Chinese Journal of Physiology 55(3): 169-177, 2012
DOI: 10.4077/CJP.2012.BAA005

Altered Short-Term Dynamics of Cardio-Respiratory Interaction during Propofol-Induced Yawning

Chih-Hsiang Tsou[1, 5], Pei-Yeh Yu[2], Pai-Yu Tu[2], Kuo-Tung Fan[3], Hsiang-Ning Luk[4], and Tsair Kao[6]

[1]*Division of Chest Medicine, Ren-Ai Branch, Taipei City Hospital, Taipei 10629*
[2]*Division of Anesthesiology, Ren-Ai Branch, Taipei City Hospital, Taipei 10629*
[3]*Institute of Health Policy and Management, National Taiwan University, Taipei 10055*
[4]*Department of Anesthesiology, Taichung Veterans General Hospital, Taichung 40705*
[5]*Department of Medicine, School of Medicine, National Yang-Ming University, Taipei 11221*
and
[6]*Department of Biomedical Engineering, Hungkuang University, Taichung 43302*
Taiwan, Republic of China

Abstract

Cardiac and respiratory oscillations have been shown to interact with each other. This interaction could reflect autonomic nervous system functionality. Propofol-induced yawning during anesthesia induction seems to be associated with sympathetic activation. Presumptively, there is high linearity among interaction of different physiologic system behaviors. Recently, investigators used coherence analysis to quantify the existence and strength of linearity between system signals for study of cardio-respiratory interaction under different physiological conditions. In this investigation, we used a method of time-frequency coherence function to analyze ECG and respiration signals to investigate the linearity of cardio-respiratory dynamics in patients undergoing routine propofol induction procedures for elective surgery. In this prospective, observational clinical study, a total of 84 eligible patients were enrolled. The patients were categorized into yawning and no-yawning groups during propofol induction. During induction, both groups demonstrated significant reduction in high frequency coherence (coh-HF) with simultaneously significant increase in very low frequency coherence (coh-VLF) compared to the pre-induction period. As yawning occurred, the yawning group had more significant changes of cardio-respiratory coherences than the no-yawning group at coh-LF and coh-VLF bands. The yawning group also showed loss of linearity at high frequency band (coh-HF > 0.5) as compared with the pre-induction period, and also showed increases in linearity at low (coh-LF > 0.5) and very low (coh-VLF > 0.5) frequency bands compared with the no-yawning group. Propofol-induced yawning alters cardio-respiratory dynamics with changes of linearity between cardio-vascular and respiratory system behaviors.

Key Words: coherence, propofol, yawning, cardio-respiratory interaction

Introduction

Yawning is a stereotypical behavioral pattern that usually occurs under physiologic and pathologic conditions (2, 26, 34, 37). The psycho-physiologic significance of yawning remains unclear but may be related to increased attention and arousal (3, 29). Anesthetic-induced yawning is common but is little

Corresponding author: Tsair Kao, Ph.D., Department of Biomedical Engineering, Hungkuang University, 34, Chung-Chie Rd., Shalu, Taichung 43302, Taiwan, R.O.C. Tel: +886-4-26318652 ext. 4310, Fax: +886-4-26313871, E-mail: tskao@sunrise.hk.edu.tw
This work was performed at Taipei City Hospital, Taipei, Taiwan.
Received: January 11, 2011; Revised: April 21, 2011; Accepted: May 9, 2011.

understood (17). In a previous study, the incidence of propofol-induced yawning was about 53% and was associated with sympathetic activation of cardiac-autonomic control (33).

The interaction among heart rate, respiration and blood pressure (BP) reflects autonomic nervous system (ANS) functionality and reflex mechanisms (1, 32). Respiration oscillation can modulate ANS activity and presents as respiratory sinus arrhythmia (RSA) (4, 9). The kind of interaction between cardio-vascular and respiratory systems has been used as a monitoring index of sedation score and anesthesia depth (7, 24, 36). Anesthetic-induced yawning has been investigated as an index of transition of arousal during anesthesia instead of as an index of anesthesia depth (14). However, there are few investigations on the dynamics of cardio-respiratory interaction during anesthetic-induced yawning.

