Noninvasive Assessment of Cardiac Performance of Intravenous Benzodiazepines by Systolic Time Intervals

Osamu KEMMOTSU, Fusazo NAKATA, Koichi TAKITA, Takehiko ISHIKAWA, Kenichi SATO and Takeyasu YAMAMURA

The effects of anesthetic induction by diazepam, flunitrazepam and midazolam on cardiac performance were evaluated in 33 ASA class I surgical patients (average age was 36 years). The patients were divided according to the 3 drug groups, and the effects of each drug assessed utilizing measurements of systolic time intervals. An increase in heart rate and decrease in blood pressure was observed following flunitrazepam and midazolam induction. There were no changes in PEPI (pre-ejection period index) and LVETI (left ventricular ejection time index) by benzodiazepines induction. The PEP/LVET ratio was increased by diazepam while the DPTI (diastolic pressure time index)/TTI (tension time index) was reduced by flunitrazepam and midazolam. However, these changes in PEP/LVET and DPTI/TTI were within normal limits. These data indicate that in healthy humans the induction dose of either diazepam, flunitrazepam or midazolam does not extremely influence either PEP/LVET for cardiac performance or DPTI/TTI for cardiac oxygen balance. The results also suggest that the simultaneous use of PEP/LVET and DPTI/TTI is more informative than any single variable for the evaluation of cardiac effects of anesthetics. (Key words: benzodiazepines, DPTI/TTI, PEP/LVET, systolic time intervals)

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The use of benzodiazepines such as diazepam, flunitrazepam and midazolam in anesthesia has increased during the recent years[1]. There are many uses for benzodiazepines in the perioperative period including premedication, anesthetic induction, and sedation for diagnostic and therapeutic procedures[2]. Midazolam is an imidazobenzodiazepine closely related to diazepam. The major difference between the physical properties of midazolam and diazepam is that midazolam is water soluble, whereas diazepam is not. Because of its water solubility, rapid, nonpainful induction and lack of venous irritation, midazolam is a promising drug for induction of anesthesia[3].

Systolic time intervals (STIs), as measured from simultaneous recordings of the electrocardiogram, phonocardiogram and carotid pulse wave, can yield valuable information regarding myocardial function[4]. It is widely used by cardiologists as a tool to assess myocardial performance, and we have used STIs for the evaluation of cardiovas-

Department of Anesthesiology, Hokkaido University School of Medicine, Hokkaido, Japan

Address reprint requests to Dr. Kemmotsu: Department of Anesthesiology, Hokkaido University School of Medicine, N-15, W-7, Kita-ku, Sapporo, 060 Japan

Table 1. Hemodynamic variables before and after administration of diazepam

	SBP (mmHg)	HR (bpm)	LVETI	PEPI	PEP/LVET	DPTI/TTI
control	118 ± 8	69 ± 6	404 ± 5	127 ± 4	0.33 ± 0.02	0.83 ± 0.07
1 min	116 ± 8	68 ± 7	406 ± 6	128 ± 5	0.34 ± 0.02	0.78 ± 0.08
2	117 ± 6	69 ± 5	400 ± 6	133 ± 4	0.37 ± 0.02*	0.76 ± 0.07
3	118 ± 6	71 ± 5	400 ± 5	133 ± 4	0.37 ± 0.02*	0.77 ± 0.05
4	116 ± 5	69 ± 4	400 ± 5	133 ± 4	0.37 ± 0.02*	0.76 ± 0.04
5	116 ± 5	68 ± 4	400 ± 5	132 ± 4	0.37 ± 0.02*	0.77 ± 0.04
6	114 ± 6	64 ± 4	399 ± 5	133 ± 4	0.37 ± 0.02*	0.82 ± 0.05
7	111 ± 4	65 ± 4	402 ± 5	133 ± 3	0.36 ± 0.02	0.78 ± 0.03
8	111 ± 4	65 ± 4	402 ± 4	135 ± 4	0.37 ± 0.02*	0.78 ± 0.03
9	110 ± 4	64 ± 4	401 ± 4	134 ± 3	0.37 ± 0.02*	0.78 ± 0.03
10	110 ± 4	63 ± 4	400 ± 4	136 ± 3	0.37 ± 0.02*	0.77 ± 0.02

mean ± SEM are shown, n = 11

*$P < 0.05$ vs control value

SBP = systolic blood pressure, HR = heart rate, LVETI = left ventricular ejection time index, PEPI = pre-ejection period index, DPTI = diastolic pressure time index, TTI = tension time index

cular effects of anesthetics[5,6]. The aim of this clinical study is to compare the cardiac effects of induction dose of diazepam, flunitrazepam and midazolam utilizing STIs. Furthermore, there are no comparative data on the changes in cardiac oxygen balance induced by benzodiazepines. Therefore, the changes in cardiac oxygen balance were evaluated using the endocardial viability ratio.

