Reports of Investigation

Transfer function analysis of the circulation in patients undergoing sevoflurane anesthesia

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Purpose: The effects of sevoflurane anesthesia on the interactions between heart rate, blood pressure and respiration were assessed using transfer function analysis.

Methods: Nine ASA I or 2 patients undergoing elective surgery were involved. They were paralysed and their lungs were mechanically ventilated during sevoflurane anesthesia. Instantaneous heart rate (IHR) from electrocardiogram, instantaneous lung volume (ILV) by respiratory inductive plethysmography and mean blood pressure (MBP) by arterial tonometry were obtained during conscious state, and 1MAC and 2MAC of sevoflurane anesthesia. Transfer function analysis for the relationships between ILV and IHR, ILV and MBP, MBP and IHR were made for five minute periods during which the respiratory rate was varied in a standardized fashion.

Results: In awake patients transfer magnitudes for the relationships between ILV and IHR and between MBP and IHR in the 0.04-0.5Hz frequency band were $8.9 \pm 7.7 \text{ bpm} \cdot \text{l}^{-1}$ and $0.95 \pm 0.44 \text{ bpm} \cdot \text{mmHg}^{-1}$ respectively. Sevoflurane 2MAC decreased these values to 1.2 ± 0.7 ($P = 0.014$) and 0.26 ± 0.14 ($P < 0.01$) respectively, but phases were not affected. Neither transfer magnitudes nor phases between ILV and MBP were affected during sevoflurane anesthesia. Coherence for the relationships between ILV and IHR and between MBP and IHR were decreased during 1MAC sevoflurane anesthesia but not affected during 2MAC sevoflurane anesthesia.

Conclusions: The interactions between heart rate, blood pressure and respiration were altered by sevoflurane anesthesia. These findings could be explained by the attenuation of autonomic nervous system activity.

Objectif : Évaluer les effets de l'anesthésie avec du sévoflurane sur les interactions entre la fréquence cardiaque, la tension artérielle et la respiration par l'analyse de la fonction de transfert.

Méthode : Neuf patients de classe I ou II ASA, devant subir une intervention élective, ont été recrutés. On les a insensibilisés et placés sous ventilation mécanique pendant l'anesthésie au sévoflurane. On a obtenu la fréquence cardiaque instantanée (FCI), de l'électrocardiogramme; le volume pulmonaire instantané (VPI), de la pléthysmographie respiratoire inductive; la tension artérielle moyenne (TAM), de la tonométrie artérielle, à l'état de conscience, puis à 1CAM et à 2CAM de sévoflurane. L'analyse de la fonction de transfert a été faite pour étudier les relations entre le VPI et la FCI, le VPI et la TAM, la TAM et la FCI pour des périodes de cinq minutes durant lesquelles le rythme respiratoire était modifié d'une façon standard.

Résultats : Chez les patients éveillés, l'ampleur du transfert pour les relations entre le VPI et la FCI, et entre la TAM et la FCI, selon la bande de fréquences de 0,04-0,5 Hz a été de $8,9 \pm 7,7 \text{ bpm} \cdot \text{l}^{-1}$ et de $0,95 \pm 0,44 \text{ bpm} \cdot \text{mmHg}^{-1}$ respectivement. Sous une concentration de 2CAM de sévoflurane, ces valeurs ont baissé à $1,2 \pm 0,7$ ($P = 0,014$) et à $0,26 \pm 0,14$ ($P < 0,01$) respectivement, mais les phases n'ont pas changé. Ni l'ampleur du transfert, ni les phases entre le VPI et la TAM n'ont été modifiées pendant l'anesthésie au sévoflurane. La cohérence de la relation entre le VPI et la FCI et entre la TAM et la FCI a diminué pendant l'anesthésie avec 1CAM de sévoflurane, mais n'a pas été modifiée pendant l'utilisation de 2CAM.

Conclusion : Les interactions entre la fréquence cardiaque, la tension artérielle et la respiration ont été modifiées par l'anesthésie au sévoflurane. Ces résultats peuvent s'expliquer par la réduction de l'activité du système nerveux autonome.