The exact interaction among physiologic systems is not fully understood. Presumptively, there is a high likelihood of linearity among interactions of different physiologic system behaviors (28). Coherence analysis is a method of quantifying the existence and strength of linearity between system signals in frequency domain, with high linearity for coherence greater than 0.5. Altered cardio-respiratory coherence is also noted in patients with syncope, acute severe brain disorders and congestive heart failure, or those under anesthesia (10, 19, 20, 40). However, most studies with coherence analysis were based on the assumption of stationary characteristics of system signals. Furthermore, most studies focused on physiologic system behaviors under full spectrum (0-0.5 Hz).

This study aimed to investigate the dynamics of cardio-respiratory interaction during anesthetic-induced yawning. It hypothesizes altered dynamic linearity between cardio-vascular and respiratory systems at different frequency bands during propofol-induced yawning. Due to the non-stationary characteristics of bio-signals during anesthesia induction, a time-frequency method of coherence was developed to explore the dynamics of physiologic systems.

Materials and Methods

Study Protocol

The local institutional review board approved the study and all patients signed informed consent before the general anesthesia. This was a prospective, non-randomized and non-invasive clinical study that enrolled 84 eligible adult patients (healthy patients or those with mild systemic diseases ASA I-II, aged 18-65 years) without cardio-vascular, pulmonary, endocrinologic, neurologic or psychiatric disorders. All of them underwent elective surgery under general anesthesia.

Anesthesia was induced by intravenous propofol infusion with a total induction dosage of 1.5 mg/kg at a fixed infusion rate of 2.25 mg/s. Clinical endpoints included loss of consciousness, yawning and apnea throughout the induction periods. Yawning was defined as the involuntary reaction involving opening of the mouth and deep inspiration, followed by expiration. The induction of anesthesia was completed by tracheal intubation in the presence of neuromuscular blocking agents.

The study patients were calm down and received continuous electrocardiogram (ECG), BP, pulse oximetry (SpO_2) and respiration signal (end-tidal CO_2; $etCO_2$) monitoring once at the operation room. The whole process of anesthesia induction was recorded and five events were marked, including: [1] baseline, 5 minutes before induction; [2] start of intravenous injection of propofol (S); [3] end of injection of propofol (E); [4] yawning (Y) or apnea (A); and [5] injection of muscle relaxant (O) and intubation. An independent anesthesiologist assessed the clinical endpoints. There was no desaturation or unstable hemodynamics during the anesthesia induction.

Data Acquisition and Signal Processing

The study used a portable measuring instrument (BP 508; Colin Co, Nippon, Japan) to acquire the cardiovascular and respiratory signals. These signals were digitized at a sampling rate of 500 Hz onto a personal computer for analysis. Detection of R wave and calculation of RR time series were performed. The RR time series was re-sampled at 5 Hz (32). The respiratory signal was also down sampled to 5 Hz.

Coherence Analysis

The coherence function of two time series signals was defined as their cross correlation, also known as the cross-spectral density normalized by the auto-spectral density of the two original signals (28).

$$C_{xy}(f) = \frac{|P_{xy}(f)|^2}{P_{xx}(f)P_{yy}(f)}$$

where x and y are the two time signals. P_{xx} denotes the auto-spectral density of signal x (respiration signal), P_{yy} denotes the auto-spectral density of signal y (RR time series) and P_{xy} denotes the cross-spectral density. Recently, due to the non-stationary characteristics of bio-signals, time-frequency maps of coherence analysis were developed (16, 21, 40).

In this study, to understand the short-term

Table 1. Demographic data of the subjects

	Y (Yawning)	NY (No yawning)
Sample size	54	30
Age (yrs)	44.2 ± 11.5	41.2 ± 12.6
Gender (M/F)	21/33	13/17
Body weight (kg)	65.4 ± 13.8	63.7 ± 14.6
Body height (cm)	162.9 ± 8.1	164.1 ± 9.5

Values are expressed as mean ± SD.

