



Short communication

Effects of thiopental and propofol on heart rate variability during fentanyl-based induction of general anesthesia

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Abstract:

Anesthetics depress the autonomic nervous system. The effects of thiopental and propofol on heart rate variability (HRV) during fentanyl-based induction of general anesthesia were studied in one hundred patients. We observed different effects of fentanyl, thiopental and propofol on HRV. Fentanyl decreased total power of HRV and low frequency power (LF), but not high frequency power (HF), indicating a greater reduction of cardiac sympathetic activity. Thiopental and propofol caused the further reduction of HRV and decreased HF power. Thiopental increased LF power and LF/HF ratio, indicating that the vagolytic effect is associated with the increase in sympathetic activity. Propofol preserved the LF power, indicating that the cardiac parasympathetic activity is reduced more than the sympathetic activity.

Key words:

thiopental, propofol, fentanyl, heart rate variability, induction of general anesthesia

Introduction

Previous studies in *unanesthetized* patients have related changes in spectral analysis of heart rate variability (HRV) to several mechanisms: alterations in sympathetic and parasympathetic activity, changes in baroreflex sensitivity, interrupted autonomic reflex pathways, impaired cerebral function (injury) and autonomic neuropathy [5, 15]. Alterations in HRV have been also related to both depth of anesthesia [19] and level of sedation [13]. If only depth of anesthesia or sedation had prominent effect on HRV, then different anesthetics would all have very similar effects on

HRV. However, if alterations in baroreflex sensitivity and/or autonomic activity also play role in anesthetic effect on HRV, then different anesthetics should have different effects on HRV.

Anesthetics used in general anesthesia depress the autonomic nervous system and contribute to the safety of general anesthesia because they not only suppress excessive sympathetic activity evoked by surgery, but also suppress parasympathetic reactions [19]. The attenuation of sympathetic activity during general anesthesia is usually assessed by monitoring changes in blood pressure or heart rate. However, because of these antagonistic effects, evaluation becomes problematic when parasympathetic activity is

simultaneously depressed. Therefore, the analysis of anesthetic effects on HRV may provide a more valuable noninvasive tool for investigating alterations in autonomic function. Previous studies have assessed the effect of thiopental [12, 15, 19, 25] and propofol [2, 6, 7, 13, 22] on the spectral analysis of HRV during induction of anesthesia, since both intravenous (*iv*) anesthetics induce different hemodynamic changes. However, all these studies were limited to single anesthetic techniques, they were performed in small study populations, and they used different analytical methods, making a comparison of the effects of these anesthetics difficult. Scheffer et al. [24] investigated the effects of thiopental and propofol during induction to general anesthesia and clearly showed differences in their effects on HRV. Contrary, Howell et al. [11] were unable to find any difference between both anesthetics. Both studies were performed in small groups of patients and no other data comparing the effects of both anesthetics on HRV are available. Therefore, the aim of the study was to compare the effects of thiopental and propofol on HRV during fentanyl-based induction of general anesthesia in a greater study population.

Materials and Methods

Following institutional approval and obtaining informed consent from all patients, one hundred physical status I and II (according to American Society of Anesthesiologists) consequent patients, scheduled for elective abdominal surgery, were included in the study. Patients were allocated randomly to receive either propofol or thiopental. Those who taken drugs that could influence hemodynamic and autonomic function were excluded from the study. Further exclusion criteria were: electrocardiographic abnormalities (a cardiac rhythm other than sinus, premature ventricular contractions, or if heart rate was less than 55 min^{-1}), severe ischemic heart disease, congestive heart failure, diabetes mellitus, or other disorders known to affect autonomic function.