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HERE are a variety of reports describing the perturbation of cardiovascular regulation during surgery and general anesthesia.

Inhalation anesthetics attenuate the baroreceptor reflex dose-dependently.¹⁻³ Donchin *et al.*⁴ showed that respiratory sinus arrhythmia (RSA) decreases during isoflurane-nitrous oxide anesthesia and increases during recovery. Kato *et al.*⁵ also described marked reductions in the power of heart rate variability (HRV) at all frequencies, indicating total attenuation of autonomic nervous system activity during isoflurane anesthesia. Sevoflurane also suppresses all frequency components of HRV, but the low frequency component reflecting sympathetic nervous activity is less affected by sevoflurane than by isoflurane.⁶ On the other hand, Hankala *et al.*⁷ reported that RSA is reversed during positive pressure ventilation. Latson *et al.*⁸ suggested that surgical stimulation might have important effects on the autonomic reflex mediating HRV and these may vary with the anesthetic technique. Thus, many factors may perturb cardiovascular regulation during surgery and general anesthesia.

Power spectral analysis of HRV is a non-invasive probe to assess cardiovascular perturbation during anesthesia. However, only limited interpretation can be made regarding system behaviour based on observation of HRV as an output variable, because the change of the magnitude of RSA might be caused not only by the alteration of autonomic nervous activity but also the change of tidal volume and so on. Determination of a more accurate and detailed characterization of system behaviour requires knowledge of the input perturbations that drive the system, as well. To characterize directly the coupling between different physiological variables, Appel *et al.*⁹ developed methods for transfer function analysis. The transfer function is the incremental gain as a function of frequency between input signal and output signal and is applicable to linear systems. The transfer magnitude reflects the degree to which input signal content at a discrete frequency becomes manifest in output energy. The phase indicates what portion of the period corresponding to the frequency the output signal is delayed with respect to the input. The coherence attains a value between zero and unity and provides a measure of the quality of the corresponding transfer function. Where the coherence falls, output fluctuations reflect the influence of system nonlinearities, loss of time invariance, other system input signals, or measurement noise.¹⁰ Saul *et al.*¹¹ described precisely the sympathetic and vagal contributions to RSA using transfer function analysis in combination with random interval breathing to broaden the frequency

content of respiration. Our objective of this study was to determine how the relations between respiration, HRV and blood pressure variation are modulated by anesthesia with sevoflurane and positive pressure ventilation using transfer function analysis.

Methods and Materials

Subjects

The study was approved by the Local Review Board and informed consent was obtained. Nine patients (two women; 36 ± 14 yr; range, 21-52 yr, ASA physical status 1 or 2) undergoing elective dental or oral surgery were involved in this study. Patients had no cardiopulmonary disease and no premedication was given.

Measurements

Continuous electrocardiogram (ECG), instantaneous lung volume (ILV) and continuous non-invasive blood pressure (CNBP) monitoring were performed throughout the experiments and recorded on a personal computer (PC386LS, EPSON, Japan). The ECG signal was obtained through the analog output port from an ECG monitor (M1166A Model 186S, Hewlett Packard, USA). The ILV was measured with two-belt chest-abdomen inductance plethysmography (TR255T, Nihon Koden, Japan). Before each data acquisition, respiratory calibration was made using a rotating vane flowmeter (RGM 5250, Ohmeda, USA). The CNBP was measured with an arterial tonometer (JENTOW, Nippon Colin, Japan). A tonometric sensor was attached to the right extended wrist. A cuff placed around the left upper arm was used for calibration of the output of the tonometric sensor. During general anesthesia, the concentrations of carbon dioxide, oxygen and sevoflurane were measured by an infrared spectrometer (5250RGM, Ohmeda, USA).