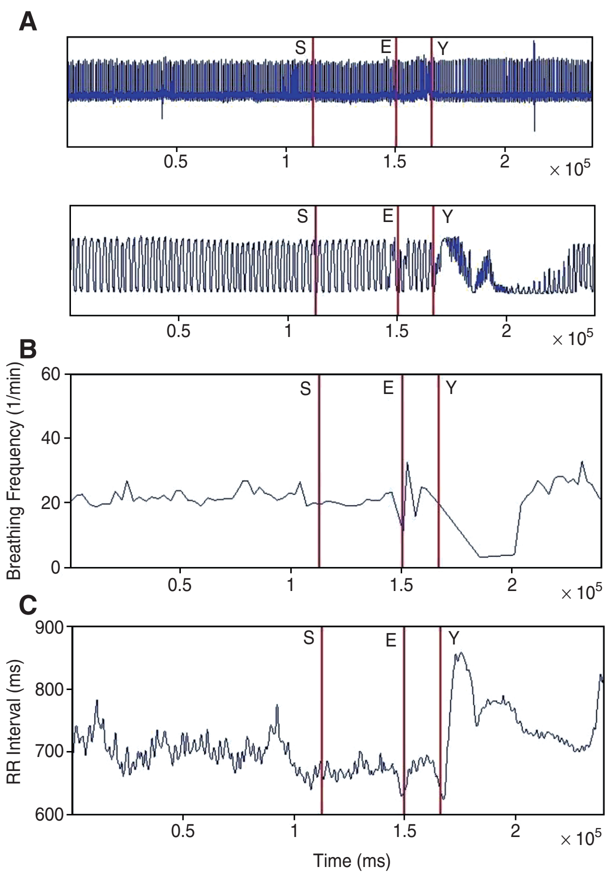

Fig. 1. Instantaneous breathing frequency and instantaneous RR interval in a patient with propofol-induced yawning. (A) Original ECG tracing (upper panel) and respiration signal (lower panel). (B) Instantaneous breathing frequency (1/min) along time axis. (C) Instantaneous RR interval (ms) along time axis. S, start of propofol infusion; E, end of propofol infusion; Y, yawning.

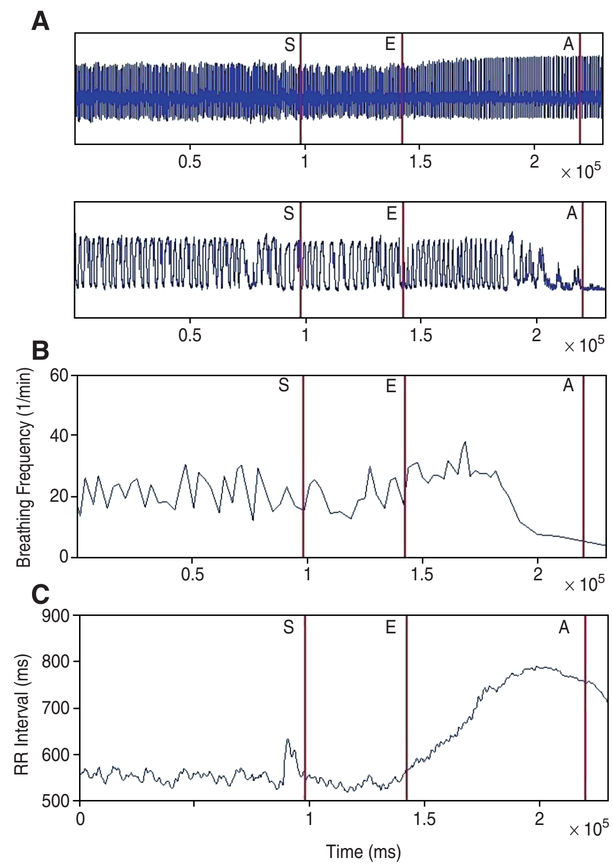

Fig. 2. Instantaneous breathing frequency and instantaneous RR interval in a patient without propofol-induced yawning. (A) Original ECG tracing (upper panel) and respiration signal (lower panel). (B) Instantaneous breathing frequency (1/min) along time axis. (C) Instantaneous RR interval (ms) along time axis. S, start of propofol infusion; E, end of propofol infusion; A, apnea.

dynamics of cardio-pulmonary interaction during anesthesia induction, the time-frequency method (short-time Fourier transform, STFT) (23) was applied to calculate the magnitude-squared coherence (MSC) between RR time series and respiration signal.