The monitoring during anesthesia included electrocardiogram (ECG), pulse oxymetry, non-invasive blood pressure measurement and capnography (end tidal CO_2). Patients were premedicated with midazolam (Dormicum, F. Hoffman-La Roche Ltd, Basel,

Switzerland) orally at $7.5 \text{ mg } 1 \text{ h}$ before induction of anesthesia. All patients received 100% oxygen *via* face mask for 2–3 min prior to induction of general anesthesia. Anesthesia was induced intravenously (*iv*) using standardized anesthetic technique, by fentanyl (Fentanyl, Polfa, Warszawa, Poland) $3 \mu\text{g kg}^{-1}$, followed 5 min later by thiopental (Thiopental, Biochemie GmbH, Vienna, Austria) $4\text{--}7 \text{ mg kg}^{-1}$, or by propofol (Diprivan, AstraZeneca UK Ltd, Cheshire, UK) $1.5\text{--}3.0 \text{ mg kg}^{-1}$. The dose of either thiopental or propofol was given over 30 s, until a loss of consciousness, while the patient was breathing 100% oxygen. The loss of consciousness was defined as a loss of the eyelash reflex and no reaction to subsequent positive-pressure mask ventilation. Following induction of anesthesia, the patients were left unstimulated for 5 min, until laryngoscopy was performed. Ventilation was assisted or controlled *via* face mask with 100% oxygen with frequency of 12 min^{-1} and tidal volume was adjusted to maintain end-tidal CO_2 between 30 and 35 mm Hg. After 5 min from thiopental or propofol injection, rocuronium (Esmeron, NV Organon, Oss, Netherlands) 0.6 mg kg^{-1} was given as a bolus injection, to facilitate endotracheal intubation.

The patients were connected to a Holter ECG (Medikorder MK.2, TOM Signaltechnik, Hashiba & Niederl OEG, Graz, Austria) and measurements were taken continuously from 5 min before induction (pre-induction period) through the induction period: at 5 min after fentanyl administration (post-fentanyl period) and 5 min after thiopental or propofol administration (post-induction period). The ECG analog signals were converted and stored in a digital form on CompactFlash card (ScanDisk Inc.) to be transferred to a computer. Successive QRS peaks were reviewed visually for R-wave determination. Records with poor identification of R-waves or with frequent ectopic beats were excluded from analysis. Spectral analysis was performed using the Medilog SimpleView software (TOM Medical Handels GmbH, Graz, Austria) and MATLAB (MathsWorks Inc., MA, USA). Since the effects of *iv* anesthetics were relatively short-lived, the length of the data segments used for HRV analysis was necessarily relatively short. A segment length of 64 seconds was selected [15]. Power spectral analysis of HRV was calculated on 64-second epoch of interpolated heart rate using the fast Fourier transformation (processed to frequency domain). Trended measurements of HRV were derived by sequential analysis overlapping 64-second data seg-

ments after the beginning of the previous segment. Integration of spectral values over the appropriate frequency ranges provides corresponding trended measurements of the frequency-specific parameters [18]. Pre-induction values of HRV were obtained by averaging the five sequential trended HRV measurements, just prior to fentanyl administration (corresponding to a 124-second time period). The post-fentanyl and post-induction measurements were obtained by averaging three sequential trended measurements just prior to administration of *iv* anesthetics and tracheal intubation, respectively.

The results were expressed as absolute values in msec² per Hz and normalized values as a proportion of total HRV power (TP) in two ranges of HRV: low-frequency power (LF; 0.04–0.15 Hz) and high-frequency power (HF; 0.15–0.4 Hz). The LF to HF ratio was calculated from absolute values. Corresponding hemodynamic pre-induction, post-fentanyl and post-induction values of mean arterial blood pressure and heart rate were compared with HRV variables. Data were expressed as the means \pm SEM unless indicated otherwise. Statistical analysis was performed with the chi-square test for gender, with the unpaired *t*-test for other demographic data, and two-way repeated analysis of variance (ANOVA) followed by the Student-Neuman-Keuls test as a *post hoc* test for blood pressure, heart rate and HRV variables. A *p* value < 0.05 was considered statistically significant. We decided that a minimum 10% difference in percent changes in HRV parameters relative to baseline between the groups, would be important with an estimated standard deviation of the population of 15%. Therefore, *n* = 48 patients in each group would be necessary to detect such a difference if α = 0.05 and β = 0.1 (GraphPAD InStat Software, Version 1.12a; Graphpad Software 108955 Sorrento Valley Rd, San Diego, CA 92121, USA).

