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Effects of pneumoperitoneum on cardiac autonomic nervous activity evaluated by heart rate variability analysis during sevoflurane, isoflurane, or propofol anesthesia

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Abstract
Background: The effects of pneumoperitoneum on the activity of the cardiac autonomic nervous system have not been completely understood.
Methods: In this study, 45 unpremedicated adult patients who underwent laparoscopic cholecystectomy were anesthetized with either 3.5% sevoflurane, 2% isoflurane, or 8 mg/kg/h propofol (15 patients in each group). The status of cardiac autonomic nervous activity was evaluated by heart rate variability analysis three times: once when the patient was awake, once after induction of general anesthesia, and once after insufflation for pneumoperitoneum. Intra-abdominal pressure was maintained automatically at 10 mmHg by a carbon dioxide (CO_2) insufflator. For each measurement, electrocardiogram was recorded for 256 s and played back offline to detect R-R intervals. Power spectral analysis of heart rate variability was applied, and the low-frequency (LF, 0.04–0.15 Hz) and high-frequency (HF, 0.15–0.40 Hz) bands of the spectral density of the heart rate variability were obtained from a power spectra of R-R intervals using the fast-Fourier transform algorithm. The HF/LF ratio also was analyzed.
Results: Measurements of heart rate variability in the three groups showed similar change. Although the power of HF, which represents parasympathetic nervous activity, did not change, the power of LF, which represents both sympathetic and parasympathetic nervous activity, decreased during the anesthetized stage and increased during the insufflated stage. The HF/LF ratio, which represents the balance of parasympathetic and sympathetic activity, increased after induction of general anesthesia, and decreased after insufflation.
Conclusions: Our results suggest that pneumoperitoneum increases sympathetic cardiac activity. The choice of general anesthetic did not seem to have a major influence on the change in the cardiac autonomic nervous system after induction of pneumoperitoneum for laparoscopic cholecystectomy.

Key words: Cardiac autonomic nervous system — Heart rate variability — Isoflurane — Pneumoperitoneum — Power spectral analysis — Propofol — Sevoflurane

Pneumoperitoneum has significant implications for cardiovascular and respiratory status [3, 23]. However, the effects of pneumoperitoneum on the cardiac autonomic nervous system (ANS) have not been reported. Moreover, it is possible that the effects of pneumoperitoneum on the cardiac ANS differ when patients are anesthetized with different anesthetics. The purpose of this prospective study was to evaluate the effects of pneumoperitoneum on the activity of the cardiac ANS in patients under anesthesia with sevoflurane, isoflurane, or propofol, which are commonly used anesthetics in clinical settings.

The cardiac ANS regulates heart rate (HR) variability. Power spectral analysis of the R-R interval in the electrocardiogram is a noninvasive tool that quantifies the contributions of the parasympathetic and sympathetic systems in the ANS [14]. The spectral components can be divided into several frequency ranges. The low frequency (LF) band is mediated by both the parasympathetic and sympathetic systems, and the high frequency (HF) component is mediated mainly by the parasympathetic system. To assess the effects of pneumoperitoneum on the ANS, power spectral analysis was used to evaluate sympathetic and parasympathetic control of HR variability.

Methods

This study was approved by our institutional ethical committee for clinical investigation, and informed consent was obtained from 45 adult patients

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scheduled to undergo laparoscopic cholecystectomy. The subjects had no significant systemic or cardiopulmonary disease such as diabetes mellitus, arrhythmia, coronary artery disease, or chronic obstructive lung disease. None of the patients was receiving beta-adrenergic-blocking drugs, calcium-channel blockers, digitalis, antihypertensives, or vasodilators preoperatively. By a closed envelope method, patients were allocated to one of three groups: isoflurane, sevoflurane, or propofol group (15 patients in each).

Patients received no preanesthetic medication. On arrival in the operating room, patients were placed in the supine position, and routine cardiovascular monitoring was applied, including electrocardiogram (ECG, lead II) and pulse oximetry, and indirect arterial pressure (M1166A, Hewlett-Packard, Palo Alto, CA, USA). After the peripheral intravenous line was secured, lactated Ringer's solution was administered at a rate of 5 ml/kg/h. A continuous 256-s ECG was recorded as the awake stage.