Methods

Thirty three ASA class I patients whose average age was 36 years and who were scheduled for various surgical procedures were studied after institutional approval and informed consent were obtained. All patients were premedicated with diazepam 10 mg p.o. 2 hr prior to the beginning of the procedure. Patients were equally divided into three drug groups, diazepam, flunitrazepam and midazolam. Each patient served as his or her own control and was allowed to breathe spontaneously with room air during the whole procedure. In all patients STIs was computed from the simultaneous processing of lead II of the electrocardiogram, phonocardiogram and carotid pulse contours, utilizing the AVL Myocard Check-970 (AVL, AG Biomedical Instruments, Switzerland) which provides fully automatic and micro-processor controlled on-line measurements of STIs. The microphone for this device was placed in the 4th intercostal space to the left of the sternum for detection of the second heart sound (S_2). The carotid pulse sensor was secured over the left carotid artery using an elastic collar.

Mean values of HR (heart rate), QS_2 (total electromechanical systole), PEP (pre-ejection period), LVET (left ventricular ejection time), the PEP/LVET ratio and S2Q (diastolic time) were computed from a 12 beat ensemble, in which the two beats that deviated most from the mean value of the heart rate were excluded from the calculation. Arterial blood pressure was measured using the oscillometric method (Nippon Colin BX-5, Japan). DPTI (diastolic pressure time index), TTI (tension time index), EVR (endocardial viability ratio), LVET index and PEP index were calculated by the following formula[7,8]. DPTI = Diastolic blood pressure × diastolic time × HR, TTI = systolic blood pressure × LVET × HR, EVR = DPTI/TTI, LVETI = 1.5 × HR + LVET, PEPI = 0.4 × HR + PEP.

After attainment of an intravenous route for lactate Ringers solution (2 $ml \cdot kg^{-1} \cdot hr^{-1}$) and placement of the monitor sensors, control data were obtained and an induction

Table 2. Hemodynamic variables before and after administration of flunitrazepam

	SBP (mmHg)	HR (bpm)	LVETI	PEPI	PEP/LVET	DPTI/TTI
control	127 ± 4	66 ± 8	401 ± 6	122 ± 5	0.32 ± 0.02	0.87 ± 0.09
1 min	122 ± 3	78 ± 5*	406 ± 6	121 ± 5	0.31 ± 0.02	0.76 ± 0.09*
2	118 ± 3	76 ± 5	405 ± 7	119 ± 4	0.31 ± 0.02	0.77 ± 0.09*
3	114 ± 4*	77 ± 5*	402 ± 7	122 ± 4	0.32 ± 0.02	0.74 ± 0.08*
4	110 ± 4*	76 ± 4	404 ± 6	123 ± 3	0.32 ± 0.02	0.75 ± 0.09*
5	109 ± 4*	79 ± 5*	402 ± 5	125 ± 3	0.33 ± 0.01	0.71 ± 0.09*
6	109 ± 4*	77 ± 5*	402 ± 5	124 ± 3	0.32 ± 0.01	0.75 ± 0.09*
7	108 ± 4*	77 ± 5*	403 ± 5	125 ± 4	0.33 ± 0.02	0.73 ± 0.10*
8	107 ± 4*	77 ± 5*	402 ± 5	126 ± 3	0.34 ± 0.02	0.74 ± 0.08*
9	109 ± 4*	75 ± 5	403 ± 5	126 ± 3	0.33 ± 0.01	0.73 ± 0.08*
10	107 ± 4*	76 ± 5	402 ± 5	128 ± 2	0.32 ± 0.02	0.76 ± 0.08

mean ± SEM are shown, n = 11

*$P < 0.05$ vs control value

SBP = systolic blood pressure, HR = heart rate, LVETI = left ventricular ejection time index, PEPI = pre-ejection period index, DPTI = diastolic pressure time index, TTI = tension time index