Modification of respiration

In order to make the respiratory signal broadened, respiration was modified as described by Saul *et al.*¹¹ Awake patients were asked to breathe and the lungs of anesthetized patients were ventilated manually by anesthesiologists with each tone of a series of auditory cues. The tones with a mean rate of 15 min^{-1} were spaced at irregular intervals according to a modified Poisson process. As the power density of a sequence of Poisson impulses is constant over all frequencies, the power spectrum of the respiratory drive chain was nearly flat, and the frequency content of the measured lung volume signal was effectively whitened. The ratio of the length of each trigger tone to the interval to the upcoming tone was set at 1:3 and the patients were asked to inspire while the tone was coming out so that

I:E ratio was maintained at 1:2. In order to avoid discomfort, minimum and maximum respiratory intervals of 1 sec and 15 sec were chosen. Care was taken to maintain mean tidal volume at about 10 ml·kg⁻¹ throughout the experiment by brief practice before the start of the experiment.

Protocol

The day before surgery patients were placed in the supine position in a quiet room and ECG, CNBP and

ILV were measured while breathing as described above. On the day of surgery, anesthesia was induced with 4 mg·kg⁻¹ thiopental and tracheal intubation was facilitated by 0.15 mg·kg⁻¹ vecuronium. After surgery began, ECG, CNBP and ILV were obtained while the lungs were ventilated manually as described above at 1.0 MAC and 2.0 MAC end-tidal sevoflurane concentrations after each end-tidal sevoflurane concentration had been maintained for more than 20 min. Nitrous oxide was not given and FiO₂ was kept at 0.3 until the completion of the study.

TABLE I Hemodynamic variables, end-tidal concentrations of carbon dioxide and sevoflurane, rectal temperature, pulse oximetry

	AWAKE	1MAC sevoflurane	2MAC sevoflurane
HR(bpm)	76 ± 13	74 ± 10	76 ± 10
SBP(mmHg)	121 ± 9	113 ± 17	93 ± 15*†
DBP(mmHg)	73 ± 9	68 ± 11	53 ± 9*†
MBP(mmHg)	88 ± 9	85 ± 14	67 ± 9*
SpO ₂ (%)	97.8 ± 1.1	99.3 ± 1.0	99.6 ± 0.7
P _{ET} CO ₂ (mmHg)		33 ± 2	31 ± 3
P _{ET} SEV(%)		1.69 ± 0.06	3.37 ± 0.09†
RT(°C)		36.4 ± 0.3	36.2 ± 0.5

HR=heart rate; BP=systemic blood pressure; DBP=diastolic blood pressure; SpO₂=arterial oxygen saturation; P_{ET}CO₂=end-tidal carbon dioxide tension; P_{ET}SEV=end-tidal sevoflurane concentration; RT=rectal temperature.

Values are mean ± S.D. *: $P < 0.05$ vs AWAKE, †: $P < 0.05$ vs 1MACsevoflurane

Data analysis

The ECG, ILV and CNBP signals were sampled and analysed off-line on a computer. All signals were sampled at 1 kHz. The R waves were detected from the ECG, and an instantaneous heart rate (IHR) time series was constructed at 4Hz. The ILV and CNBP signals were digitally filtered and decimated to 4Hz. A

TABLE III Coherence functions for each relationships.

	AWAKE	1MAC sevoflurane	2MAC sevoflurane
Coherence ILV-HRV	0.72 ± 0.06	0.54 ± 0.14*	0.62 ± 0.09
ILV-MBP	0.72 ± 0.08	0.78 ± 0.11	0.82 ± 0.08
MBP-HRV	0.69 ± 0.04	0.55 ± 0.09*	0.64 ± 0.10

Values are mean ± S.D. *: $P < 0.05$ vs AWAKE

TABLE II The effect of sevoflurane on average transfer function magnitude and phase between ILV - IHR, ILV - MBP and MBP - IHR.