The power of each spectrum in MSC was calculated at different frequency bands. The very low (VLF), low (LF) and high (HF) frequency bands were defined as 0 to 0.04 Hz, 0.04 to 0.15 Hz, and 0.15 to 0.50 Hz, respectively. Instantaneous coherence at one instant was calculated as the average of instantaneous MSC within these different frequency bands (*i.e.*, coh-VLF: 0-0.04 Hz; coh-LF: 0.04-0.15 Hz; and coh-HF: 0.15-0.5 Hz, respectively).

The whole time course of propofol-induction was classified as follows: [1] stage 1, baseline; [2] stage 2, from start (S) to end (E) of propofol infusion; and [3] stage 3, from end (E) of propofol infusion to

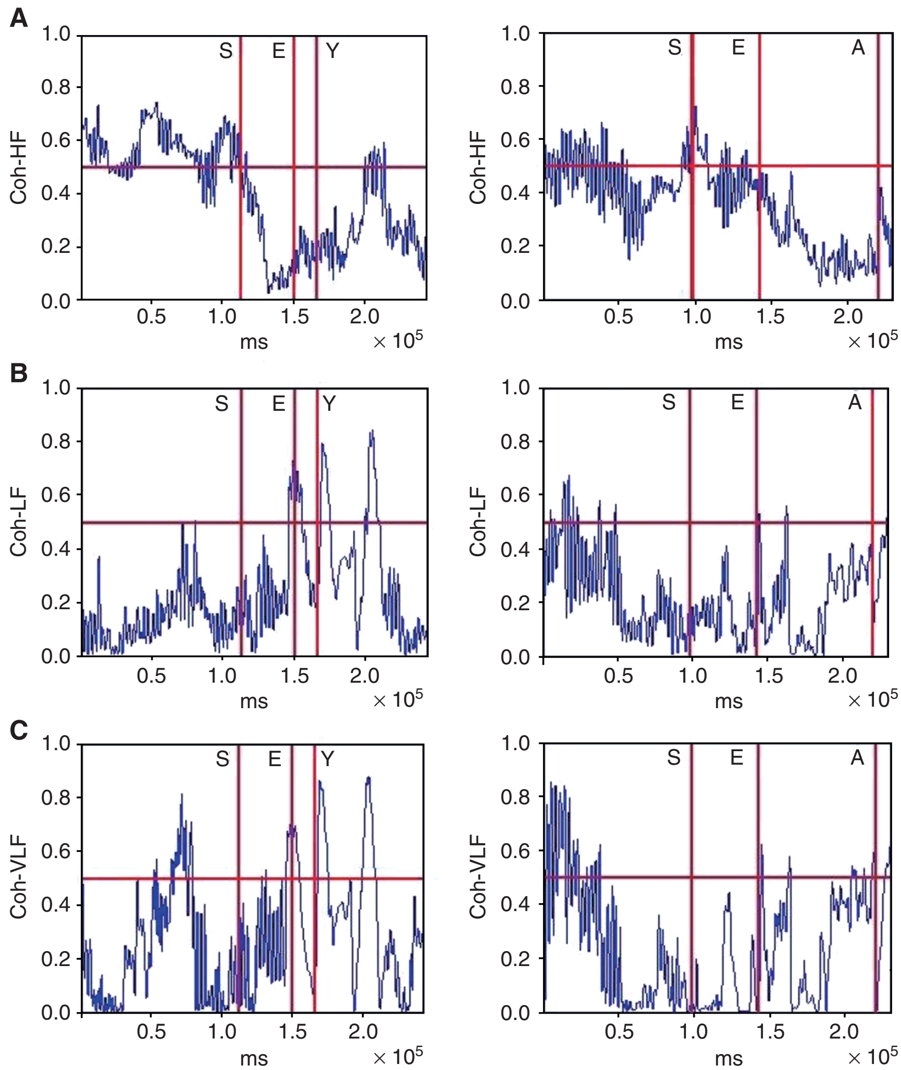

Fig. 3. The time course of instantaneous coherence in the representative individuals during induction of anesthesia. Left panels: A patient with propofol-induced yawning. Right panels: A patient without propofol-induced yawning. (A) Instantaneous coherence at HF band (0.15-0.5 Hz). (B) Instantaneous coherence at LF band (0.04-0.15 Hz). (C) Instantaneous coherence at VLF band (0-0.04 Hz). Horizontal line, coherence value is 0.5; S, start of propofol infusion; E, end of propofol infusion; Y, yawning; A, apnea.

yawning (Y) or apnea (A). The mean of instantaneous coherence for each stage was calculated as the mean coherence (*i.e.*, mean coh-VLF, mean coh-LF, and mean coh-HF, respectively). Moreover, the percentage of time interval for instantaneous coherence greater than 0.5 at different stages was also calculated to investigate the change of linearity between RR time series and respiration signal.