Table 3. Hemodynamic variables before and after administration of midazolam

	SBP (mmHg)	HR (bpm)	LVETI	PEPI	PEP/LVET	DPTI/TTI
control	121 ± 3	66 ± 3	418 ± 6	130 ± 5	0.33 ± 0.02	0.89 ± 0.06
1 min	114 ± 2	75 ± 4*	415 ± 6	132 ± 5	0.34 ± 0.02	0.79 ± 0.07*
2	111 ± 2*	73 ± 3*	412 ± 5	133 ± 5	0.34 ± 0.02	0.80 ± 0.06*
3	107 ± 3*	73 ± 3*	410 ± 6	135 ± 4	0.35 ± 0.01	0.80 ± 0.05*
4	107 ± 3*	70 ± 3	413 ± 6	134 ± 4	0.34 ± 0.01	0.80 ± 0.05*
5	106 ± 3*	70 ± 3	412 ± 5	134 ± 5	0.34 ± 0.02	0.82 ± 0.06
6	107 ± 3*	69 ± 3	410 ± 5	134 ± 5	0.34 ± 0.02	0.83 ± 0.06
7	105 ± 3*	69 ± 3	408 ± 6	136 ± 4	0.36 ± 0.02*	0.85 ± 0.06
8	104 ± 3*	69 ± 3	411 ± 6	133 ± 4	0.35 ± 0.01	0.83 ± 0.05
9	107 ± 3*	68 ± 3	412 ± 5	133 ± 3	0.34 ± 0.02	0.85 ± 0.05
10	108 ± 3*	68 ± 3	412 ± 6	134 ± 3	0.34 ± 0.02	0.85 ± 0.05

mean ± SEM are shown, n = 11

*$P < 0.05$ vs control value

SBP = systolic blood pressure, HR = heart rate, LVETI = left ventricular ejection time index, PEPI = pre-ejection period index, DPTI = diastolic pressure time index, TTI = tension time index

dose of each benzodiazepine was administered intravenously in 30 sec in all groups of patients. Measurements of STIs and blood pressure were repeated every min for 10 min. Dosages of the three intravenous benzodiazepines per kg of body weight were diazepam 0.4 mg, flunitrazepam 0.04 mg and midazolam 0.2 mg. The dosages compared were selected on the basis of clinical as well as laboratory data showing midazolam approximately 2 times, and flunitrazepam 10 times as potent, with regard to producing loss of consciousness, as diazepam[1,2,9].

All values were expressed as mean ± SEM and statistical analyses were performed using a paired Student's t-test to analyze progressive changes in values within each group. An analysis of variance (ANOVA) was used to determine if there were significant differences between groups. A probability value of less than 0.05 was considered statistically significant.

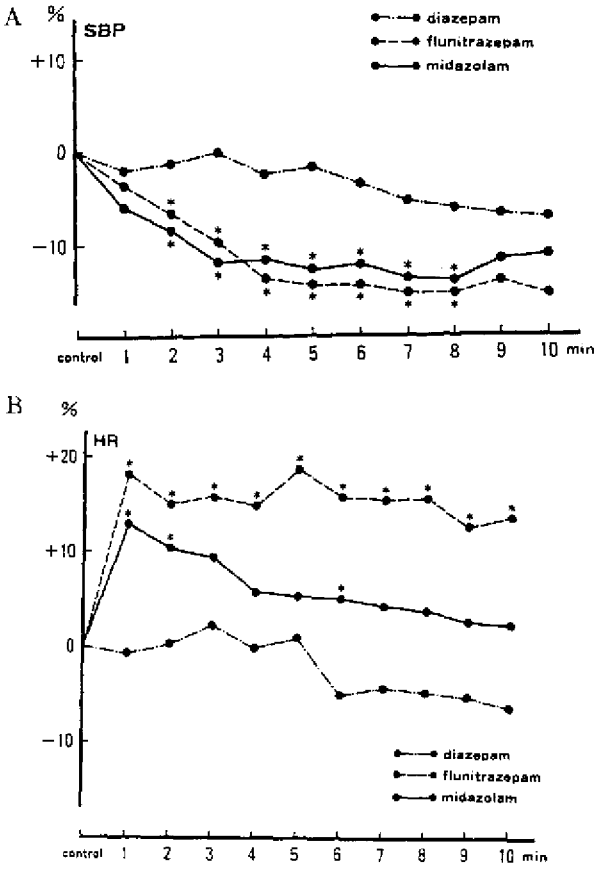

Fig. 1. Comparative changes in SBP (A) and HR (B) following induction dose of diazepam, flunitrazepam and midazolam.