Results

There were no significant differences between the two groups in demographic data likely to have influenced the outcome variables (Tab. 1). Fentanyl produced a significant decrease in mean arterial pressure and heart rate and caused a significant, to similar degree, reduction in the absolute measurements of TP and LF

power but not that of HF power in both studied groups (Tab. 2). This differential effect of fentanyl on LF power and HF power was not accompanied by significant changes in the normalized measurements of LF and HF power, and in the absolute value of the ratio LF/HF power, as compared with pre-induction period (Fig. 1, Tab. 2).

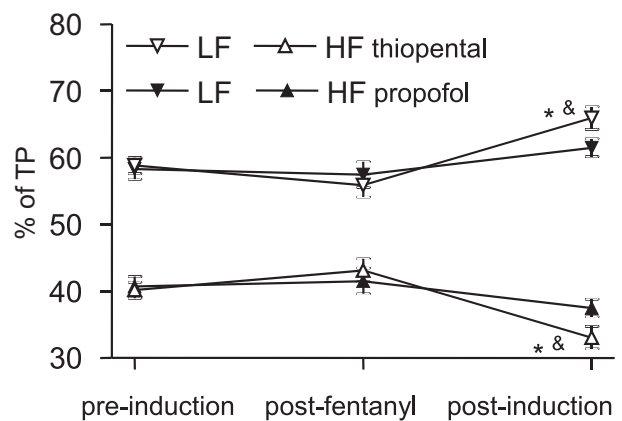


Fig. 1. Normalized values (mean \pm SEM) of low frequency power (LF) and high frequency power (HF) of HRV before (pre-induction), after fentanyl (post-fentanyl) and after induction (post-induction) of general anesthesia with thiopental and propofol. * *p* < 0.01 vs. previous period; & *p* < 0.05 vs. propofol

Tab. 1. Demographic characteristics of two anesthetic groups

Dose (mg kg ⁻¹)	Thiopental	Propofol
	5.21 \pm 0.08	2.14 \pm 0.02
<i>n</i>	48	52
Sex (female/male)	45/3	45/7
Age (yr)	38.6 \pm 1.6	42.8 \pm 1.5
Weight (kg)	65.6 \pm 1.9	68.2 \pm 1.6
Height (cm)	165.9 \pm 0.9	168.1 \pm 0.9

Values are the means \pm SEM or number of patients

Following fentanyl, thiopental or propofol was given *iv* in a dose range between 4.3–7.0 mg kg⁻¹ and 1.7–2.7 mg kg⁻¹, respectively, at sufficient dose to produce the loss of conscious. Thiopental and propofol induced further decrease in the mean arterial pressure, but the decrease was still less than 20%, relative

Tab. 2. Heart rate variability power ($\text{ms}^2 \text{Hz}^{-1}$), the ratio of low-frequency to high-frequency power, mean arterial blood pressure (mmHg) and heart rate (min^{-1}) in three specific time periods

		Time period		
		Pre-induction	Post-fentanyl	Post-induction
Total power	Thiopental	3111 ± 243	2734 ± 264 (88%)*	1757 ± 150 (56%)*
	Propofol	2976 ± 216	2294 ± 183 (77%)*	2052 ± 140 (69%)*
High-frequency power	Thiopental	1273 ± 109	1212 ± 148 (95%)	567 ± 49 (45%)*
	Propofol	1222 ± 106	979 ± 100 (80%)	735 ± 67 (60%)*
Low-frequency power	Thiopental	1839 ± 146	1522 ± 133 (83%)*	1201 ± 116 (65%)*
	Propofol	1754 ± 129	1316 ± 105 (75%)*	1205 ± 84 (69%)
Low/high ratio	Thiopental	1.58 ± 0.08	1.42 ± 0.10 (90%)	2.38 ± 0.19 (151%)* &
	Propofol	1.61 ± 0.08	1.62 ± 0.13 (101%)	1.90 ± 0.14 (118%)*
Mean blood pressure	Thiopental	98.7 ± 3.1	90.4 ± 2.5 (92%)*	83.6 ± 2.8 (85%)*
	Propofol	98.6 ± 1.7	91.3 ± 2.3 (93%)*	80.5 ± 1.5 (82%)*
Heart rate	Thiopental	95.3 ± 2.1	80.1 ± 1.9 (84%)*	89.9 ± 2.0 (94%)* &
	Propofol	92.6 ± 2.0	76.5 ± 2.6 (83%)*	78.9 ± 1.7 (85%)