In the isoflurane and sevoflurane groups, anesthesia was induced with fentanyl (3 μg/kg) and thiamylal (3 mg/kg), then maintained with 3.5% sevoflurane (endexpiratory concentration) or 2% isoflurane in oxygen. In the propofol group, anesthesia was induced with fentanyl (3 μg/kg) and propofol (2 mg/kg), then maintained with propofol (8 mg/kg/h) according to Giradis et al. [9]. A 1.75 MAC concentration of sevoflurane and isoflurane was used to compare their effects with those of propofol because 1 MAC is comparable to 2% sevoflurane and 1.15% isoflurane [2, 6]. Endotracheal intubation was facilitated with 0.15 μg/kg vecuronium. Ventilation was mechanically controlled (NAD IIb, North American Dräger, Telford, PA, USA) at a frequency of 18 cycles/min, with a tidal volume (V_T) sufficient to maintain end-tidal CO_2 (E_TCO_2) between 30 to 35 mmHg. The E_TCO_2 was measured by a capnometer (M1026A, Hewlett-Packard, Palo Alto, CA, USA). After arterial pressure and heart rate (HR) became stable for 10 min, a continuous 256-s ECG was recorded as the anesthetized stage.

Pneumoperitoneum was introduced by insufflation of CO_2 via a Veres needle inserted into a small umbilical incision. Intra-abdominal pressure was maintained automatically at 10 mmHg by a CO_2 insufflator. After the completion of pneumoperitoneum, a continuous 256-s ECG was recorded as the insufflated stage. Ventilator settings were not changed, and the patients were kept in a horizontal position during the study.

Measurements including arterial pressure, HR, (at all three stages) SpO_2, E_TCO_2, and peak airway pressure (PAP) (anesthetized and insufflated stages) were obtained at the start and end of each ECG recording. The V_T (during anesthetized and insufflated stages) was obtained at the middle of ECG recordings. The PAP and V_T were observed using a built-in monitor. Mean arterial pressure (MAP) was calculated as:

$$\text{MAP} = [(\text{systolic pressure}) + 2 \times (\text{diastolic pressure})] \div 3$$

Power spectral analysis of the R-R intervals was performed as previously described [14]. In brief, the ECG channel output was recorded onto a floppy diskette (RD-F1, TEAC, Tokyo, Japan) and digitized at 500 Hz for offline analysis. The computer program processed the digitized data using a 14-bit A-D converter-equipped desktop computer (PC98, NEC, Tokyo, Japan) and analyzed electrocardiographic wave. The program measured the time difference between two R waves to create an R-R interval tachogram. The contamination of artifacts was erased beat by beat manually. Instantaneous 1024-HR data from 256-s R-R interval segments were converted to 1/R-R interval by sampling at 4 Hz, and the 256-s segment of R-R intervals were subjected to offline power spectral analysis by fast-Fourier transform. A rectangular local window periodogram method was used as a low-pass antialiasing digital filter at a point above the Nyquist sampling rate (2 Hz), which allowed spectral estimates between 0 and 1 Hz to be computed reliably. The power spectra at frequencies less than 0.5 Hz were standardized as the square of the mean HR (Hz). The spectra were quantified by examining two areas of the spectrum: the LF (0.04–0.15 Hz) and HF (0.15–0.40 Hz) band areas. The peak areas of the power spectral densities were integrated, and the HF/LF ratio was computed. Then the log power of these peak areas and the HF/LF ratio were calculated by taking their common logarithm.

Data were expressed as mean ± standard deviation (SD). Demographic data were analyzed by one-way analysis of variance (ANOVA). Proportions of gender in each group were compared by the chi-square test. For data analysis of cardiovascular and respiratory measures and the measures from power spectral analysis, intergroup and intragroup differences were evaluated by two-way ANOVA for repeated measures. Once the intragroup differences were identified, the effects of the successive steps in the procedure were analyzed by paired *t*-test. A p of less than 0.05 was considered significant.

Table 1. Patient demographic characteristics

	Sevoflurane group	Isoflurane group	Propofol group
Age (year)	47 ± 10	47 ± 13	45 ± 10
Sex (male/female)	6/9	6/9	5/10
Height (cm)	160 ± 8	161 ± 10	157 ± 9
Weight (kg)	59 ± 10	63 ± 14	63 ± 10

Values are mean ± SD or n

Results

The three groups were similar with respect to demographic data including age, gender, height, and body weight (Table 1).