*$P < 0.05$ vs diazepam

SBP = systolic blood pressure, HR = heart rate

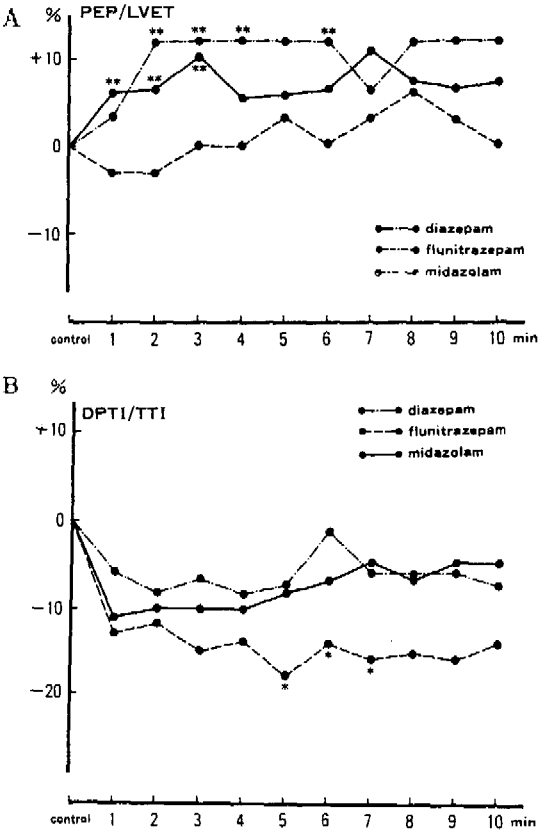

Fig. 2. Comparative changes in PEP/LVET (A) and DPTI/TTI (B) following induction dose of diazepam, flunitrazepam and midazolam.

*$P < 0.05$ vs diazepam

**$P < 0.05$ vs flunitrazepam

PEP = pre-ejection period, LVET = left ventricular ejection time, DPTI = diastolic pressure time index, TTI = tension time index

Results

There was no difference between groups concerning age and body weight or control values of STIs, heart rate and blood pressure. No side effects related to intravenous administration of these benzodiazepines were observed.

Administration of diazepam did not change SBP (systolic blood pressure), HR, LVETI, PEPI and DPTI/TTI (EVR) (table 1). However, PEP/LVET was significantly increased after diazepam. By administration of flunitrazepam SBP was gradually decreased and values through 3 to 10 min following induction were significant, and HR was concomitantly increased (table 2). Although there were no changes in LVETI, PEPI, and PEP/LVET, DPTI/TTI (EVR) was significantly decreased after flunitrazepam. Midazolam caused decreases in SBP and transient increases in HR but no changes in LVETI and PEPI (table 3). PEP/LVET was increased 7 min after start of the procedure and DPTI/TTI (EVR) was decreased during the first 4 min after midazolam. When percentage changes in SBP and HR by these benzodiazepines were compared (fig. 1), reductions in SBP were concomi-

tant with increases in HR after flunitrazepam and midazolam induction, but no changes in SBP and HR was observed by the use of diazepam. Reductions in SBP by flunitrazepam and midazolam were significantly greater than those by diazepam during the period from 3 to 7 min following induction. Increases in HR by flunitrazepam and midazolam were significantly greater than those by diazepam. The PEP/LVET ratio was increased following diazepam induction (fig. 2), while the DPTI/TTI ratio was decreased by flunitrazepam. However, only small changes were observed in PEP/LVET or DPTI/TTI by the other benzodiazepines. Changes in PEP/LVET by diazepam were significantly greater than those by flunitrazepam from 2 to 4 min after induction. Although the DPTI/TTI ratio was decreased by all three benzodiazepines, decreases in this ratio by flunitrazepam were significantly greater than those by diazepam during the 5 to 7 min following induction.