Values are the means ± SEM; in parenthesis percentage relative to pre-induction period; * $p < 0.05$ vs. previous period; & $p < 0.05$ vs. propofol

to pre-induction values (Tab. 2). Both induction techniques produced differential effect on the heart rate. Thiopental significantly increased, while propofol did not change the heart rate.

Both *iv* anesthetics induced further significant reduction in the absolute measurements of TP and HF power (Tab. 2). Although there was a trend toward a greater effect of thiopental on reduction of TP and HF power, this trend did not reach statistical significance. Compared with propofol, thiopental caused significant reduction, while propofol did not change the absolute measurements of the LF power, as compared with post-fentanyl period.

The effects of the two induction techniques on the normalized measurements of LF power and HF power are shown in Fig. 1. Thiopental induction evoked significant increase in the normalized measurements of LF power and significant decrease in the normalized measurements of HF power, as compared with post-fentanyl period and with propofol induction. This dif-

ferential effect of thiopental caused significant increase in the absolute value of the ratio LF/HF power, as compared with post-fentanyl period and with propofol induction (Tab. 2).

Discussion

Opioids are known to exert a parasympathomimetic effect on HRV and to induce centrally mediated bradycardia and hypotension [15]. In the present study, we observed a slowing of heart rate and a decrease in blood pressure with fentanyl. Fentanyl caused a significant reduction in TP and LF power, but not in HF power. Preservation of HF absolute values with a simultaneous decrease in LF component may indicate greater reduction in sympathetic than parasympathetic tone. However, no changes in the LF/HF ratio and in normalized values of LF and HF may suggest that

parasympathomimetic effect of fentanyl was at least partially counteracted by the increase in sympathetic tone. Patients treated with fentanyl were breathing spontaneously and it is possible that any transient respiratory depression with retention of carbon dioxide would have altered the balance toward sympathetic tone [8]. Fentanyl has an analgesic effect that is preferable during anesthesia induction for tracheal intubation, but the lack of an amnesic effect may be its disadvantage [26]. Therefore, midazolam premedication was selected because of its potent amnesic and anxiolytic effect. The type of premedication administered prior to a potent opioid induction may influence the hemodynamic and autonomic responses to induction [15]. However, it was shown that midazolam given intramuscularly, at the dose used in this study, only slightly depressed both LF and HF but did not change the LF/HF ratio [17]. Interaction of midazolam and fentanyl with *iv* anesthetics is synergistic [27], therefore, these drugs were used to ensure a smooth induction of general anesthesia, according to the accepted and standardized anesthetic procedures in our hospital.

The HF power reflects solely the parasympathetic activity and is linked to respiration [21]. The reduction of parasympathetic input during apnea causes a decrease in HF. Fluctuations in the intrathoracic pressure and venous return resulting from respiratory movement produce changes in blood pressure. These changes increase HF by activating the vagally mediated arterial baroreceptor reflex. In addition, direct stimulation of the vagus nerve by respiratory center may also contribute to HF independent of chest movement [10]. During the deep anesthesia, neither LF nor HF changed in the absence of respiratory activity, when electroencephalogram was isoelectric [19]. An important consideration in HRV studies is that the power of the HF component is related to the frequency and depth of ventilation [13]. Any technique that alters ventilation alters absolute and normalized HF power. Therefore, it is important to maintain constant ventilation conditions. In the present study, we maintained steady state respiration in the studied groups, after induction of anesthesia to minimize its influence on HRV.

The range of LF power of HRV represents the fluctuation of blood pressure associated with sympathetic activity, which initiates changes in heart rate mediated by parasympathetic arterial baroreceptor reflex, as the compensatory arterial pressure control mechanism [1]. The LF power is thus influenced by both sympa-

thetic and parasympathetic activity [16] and appears to represent sympathetic modulation particularly under conditions of parasympathetic withdrawal [1]. The ratio of LF/HF provides a useful insight into the sympathovagal balance [16].

