2/Hz)	819.6 (116.5)	177.6 (31.7)*
HF component ((beat min^{-1})^2/Hz)	770.6 (109.2)	192.0 (41.4)*
LF/HF ratio	1.41 (0.25)	1.62 (0.30)
Total power of HR variability ((beat min^{-1})^2/Hz)	1590.2 (209.9)	369.6 (64.6)*

LF/HF ratio was slightly higher in the elderly than in the young, but this difference was not significant (table 2).

EFFECTS OF ENTERING THE OPERATING ROOM WITHOUT PREMEDICATION ON HR VARIABILITY

Table 3 shows the effects of entering the operating room without premedication on HR and HR variability. In elderly patients who received no premedication, the LF/HF ratio increased significantly compared with the baseline value. On the other hand, in young patients who received no premedication, the LF/HF ratio did not change signifi-

Table 3 Mean (SEM) heart rate (HR) and HR variability data in patients who did not receive premedication at baseline and in the operating room (OR). * $P < 0.05$ compared with baseline value. OR = operating room

	Young ($n = 8$)		Elderly ($n = 8$)	
	Baseline	OR	Baseline	OR
HR (beat min^{-1})	70.4 (1.8)	77.1 (4.6)	66.4 (5.5)	66.3 (4.3)
LF component ((beat $min^{-1})^2$/Hz	1101.7 (274.4)	1343.3 (374.0)	100.4 (36.1)	251.7 (76.3)
HF component ((beat $min^{-1})^2$/Hz)	975.4 (188.2)	1290.5 (411.0)	155.4 (56.4)	184.9 (72.4)
LF/HF ratio	1.12 (0.14)	1.08 (0.23)	0.98 (0.25)	2.06 (0.54)*
Total power of HR variability ((beat $min^{-1})^2$/Hz)	2077.1 (430.4)	2633.8 (751.8)	255.7 (83.8)	436.6 (134.4)

Table 4 Effects of midazolam as premedication on heart rate (HR) and HR variability (mean (SEM)). Post-medication values were obtained in the operating room

	Young ($n = 8$)		Elderly ($n = 8$)	
	Baseline	After medication	Baseline	After medication
HR (beat min^{-1})	69.6 (4.7)	69.8 (6.4)	73.4 (5.0)	73.2 (5.3)
LF component ((beat $min^{-1})^2$/Hz	783.5 (172.5)	1183.5 (321.8)	246.2 (49.7)	258.6 (74.2)
HF component ((beat $min^{-1})^2$/Hz)	840.3 (243.5)	785.1 (244.0)	321.0 (96.9)	166.2 (44.6)
LF/HF ratio	1.63 (0.64)	3.22 (1.24)	1.32 (0.37)	2.34 (0.80)
Total power of HR variability ((beat $min^{-1})^2$/Hz)	1623.8 (405.9)	1968.6 (520.9)	567.2 (138.0)	424.8 (85.3)

Table 5 Effects of diazepam as premedication on heart rate (HR) and HR variability (mean (SEM)). Post-medication values were obtained in the operating room. * $P < 0.05$ compared with baseline value

	Young ($n = 8$)		Elderly ($n = 8$)	
	Baseline	After medication	Baseline	After medication
HR (beat min^{-1})	68.0 (3.4)	71.9 (4.9)	78.1 (4.7)	73.5 (5.6)
LF component ((beat $min^{-1})^2$/Hz)	573.7 (92.8)	1477.1 (319.4)*	186.3 (68.0)	354.6 (104.4)*
HF component ((beat $min^{-1})^2$/Hz)	496.1 (73.3)	777.9 (261.2)	99.7 (22.7)	194.4 (51.6)
LF/HF ratio	1.48 (0.39)	3.00 (0.95)	2.57 (0.71)	2.61 (1.03)
Total power of HR variability ((beat $min^{-1})^2$/Hz)	1069.7 (108.5)	2254.9 (547.1)*	286.0 (81.3)	549.0 (121.3)*