			AWAKE	1MAC sevoflurane	2MAC sevoflurane
ILV - IHR	Magnitude (bpm/l)	LF	11.3 ± 11.3	2.6 ± 2.8*	2.1 ± 1.7*
		HF	8.2 ± 6.5	0.7 ± 0.5*	0.9 ± 0.4*
		TF	8.9 ± 7.7	1.2 ± 1.0*	1.2 ± 0.7*
		LF/HF	2.0 ± 0.6	6.2 ± 5.5*	3.6 ± 2.5
	Phase (degree)	LF	-15 ± 45	-54 ± 59	-19 ± 43
		HF	-2 ± 52	-12 ± 45	-26 ± 30
ILV - MBP	Magnitude (mmHg/l)	TO	-5 ± 50	-22 ± 49	-24 ± 33
		LF	7.4 ± 9.9	8.1 ± 4.6	6.7 ± 2.9
		HF	5.9 ± 4.6	4.6 ± 1.0	4.5 ± 1.0
		TF	6.3 ± 5.9	5.4 ± 1.9	5.0 ± 1.4
	Phase (degree)	LF/HF	11.1 ± 6.8	8.5 ± 3.8	8.3 ± 2.9
		LF	32 ± 47	-11 ± 35	-18 ± 27
MBP - IHR	Magnitude (bpm/mmHg)	HF	-33 ± 49	-22 ± 14	-10 ± 14
		TO	-17 ± 49	-19 ± 19	-12 ± 17
		LF	0.83 ± 0.58	0.30 ± 0.13*	0.29 ± 0.10*
		HF	0.99 ± 0.42	0.25 ± 0.10*	0.25 ± 0.17*
	Phase (degree)	TF	0.95 ± 0.44	0.26 ± 0.10*	0.26 ± 0.14*
		LF/HF	0.80 ± 0.29	1.28 ± 0.57	1.50 ± 0.78
		LF	66 ± 28	14 ± 23	-6 ± 31
		HF	36 ± 35	-23 ± 35	-3 ± 34
		TF	44 ± 33	-14 ± 32	-4 ± 33

Values are mean ± S.D. *: $P < 0.05$ vs AWAKE

FIGURE Representative results of transfer function analysis for the relationship between ILV and IHR in an awake patient. A; respiratory and heart rate power spectra, B; transfer magnitude, C; transfer phase, D; coherence

512-sec segment of data that was free from artifact and hemodynamically stable from each 30-min random interval breathing was chosen for off-line analysis. Spectral analysis for IHR, mean CNBP (MBP) and ILV was performed by a fast Fourier transform. The cross-spectra between ILV and IHR, between ILV and MBP and between MBP and IHR were also obtained. Then, transfer function analysis was performed using the equation shown in the Appendix.

Statistical analysis

Averaged transfer function magnitude, phase and coherence for all frequency (0.04-0.5 Hz, TF), for low frequency component (0.04-0.15 Hz, LF) and for high frequency component (0.15-0.5 Hz, HF) were calculated in order to determine the statistical difference. One

way analysis of variance with replication followed by Bonferroni *post hoc* test was used to assess the difference between awake, 1.0 MAC and 2.0 MAC sevoflurane values. Values of $P < 0.05$ were considered significant.

Results

Mean heart rate, blood pressure, pulse oxymetry arterial oxygen saturation, $P_{ET}CO_2$, sevoflurane concentration, and rectal temperature during the experiment are shown in Table I. Although sevoflurane did not affect HR, 2 MAC sevoflurane decreased MBP values compared with the conscious state.

Power spectra and transfer function for the ILV and IHR from a representative patient are shown in Figure 1. The power of ILV (Figure 1A) is spread over a wide frequency range due to the random respiration interval. In this patient, transfer magnitude (Figure 1B) decreased markedly above 0.1 Hz and phase (Figure 1C) approached 180 at 0 Hz and gradually decreased as frequency increased, which resembles the sympathetic case reported by Saul *et al.*¹¹ Coherence function is more than 0.5 over a wide frequency range, suggesting that the relationship between ILV and IHR is relatively linear (Figure 1D).

Averaged magnitudes and phases for LF, HF, TF and LF/HF ratio for each relationship are shown in Table II.