All of the time-frequency analysis of MSC was performed based on the software of MATLAB (MathWorks Inc., MA, USA).

Statistical Analysis

Analysis was carried out using the SPSS 11.0.1 software (SPSS Inc., Chicago, IL, USA). Data were presented as mean ± standard deviation. Mann-Whitney U test was used to compare two continuous independent variables, while Wilcoxon signed-rank test was used for two continuous dependent variables. A P value < 0.05 was considered statistically significant.

Results

Demographic data in age, gender, body height and body weight were comparable between the two groups (Table 1). The original ECG tracing and respiration signal in a representative patient with or without propofol-induced yawning are shown in Figs. 1 and 2. There was instantaneous shortening of RR followed by abrupt lengthening of RR interval, with

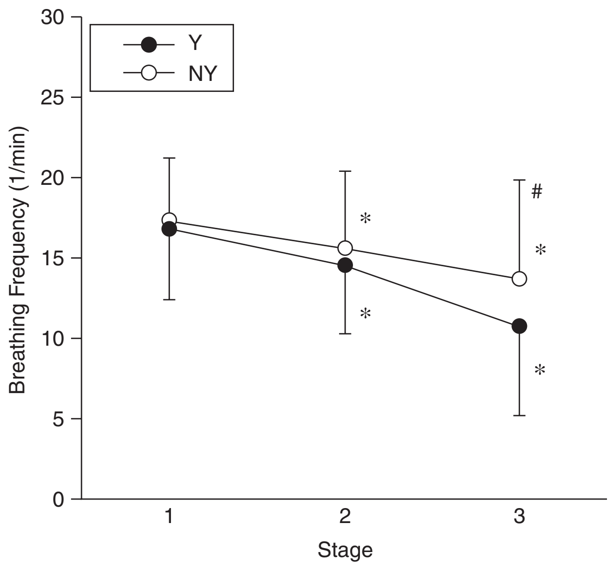

Fig. 4. Changes of mean breathing frequency during induction of anesthesia. Y, yawning group; NY, no yawning group; stage 1, baseline; stage 2, from start to end of propofol infusion; stage 3, from end of propofol infusion to yawning or apnea. *$P < 0.05$ *vs.* stage 1. #$P < 0.05$ yawning *vs.* no yawning.

simultaneously decreased breathing frequency (BF) during the yawning (Fig. 1). In the patient without yawning, slow lengthening of RR, instead of abrupt lengthening, occurred together with slowing down of BF (Fig. 2). The time course of changes of instantaneous coherence during anesthesia induction for these representative individuals is shown in Fig. 3. There was a decrease in coh-HF occurring simultaneously with increases in coh-LF and coh-vLF in the yawning patient (left panels, Fig. 3). Decreased coh-HF occurred without prominent changes in coh-LF and coh-VLF in a patient without yawning during propofol induction (right panels, Fig. 3).

In the yawning group, the mean BF decreased significantly during stages 2 (13.14 ± 4.31 1/min, $P <$ 0.05) and 3 (6.20 ± 3.58 1/min, $P < 0.05$) compared with stage 1 (15.68 ± 4.20 1/min). There was also a significant decrease of BF compared with the no-yawning group in stage 3 (Fig. 4). Furthermore, in the yawning group, the mean HF band coherence decreased significantly during the induction period compared with the pre-induction period (stage 1: 0.38 ± 0.11; stage 2: 0.31 ± 0.10, $P < 0.05$; stage 3: 0.23 ± 0.07, $P < 0.05$) (Fig. 5A).