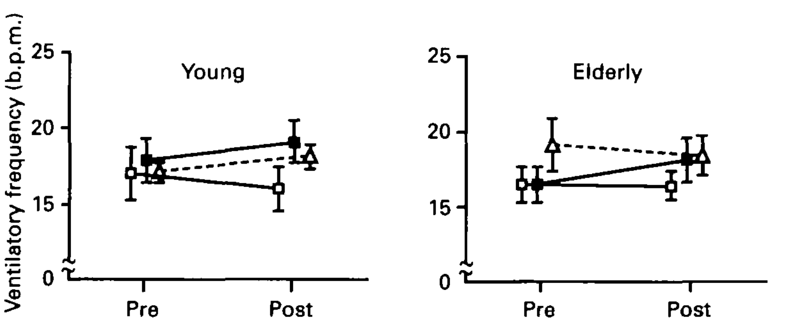

Figure 2 Mean (SEM) changes in ventilatory frequency caused by premedication with midazolam (■), diazepam (△) or by no premedication (□) in young and elderly patients. No significant differences were observed.

cantly. The LF and HF components and total power of HR variability increased slightly both in the young and elderly, but this increase was not significant.

EFFECTS OF MIDAZOLAM AS PREMEDICATION ON HR VARIABILITY

Table 4 shows the effects of midazolam as premedication on HR and HR variability. In the elderly, the LF/HF ratio did not increase significantly. The HF component and total power of HR variability in the elderly and HF component in the young decreased compared with baseline values, but these decreases were not significant.

EFFECTS OF DIAZEPAM AS PREMEDICATION ON HR VARIABILITY

Table 5 shows the effects of diazepam as premedication on HR and HR variability. In the elderly, the LF/HF ratio did not increase significantly. Both in the young and elderly, the LF component and total power of HR variability increased significantly compared with baseline values.

EFFECTS OF PREMEDICATION ON VENTILATORY FREQUENCY

Changes in ventilatory frequency caused by premedication are shown in figure 2. There were no significant changes in any group.

Discussion

The significant reductions in total power, LF component power and HF component power of baseline HR variability in supine elderly compared with young patients are consistent with the findings of a previous report by Lipsitz and colleagues [9]. However, they did not compare LF/HF ratios in young and elderly subjects. Our data showed that the LF/HF ratio was slightly higher in the elderly than in the young, but this difference was not significant. The significant reduction in the HF component suggests that parasympathetic nerve activity declines with age. On the other hand, sympathetic nerve activity has been reported to increase with age, as denoted by plasma concentrations of noradrenaline [6] or muscle sympathetic nerve activity [10]. However, in our study, the LF/HF ratio, which is considered a useful index of cardiac sympathetic nerve activity, did not increase with age. The discrepancy between our data and those of other reports on plasma concentrations of noradrenaline or muscle sympathetic nerve activity may be associated with a reduced affinity of the β adrenergic receptor for β adrenergic agonists in the elderly [11, 12].

Our study has demonstrated that the LF/HF ratio, which is considered an index of cardiac sympathetic nerve activity, increased significantly after arrival in the operating room compared with preoperative baseline values in elderly patients who did not receive premedication. This result suggests that the absence of premedication may cause an elevation in cardiac sympathetic nerve activity in elderly patients.

As it took more than 30 min from i.m. or oral medication until post-medication ECG recording, the effects of the two methods of administration could be ignored. Our results showed that, in the elderly, midazolam and diazepam suppressed the significant increase in the LF/HF ratio that was observed in patients who did not receive premedication. Nuotto and colleagues suggested that a dose of diazepam at least four times higher than that of midazolam is required to produce equally severe psychomotor impairment [13].

Marty and colleagues showed that both midazolam 0.3 mg kg^{-1} and diazepam 0.4 mg kg^{-1} produced alterations in baroreflex activity and a decrease in sympathetic tone [14]. Our results suggest that midazolam 0.06 mg kg^{-1} i.m. or diazepam 0.2 mg kg^{-1} orally was effective in reducing the increased sympathetic nerve activity before surgery in the elderly.

We observed differences in the effects of midazolam and diazepam on the total power of HR variability. Diazepam caused significant increases in LF and the total power of HR variability both in the young and in the elderly. On the other hand, midazolam did not exhibit such effects. It has been suggested that most inhalation or i.v. anaesthetics decrease HR variability [15–20]. Latson and colleagues suggested that a decrease in the total power of HR variability caused by anaesthetics is a result of loss of consciousness [19]. In our study, we observed differences in the effects of diazepam on HR variability.

Hirsch and Bishop suggested that respiratory sinus arrhythmia was affected by both the frequency of breathing and tidal volume [3]. In our study, the frequency of breathing remained virtually constant in all groups. However, our study did not consider the effects of tidal volume on HR variability.

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