Discussion

The efficacy and hemodynamic stability afforded by the benzodiazepines for induction of anesthesia have been previously reported[10–13]. However, this is the first report on comparative cardiac effects of these benzodiazepines evaluated by STIs measurements. The intravenous bolus administration of diazepam 0.4 $mg \cdot kg^{-1}$, flunitrazepam 0.04 $mg \cdot kg^{-1}$ and midazolam 0.2 $mg \cdot kg^{-1}$ in our premedicated patients resulted in clinically rapid, smooth induction of anesthesia.

The most consistent hemodynamic changes following induction by flunitrazepam and midazolam in this study are a decrease in blood pressure and increase in heart rate. These findings are in accordance with previous reports[10,11]. Of note is the statistically significant greater increase in heart rate and decrease in blood pressure following flunitrazepam and midazolam vs. diazepam. Samuelson, et al.[13], reported that midazolam produces a greater decrease in blood pressure than diazepam. Hemodynamic changes after midazolam induction are similar to those following flunitrazepam as reported by Morel and associates[14].

In this study only diazepam consistently increased PEP/LVET, which is not observed with flunitrazepam and midazolam. This means that diazepam decreases left ventricular performance even in healthy humans. However, the PEP/LVET ratio of 0.37 in the group receiving diazepam is smaller than 0.42, which suggests reduced left ventricular performance[15]. The typical pattern of left ventricular dysfunction observed by STIs is prolongation of PEP and shortening of LVET, which leads to the increased PEP/LVET ratio. Our results suggest that the PEP/LVET ratio is the single best estimate of left ventricular performance from STIs, since there were no significant changes in both PEPI and LVETI in our study. As PEP/LVET is well correlated with stroke volume or LV dp/dtmax[4,15], our results indicate that cardiac performance is well maintained by induction by benzodiazepines in healthy humans. Although benzodiazepines appear to have negative inotropic effects in isolated heart preparations[16], these effects are usually compensated for by sympathetic reflexes that maintain cardiac output in the intact organism. However, patients with an impaired reflex adrenergic system or myocardial function would manifest the negative inotropic effects of benzodiazepines, especially diazepam. It may be suggested that midazolam or flunitrazepam is a better choice than diazepam as an induction agent in such patients.

Although STIs provide information on cardiac function in a noninvasive fashion, they do not directly tell us about cardiac oxygen balance. However, STIs are useful in the computation of the pressure time indices which provide indications of the balance between cardiac oxygen consumption and supply[8,17]. For this the DPTI/TTI ratio or endocardial viability ratio (EVR) is used. The DPTI is used to assess the oxygen supply and the TTI is utilized for oxygen consumption or demand. In this study, we observed that DPTI/TTI was significantly reduced by flunitrazepam and midazolam. Hoffman[18] suggested that a DPTI/TTI ra-

tio below 0.7 was associated with decreased blood flow and decreased distribution to the subendocardium, while a ratio above 0.7 indicated an even distribution of myocardial blood flow and resulted in no evidence of left ventricular dysfunction. Although DPTI/TTI was reduced by flunitrazepam and midazolam, the value was never below 0.7 in our study. Therefore, our data indicate that cardiac oxygen balance was well maintained following induction by these benzodiazepines.

The indirect, noninvasive data obtained from STI measurements are mixed indices reflecting a series of components of myocardial contractility and/or pump function. We should keep in mind that we also would like to know about pressure, flow and volume values and changaes. Yet, with STIs we are measuring only time intervals. However, the fast changes of STI variables following the administration of drugs in self-controlled clinical pharmacologic studies make the technique particularly suitable for the evaluation of drug action in humans. As we previously reported[17], the simultaneous use of PEP/LVET and DPTI/TTI is more informative than the use of any single variable for the evaluation of anesthetics.

In conclusion, our results indicate that the hemodynamic state is well maintained by the used induction doses of diazepam, flunitrazepam and midazolam in healthy humans, judging from both PEP/LVET as a measure of cardiac performance and DPTI/TTI as a measure of cardiac oxygen balance.

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