At the same time, mean LF and VLF band coherences increased significantly (LF, stage 1: 0.22 ± 0.13; stage 3: 0.32 ± 0.10, $P < 0.05$, Fig. 5B. VLF, stage 1: 0.170 ± 0.08; stage 2: 0.21 ± 0.11, $P < 0.05$; stage 3: 0.32 ± 0.11 $P < 0.05$, Fig. 5C). Compared with the no-yawning group, the yawning group showed more significant increases of mean LF and VLF coherences in stage 3 (LF, $P < 0.05$) and in stages 2 and 3 (VLF, $P < 0.05$), respectively. The numerical values of the above parameters are shown in Table 2.

To further investigate changes in linear interactions between the cardio-vascular and respiratory systems, percentage of time interval for coherence > 0.5 was used as the evaluation index. Coherence > 0.5 represents the linear relation between two system behaviors. The percentage of time interval for cardio-respiratory linearity significantly decreased at HF band in the yawning group without inter-group difference during propofol induction (Fig. 6A). At LF band, the yawning group had significantly increased percentage of time interval compared with stage 1 (23 ± 17% *vs.* 8 ± 14%, $P < 0.05$) and with the no-yawning group in stage 3 (23 ± 17% *vs.* 12 ± 15%, $P < 0.05$) (Fig. 6B). There was no significant difference in percentage of time interval of linearity in the no-yawning group compared with the baseline.

At VLF band, there was significantly increased percentage of time interval of linearity in stage 3 compared with stage 1 in both groups. Significant difference of percentage of linearity between inter-groups existed in stage 2 (Y group: 15 ± 18%; NY group: 8 ± 11%, $P < 0.05$) (Fig. 6C). The numerical values of these parameters are shown in Table 3.

Discussion

In this study, the time-frequency coherence method was used to estimate the short-term dynamics of cardio-respiratory interaction during propofol-induced yawning. The results revealed that propofol induction was associated with reduced mean HF coherence and increased mean LF and VLF coherences. Yawning would augment the increase of the latter two coherences. In addition, the dynamics of cardio-respiratory interaction moved towards reducing linearity at the HF band, with simultaneous increase in linearity at LF and VLF bands during propofol-induced yawning.

Previous studies have demonstrated the certain changes of interaction between cardiovascular and respiratory systems in patients undergoing general anesthesia (10, 11). The current study focused on cardio-respiratory interaction during propofol anesthesia induction. The results demonstrated that the trends of change in cardio-respiratory coherence depended on different frequency bands instead of a single band. The phenomenon of increased LF coherence could be partly explained by findings in the previous study, the power spectrum of heart rate variability (HRV) would move towards the low frequency band as BF decreased (27). Besides, our previous study also demonstrated the reduction in the HF power with a simultaneous increase in the LF