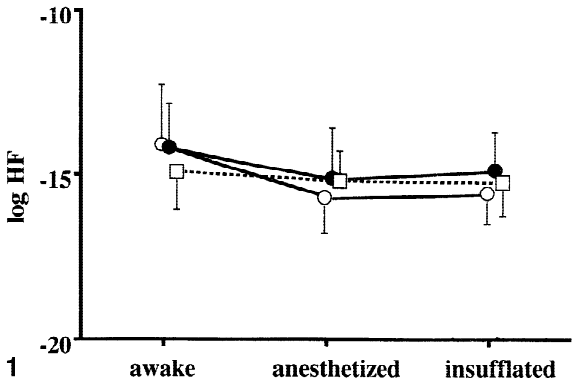
Mean arterial pressure and HR were decreased at the anesthetized stage, then restored to the control level at the end (MAP) or start (HR) of the insufflated stage (MAP: $p < 0.0001$; HR: $p < 0.0001$) (Table 2). Peak airway pressure and E_TCO_2 were increased at the start (PAP) or end ($EtCO_2$) of the insufflated stage (PAP: $p < 0.0001$; $EtCO_2$: $p < 0.0001$). As a result of insufflation, V_T decreased ($p < 0.0001$). There were no intergroup differences among the three groups in MAP, HR, PAP, E_TCO_2, and V_T.

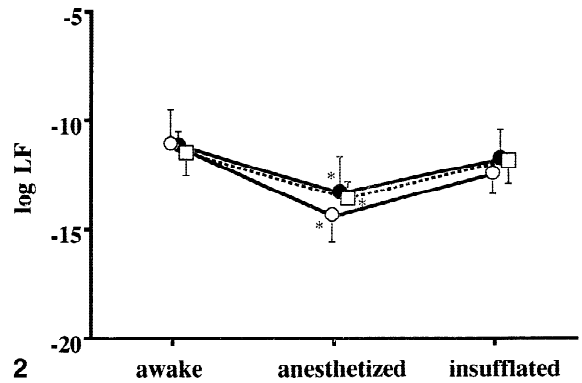
Log HF, which indicates parasympathetic activity, did not change throughout the study ($p = 0.08$; Fig. 1). Log LF, which represents sympathetic activity, decreased at the anesthetized stage, then increased to the control level at the insufflated stage ($p < 0.0001$; Fig. 2). Log HF/LF, the balance of the sympathetic and parasympathetic activity, increased with induction of anesthesia and decreased to the control level after pneumoperitoneum ($p < 0.0001$; Fig. 3). These three measurements made by power spectral analysis did not differ among the three groups [log HF: $p = 0.19$; log LF: $p = 0.16$; log HF/LF: $p = 0.97$].

Discussion

The results of this study suggested that pneumoperitoneum with the patient under general anesthesia increased cardiac sympathetic activity. The increase in MAP and HR during pneumoperitoneum also may reflect the increase in cardiac sympathetic activity. Three possible mechanisms may explain the increase in cardiac sympathetic activity. First, the increase in intra-abdominal pressure may have caused initial reduction in venous return and cardiac output [10, 11], resulting in reflexed increase of sympathetic activity. However, some authors have reported that pneumoperitoneum alone does not cause significant change in cardiac output [17, 19]. Therefore, further investigation is required to clarify whether this mechanism is possible when pneumoperitoneum is applied.

Second hypercarbia itself may have directly stimulated the sympathetic nervous system, resulting in increased cardiac output and MAP [18, 21]. Then hypercarbia also may have stimulated sympathetic nervous system indirectly by increasing plasma catecholamine concentration, including epinephrine and norepinephrine [21]. Indeed, the plasma concentration of dopamine, vasopressin, epinephrine, norepinephrine, rennin, and cortisol increased shortly after in-





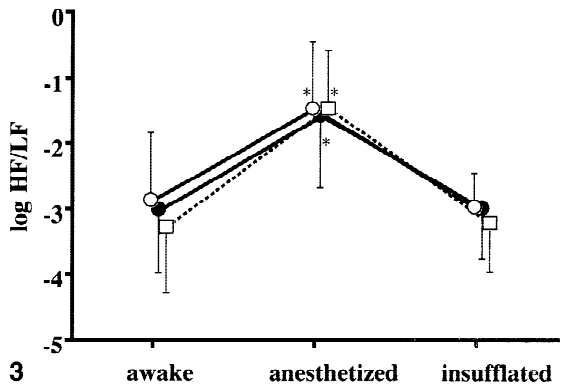


Fig. 1. Change in log HF, which indicates cardiac parasympathetic activity in each group. Each point represents the mean of 15 patients, and the error bar indicates standard deviation. –○– sevoflurane group, –●– isoflurane group, ··□·· propofol group.