ILV-IHR transfer relations

Magnitudes for LF, HF and TF were decreased during 1 MAC and 2 MAC sevoflurane anesthesia compared with awake values. The LF/HF was increased only during 1 MAC sevoflurane anesthesia. Phases were not affected by sevoflurane anesthesia.

ILV-MBP transfer relations

Neither magnitudes nor phases for any frequencies were affected by sevoflurane anesthesia.

MBP-IHR transfer relations

Magnitudes for any frequencies except LF/HF ratio were decreased during 1 MAC and 2 MAC sevoflurane anesthesia. Phases for any frequencies were not affected by sevoflurane anesthesia.

Coherence

Averaged coherence for all frequencies are shown in Table III. Coherence for the relationship between ILV and IHR, and between MBP and IHR are decreased during 1 MAC sevoflurane anesthesia but are not affected during 2 MAC sevoflurane anesthesia, although the coherence for the relationship between ILV and MBP were not affected at any depth of anesthesia.

Discussion

In the present study, the effect of sevoflurane anesthesia on transfer function of cardiovascular control during controlled ventilation with broad band frequency was studied. When RSA is investigated more precisely, we must consider the changes of V_T and RR because those might affect the magnitude of RSA. Transfer function analysis provides information about how much a unit of V_T is reflected in the magnitude of RSA at each frequency. The results showed variable degree of perturbation in the cardiovascular regulation during sevoflurane anesthesia.

Transfer magnitude for the relation between ILV and IHR was decreased during sevoflurane anesthesia. We suggest that this result is supported by a report that described the marked reductions in the power of HRV at all frequencies during inhalation anesthesia.⁵ Surprisingly, LF/HF ratio increased during 1MAC sevoflurane anesthesia. Although RSA is mediated by a combination of changing levels of efferent cardiac vagal and sympathetic activity, sympathetic activity only influences heart rate at frequencies < 0.15 Hz due to frequency-limited adrenergic receptor responses. Sympathetic RSA is characterised by markedly reduced magnitude at frequencies above 0.1 Hz and a phase delay, whereas vagal RSA is characterised by higher magnitude at all frequencies and a slight phase lead.¹¹ We may speculate that 1MAC sevoflurane anesthesia attenuated vagal RSA more profoundly than sympathetic RSA. Fujisato *et al.*⁶ demonstrated that the Mayer wave related sinus arrhythmia reflecting sympathetic activity was less affected by sevoflurane than by halothane or isoflurane. Interestingly, Hankala *et al.*⁷ reported that considerable RSA was caused by ventilation frequency of 6 min⁻¹ (i.e. 0.1 Hz), which is relevant to sympathetic RSA control, even during deep anesthesia. On the contrary, others^{4,5} reported the effect of inhalation anesthetics on RSA when the ventilation rate was set to > 6 min⁻¹ which is relevant to vagal RSA control. They showed a decrease or disappearance of RSA during deep anesthesia. The difference in these results might be caused by the difference of ventilation rate. Alternatively, as coherence during 1MAC sevoflurane anesthesia was lower, presumably due to inadequate blockade of autonomic response to the surgical stimuli, the LF/HF ratio might simply be affected by cardiovascular instability.

The magnitude of the relation between ILV and MBP was not affected by sevoflurane anesthesia. Although there is some controversy,^{12,14} respiratory fluctuation of arterial pressure is considered to be due to both mechanical thoracic coupling between respiration and the vasculature, and the neurally mediated

effects of respiratory induced fluctuations of IHR.⁸ Saul *et al.*¹¹ concluded that, at frequencies between 0.05 Hz and 0.25 Hz, some of the respiratory variance in arterial pressure is due to HRV. On the other hand, above 0.25 Hz, RSA plays little role in mediating arterial pressure variation, i.e. respiration mechanically influences arterial pressure variation. Wang *et al.*¹⁵ also reported that HF component of systemic blood pressure variation was not affected by propofol anesthesia, which is reported to attenuate autonomic nervous function to some extent,^{16,17} although the total power of systemic arterial pressure spectrum was decreased. Our results are consistent with these reports in terms of HF component but we could not find any decrease in magnitude for any frequency component. This may be because we divided frequency into two components (LF and HF) at 0.15 Hz compared with four component in Wang's study¹⁵ or may be because of the difference of anesthetics administered. We speculate that the magnitude between ILV and MBP was not affected by sevoflurane anesthesia because respiration influences arterial blood pressure variability via mechanical thoracic coupling between respiration and the vasculature rather than via autonomic nervous activity.