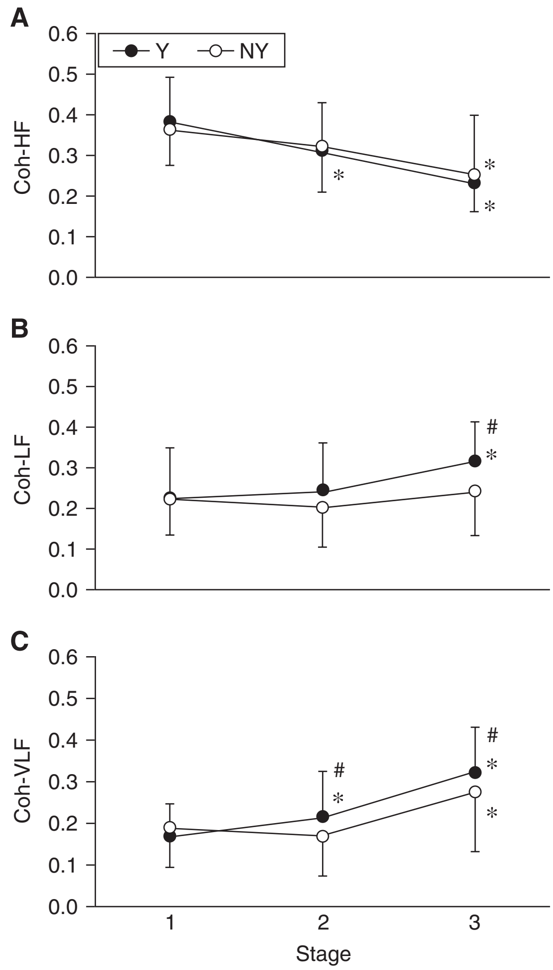

Fig. 5. Changes of mean coherence at different frequency bands during induction of anesthesia. (A) Mean coherence at HF band (0.15-0.5 Hz). (B) Mean coherence at LF band (0.04-0.15 Hz). (C) Mean coherence at VLF band (0-0.04 Hz). Y, yawning group; NY, no yawning group; stage 1, baseline; stage 2, from start to end of propofol infusion; stage 3, from end of propofol infusion to yawning or apnea. *$P < 0.05$ *vs*. stage 1. #$P < 0.05$ yawning *vs.* no yawning.

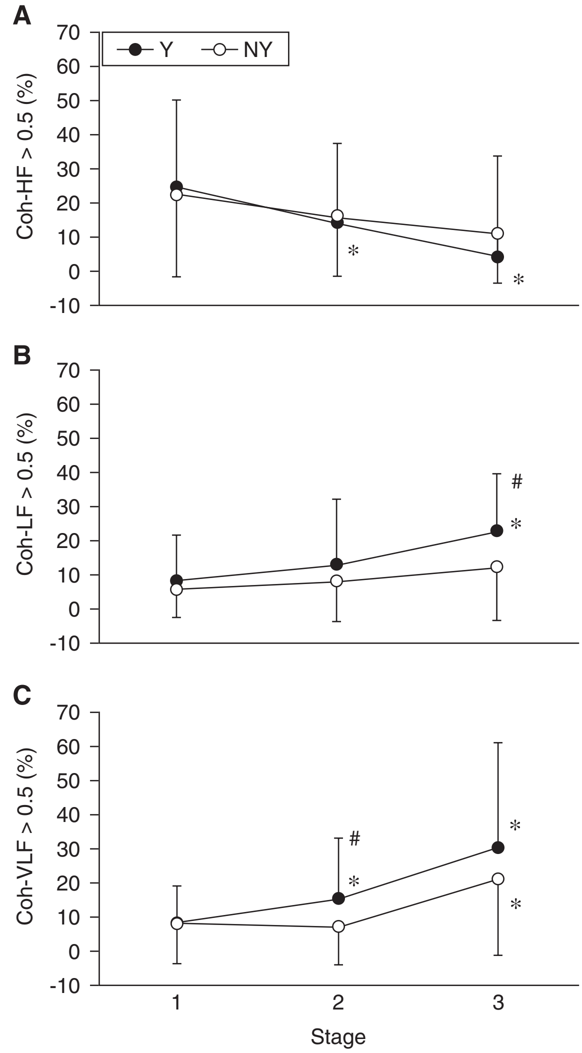

Fig. 6. Changes of mean percentage of time interval for coherence greater than 0.5 at different frequency bands during induction of anesthesia. (A) Mean percentage of time interval at HF band (0.15-0.5 Hz). (B) Mean percentage of time interval at LF band (0.04-0.15 Hz). (C) Mean percentage of time interval at VLF band (0-0.04 Hz). Y, yawning group; NY, no yawning group; stage 1, baseline; stage 2, from start to end of propofol infusion; stage 3, from end of propofol infusion to yawning or apnea. *$P < 0.05$ *vs.* stage 1. #$P < 0.05$ yawning *vs.* no yawning.

power of HRV during propofol-induced yawning (33).

In a normal subject, respiration mainly affects the HF power of HRV. This kind of cardio-respiratory association is referred to as RSA. Previous studies revealed that abnormal respiration influenced the HRV with altered cardio-respiratory coherence (18, 25, 31). Yawning, a kind of respiratory movement, is characterized by deep inspiration and mouth opening followed by expiration with trunk extension. The current study showed that yawning patients had increased cardio-respiratory coherences at LF and VLF bands, instead of HF band, during propofol-induction. These study findings seem to be compatible with the findings of the previous study.