Thiopental induction decreased cardiac parasympathetic activity, as the absolute value of HF power (55%) dropped much more than the absolute values of LF power (35%). The significant increase in the normalized values of LF power and significant decrease in the normalized measurements of HF power were observed, as compared with post-fentanyl period and with propofol induction. It is important to distinguish between absolute HRV power measurements and data normalized to TP values. The latter are considered to be a more sensitive indicator of the sympathetic to parasympathetic balance under conditions of reduced total HRV [15]. The significant increase in the ratio of LF/HF power was also observed. This increase was probably caused by parasympathetic withdrawal (as evidenced by the decrease in normalized HF power). Although both parasympathetic and sympathetic absolute variables decreased following thiopental, vagal activity declined more significantly than sympathetic, leading to a striking autonomic imbalance. Thiopental induction significantly increased the heart rate. Latson et al. [14] in a preliminary report showed that tachycardia following anesthesia induction with thiopental and vecuronium, coincided with a decrease in the index of vagal activity in power spectrum analysis of HRV. In the further study, Latson et al. [15] observed that immediately following the induction with fentanyl and thiopental and before tracheal intubation, in most of the patients the spectral ratio of LF/HF was increased. Similar findings have also been reported by Schubert et al. [25] and by Nishiyama et al. [20], confirming the autonomic imbalance after induction with thiopental and fentanyl or thiopental alone, in 26 and 20 patients, respectively. Both sympathetic and parasympathetic autonomic contributions to HRV appear to be affected, and a marked reduction in overall HRV (TP, LF and HF powers) is consistent with previous report [4]. It is conceivable that the barbiturate vagolytic effect and increased sympathetic activity account for these observations.

In contrast to thiopental, propofol induction of anesthesia caused a decrease in blood pressure without an increase in the heart rate, and a reduction in the absolute values of HF power, but not the values of LF power, as compared with the post-fentanyl period.

Concomitantly, propofol produced the increase in the ratio of LF/HF power, but less than thiopental. Despite the lack of propofol effect on the normalized values of LF and HF power, the significant increase in the ratio of LF/HF power suggests that propofol induction of anesthesia might reduce a cardiac parasympathetic tone more than sympathetic tone. Similar results were observed after induction of anesthesia with propofol in humans [2, 13]. Propofol anesthesia is known to cause a reduction in blood pressure and heart rate in humans and the inhibition of sympathetic nerve activity is believed as one major mechanism underlying the propofol-induced hemodynamic changes [3, 23]. In a study measuring the peripheral sympathetic nerve activity, propofol anesthesia was reported to reduce muscle sympathetic nerve activity [3]. The fact that induction of anesthesia with propofol caused decreases in muscle sympathetic nerve activity and blood pressure (indicating a decrease in peripheral sympathetic activity), with a small increase in heart rate (indicating a decrease in cardiac parasympathetic activity), in humans [3] supports our HRV data. Kanaya et al. [13] using a maximum-entropy method for HRV assessment, confirmed that propofol anesthesia caused reduction in HF power but not in LF power, indicating that induction of anesthesia with propofol might reduce a cardiac parasympathetic tone more than sympathetic tone. Additionally, a decrease in HF and entropy during propofol anesthesia correlated with the level of sedation (assessed by Bispectral Index). Recently, Hamada et al. [9] using two methods: a maximum-entropy method for HRV and a fractal analysis of ECG, confirmed the observation of Kanaya et al. [13], concluding that propofol decreased parasympathetic activity, but increased sympathetic activity, because of the baroreflex mechanism.

Concluding, both *iv* anesthetics produced a significant reduction of HRV with a different effect on autonomic balance, only thiopental evoked changes of normalized parameters of HRV, indicating that vagolytic effect was associated with a greater increase in sympathetic activity, than it was after propofol.

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Received:

October 8, 2004; in revised form: January 12, 2005.