The transfer magnitude between MBP and IHR was comparable to the values reported by Saul *et al.*¹¹ As they described, care is required in interpreting the transfer relations between MBP and IHR, because the transfer functions between MBP and IHR represent the combined effects of the IHR baroreflex and the mechanical feed-forward from IHR to MBP and do not necessarily reflect the open-loop characteristics of the IHR baroreflex. We speculate that the modulation of these two mechanisms by sevoflurane anesthesia might be responsible for the decrease in transfer magnitude.

Phases for any relations were not affected by sevoflurane anesthesia in the present study. This result was surprising, because the patients were receiving positive pressure ventilation during sevoflurane anesthesia and our results were not in accord with Hankala *et al.*⁷ who showed that RSA is reversed during positive pressure ventilation. They demonstrated that the typical phase relationship of RSA is a decrease in inspiration and an increase in expiration, which is reversed in awake, actively breathing subjects.¹⁸ Furthermore, if respiratory fluctuation of MBP is mediated by mechanical factors, phases for the relation between respiration and MBP are also expected to be affected during sevoflurane anesthesia. We do not know why phases were not affected. One possibility is the difference of respiratory pattern. We modified respiration to make the respiratory signal broadened rather than remaining at a fixed rate. The phase relations between respiration, HRV and MBP are

relatively frequency-dependent phenomena. Thus, alteration of the phase relationships during sevoflurane anesthesia might have been impeded in our experiment. Another explanation is the interference of the relations between respiration, HRV and MBP caused by burst suppression in electroencephalography as reported by Hankala *et al.*¹³ due to sevoflurane anesthesia¹⁹ although we did not measure electroencephalography in this study. Moreover, we obtained ECG signal from an analog output port used for synchronising the firing of a defibrillator in an ECG monitor. The output has a delay of less than 20 msec because the monitor has its internal path contaminated by electronic digitizer/data manipulator which may hold the signal in a digital buffer and send the signal to the analog output jack with an unpredictable time-varying delay. As shown in the very high variance in the phase data, this might have disturbed transfer phase analysis and might be one of the reason why any effect of sevoflurane anesthesia on the phase data could not be found.

We conclude that sevoflurane reduced the transfer magnitude between ILV and IHR, MBP and IHR but had no effect on that between ILV and MBP. Phases for any relationships were not affected. It is suggested that these phenomena are related to the attenuation of ANS activity by sevoflurane but we could not detect any effect of IPPV on the interaction between ILV, IHR and MBP.

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Appendix

The complex transfer function $H(q)$ was evaluated using the relation

$$H(q) = S_{xy}(q) / S_{xx}(q) \quad (1)$$

where $S_{xx}(q)$ is the input autospectral density function, $S_{yy}(q)$ is the output autospectrum, and the

$S_{xy}(q)$ is the cross-spectrum. Magnitude and phase components, $H(q)$ and $\theta(q)$, were derived from the real part $H_R(q)$ and the imaginary part $H_I(q)$ of the complex transfer function as

$$H(q) = \{ [H_R(q)]^2 + [H_I(q)]^2 \}^{1/2}$$

$$\theta(q) = \tan^{-1}(H_I(q)/H_R(q))$$

The squared coherence function, $\gamma^2(q)$, which ranges between 0 and 1, was used to assess the statistical reliability of the transfer function estimates at each frequency.

$$\gamma^2(q) = S_{xy}(q)^2 / S_{xx}(q) S_{yy}(q)$$

A value of unity indicates a perfectly linear relationship between the input and output at that frequency.