Fig. 2. Change in log LF, which indicates cardiac sympathetic activity in each group. Each point represents the mean of 15 patients, and the error bar indicates SD. –○– sevoflurane group, –●– isoflurane group, ··□·· propofol group. *Significantly different ($p < 0.05$) when compared with awake stage (paired t test).

Fig. 3. Change in log HF/LF, the balance of the sympathetic and parasympathetic activity in each group. Each point represents the mean of 15 patients, and the error bar indicates standard deviation. –○– sevoflurane group, –●– isoflurane group, ··□·· propofol group. *Significantly different ($p < 0.05$) when compared with awake stage (paired t test).

Table 2. Changes in cardiovascular and ventilatory measures

	Awake		Anesthetized		Insufflated	
	Start	End	Start	End	Start	End
MAP (mmHg)						
Sevoflurane	96.3 (13.3)	95.8 (13.8)	65.4 (12.2)[a]	64.1 (14.8)[a]	82.8 (11.2)[a,b]	91.9 (14.3)[b]
Isoflurane	99.5 (13.0)	96.1 (13.9)	66.2 (10.5)[a]	60.3 (11.3)[a]	81.5 (10.8)[a,b]	104.2 (16.0)[b]
Propofol	99.1 (16.6)	99.6 (15.3)	74.2 (11.6)[a]	73.2 (11.8)[a]	92.6 (17.7)[a,b]	105.8 (17.5)[b]
HR (beats/min)						
Sevoflurane	75.1 (13.1)	76.4 (15.1)	68.0 (16.6)[a]	68.4 (17.0)[a]	76.7 (16.9)[b]	79.2 (19.5)[b]
Isoflurane	78.8 (19.2)	78.9 (18.4)	72.5 (15.0)[a]	68.6 (13.2)[a]	76.3 (14.1)[b]	83.1 (13.6)[b]
Propofol	83.9 (14.8)	85.2 (14.9)	62.3 (9.5)[a]	61.1 (9.2)[a]	70.0 (10.1)[a,b]	71.2 (9.2)[a,b]
PAP (mmHg)						
Sevoflurane			9.7 (2.2)	9.7 (2.2)	13.7 (2.4)[b]	14.1 (2.8)[b]
Isoflurane			10.0 (1.8)	10.1 (1.8)	13.8 (3.1)[b]	13.9 (3.0)[b]
Propofol			10.5 (2.4)	10.7 (2.4)	14.2 (2.3)[b]	14.5 (2.3)[b]
E_TCO_2 (mmHg)						
Sevoflurane			32.2 (1.8)	31.8 (1.6)	32.6 (2.5)	35.0 (3.1)[b]
Isoflurane			32.1 (1.7)	31.6 (1.8)	32.0 (2.1)	34.5 (3.4)[b]
Propofol			32.3 (2.1)	31.8 (2.2)	32.5 (2.4)	35.3 (2.9)[b]
V_T (ml)						
Sevoflurane			370.8 (105.0)		355.4 (101.2)[c]	
Isoflurane			379.5 (66.1)		369.0 (65.3)[c]	
Propofol			334.7 (40.5)		316.2 (44.2)[c]	

Values are mean ± SD; n = 15 in each group; MAP = mean arterial pressure; HR = heart rate; PAP = peak airway pressure; $EtCO_2$ = end-tidal CO_2 concentration; Vt = tidal volume

[a] Significantly different ($p < 0.05$) from start of awake stage (paired t test)

[b] Significantly different ($p < 0.05$) from start of anesthetized stage (paired t test)

[c] Significantly different ($p < 0.05$) from anesthetized stage (paired t test)

Start, end; measurement at the start or end of each EEG recording

duction of pneumoperitoneum [1, 4, 12]. However, O'leary et al. [20] demonstrated that only renin-aldosterone increased in parallel with the MAP increase after induction of pneumoperitoneum. Epinephrine, norepinephrine, and cortisol increased only after deflation of the pneumoperitoneum. Therefore, the contribution of neumoendocrine response to the increase in sympathetic activity shortly after induction of pneumoperitoneum still is uncertain.

Third, the increase in log LF might have represented direct stimulation with pneumoperitoneum. Distention of the abdominal muscles might have produced pain [15]. Furthermore, some authors consider that insufflated carbon dioxide, diaphragmatic distention, or both may be the cause of irritation at the phrenic nerve distribution area, resulting in postoperation pain after laparoscopic cholecystectomy [5, 16]. Similarly, it is speculated that mechanical stimulation and stimulation by insuffulated carbon dioxide may directly cause sympathetic activation as nociceptive stimulation.

In this study, although log LF decreased in all three groups after induction of anesthesia, log HF did not change. Several reports showed the effect of anesthetics used in this study on the cardiac autonomic nervous system, evaluated using spectral analysis of HR or systemic arterial pressure. Kato et al. [13] showed dose-related decreases in three bands of spectral analysis of HR variability (low, 0.04–0.09 Hz; mid, 0.09–0.15 Hz; and high, 0.15–0.4 Hz) during isoflurane anesthesia. Galletly et al. [8] also demonstrated a decrease in three frequency bands of HR variability (low, 0.02–0.08 Hz; mid, 0.08–0.15 Hz; and high, 0.15–0.45 Hz) under 1.5% isoflurane with 66% nitrous oxide anesthesia.

Scheffer et al. [22] showed both a low (0.06–0.12 Hz) and a high (0.12–0.36 Hz) frequency spectral power decrease after 2.5 mg/kg bolus administration of propofol. Furthermore, Galletly et al. [7] demonstrated that propofol induces a significant reduction in all component frequencies (low, 0.02–0.08 Hz; mid, 0.08–0.15 Hz; and high, 0.15–0.45 Hz) of spectral power of HR variability under continuous infusion of propofol (mean infusion rate, 0.19 mg/kg/min). However, Wang et al. [24] showed a significant decrease in powers of very low frequency (0.00–0.08 Hz), low frequency (0.08–0.15 Hz), and very high frequency (0.80–1.60 Hz), but not in powers of high frequency (0.15–0.25 Hz) under continuous infusion of propofol (5 and 10 mg/kg/min) using spectral analysis of systemic arterial pressure.

Little is known about sevoflurane anesthesia. Therefore, direct comparison between current and previous studies is difficult because study conditions such as the age of the patients, doses of the anesthetics, coadministered drugs, definition of each frequency bandwidth, and mode of ventilation differ from study to study. However, because the log HF is coupled with respiration, the relatively unaltered log HF in the current study may be caused partly by the controlled respiration [24].

Three different anesthetics commonly used in daily anesthesia practice were employed in this study. Propofol anesthesia was prepared by the same recipe that Giradis et al. [4] used. The cardiovascular and ventilatory measurements in the current propofol group almost agreed with their results. For sevoflurane and isoflurane anesthesia, 1.75 MAC of each were used to match the cardiovascular response to pneumoperitoneum. Indeed, no difference was noted among the three groups in cardiovascular measurements as a response to the pneumoperitoneum. Neither was any difference noted in ventilatory measurements among the three groups. Therefore, cardiovascular and ventilatory response to pneumoperitoneum seemed to be identical among the three groups.

Three measurements from HR variability analysis, log HF, log LF, and log HF/LF, showed similar change in response to pneumoperitoneum in all three groups. The different anesthesias used in this study did not have major effect on cardiac ANS as measured by HR variability analysis. These results indicate that changes in HR variability are similar no matter what anesthesia is used when the cardiovascular and ventilatory changes are equivalent. The authors suggest that measurements from HR variability analysis mainly reflect cardiovascular and ventilatory change rather than the characteristics of the anesthetics used.

In summary, the findings of this study showed that pneumoperitoneum increased sympathetic cardiac activity as evaluated by HR variability analysis. The choice of general anesthetic did not seem to have a major influence on the changes in cardiac ANS induced by pneumoperitoneum.

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