Cardio-respiratory coherence analysis can provide more information on the cardio-respiratory dynamics and ANS functionality under different physiologic and pathologic conditions (16, 39, 40). Higher incidence of reduced cardio-respiratory coherence was noted in patients with vaso-vagal syncope (21). Besides, the relationship between HRV and anesthesia depth during propofol anesthesia has also been studied (14). Hence, cardio-respiratory coherence analysis might be used to quantify the level of anesthesia depth. In our study, significant reduction in HF coherence, both in yawning and no-yawning

Table 2. Mean breathing frequency and mean coherence in different stages

A

	Yawning		
	Stage 1	Stage 2	Stage 3
BF	15.68 ± 4.20	13.14 ± 4.31*	6.20 ± 3.58*#
coh-HF	0.38 ± 0.11	0.31 ± 0.10*	0.23 ± 0.07*
coh-LF	0.22 ± 0.13	0.24 ± 0.12	0.32 ± 0.10*#
coh-VLF	0.17 ± 0.08	0.21 ± 0.11*#	0.32 ± 0.11*#

B

	No Yawning		
	Stage 1	Stage 2	Stage 3
BF	16.45 ± 3.84	14.58 ± 4.85*	10.83 ± 5.88*#
coh-HF	0.36 ± 0.13	0.32 ± 0.11	0.25 ± 0.15*
coh-LF	0.22 ± 0.09	0.20 ± 0.10	0.24 ± 0.11*#
coh-VLF	0.19 ± 0.09	0.17 ± 0.09#	0.27 ± 0.14*#

A, yawning group; B, no-yawning group. Values are expressed as mean ± SD.
*$P < 0.05$ *vs*. stage 1. #$P < 0.05$ yawning *vs*. no-yawning.
Abbreviations: BF: breathing frequency (1/min); coh-HF: mean coherence at high frequency band; coh-LF: mean coherence at low frequency band; coh-VLF: mean coherence at very low frequency band.

Table 3. Mean percentage of time interval for coherence greater than 0.5 in different stages

A

	Yawning		
	Stage 1	Stage 2	Stage 3
coh-HF > 0.5	0.25 ± 0.26	0.14 ± 0.15*	0.04 ± 0.08*
coh-LF > 0.5	0.08 ± 0.14	0.13 ± 0.19	0.23 ± 0.17*#
coh-VLF > 0.5	0.08 ± 0.11	0.15 ± 0.18*#	0.31 ± 0.30*

B

	No Yawning		
	Stage 1	Stage 2	Stage 3
coh-HF > 0.5	0.22 ± 0.28	0.16 ± 0.22	0.11 ± 0.23
coh-LF > 0.5	0.06 ± 0.09	0.08 ± 0.11	0.12 ± 0.15#
coh-VLF > 0.5	0.09 ± 0.11	0.08 ± 0.11#	0.21 ± 0.22*

*$P < 0.05$ *vs*. stage 1. #$P < 0.05$ yawning *vs*. no-yawning.
Abbreviations: coh-HF > 0.5: percentage of time interval for instantaneous coherence > 0.5 at high frequency band; coh-LF > 0.5: percentage of time interval for instantaneous coherence > 0.5 at low frequency band; coh-VLF > 0.5: percentage of time interval for instantaneous coherence > 0.5 at very low frequency band.

groups, may be associated with altered functionality of ANS during anesthesia induction with propofol. Coherence at HF band during anesthesia might be used to evaluate the level of anesthesia depth. Further investigation of the link between HF coherence and anesthesia depth is needed in the future.

Presumptively, most mathematical behaviors of regulatory mechanisms in human physiologic systems have high linearity. Coherence function > 0.5 represents linearity between system behaviors. The current study shows that propofol-induced yawning may be associated with the trend towards more linear at the LF and VLF oscillations between cardio-vascular and respiratory systems. Besides, anesthetic-induced yawning could represent a clinical index of transient arousal-shift during progressive loss of consciousness in Kasuya's study. Arousal from sleep is accompanied by sympathetic activation, which could be represented with increased LF power of HRV (6). So the origin of increased high linearity at LF band oscillation during propofol-induced yawning may come from the central origin (yawning-arousal) in our study. Increased high linearity at LF band oscillation might be used as index of monitoring sympathetic activation and arousal-shift during anesthesia induction.

Many studies have explored the mathematical relation between respiration and heart rhythm. Eckberg's study revealed hysteresis of phase relation between heart rate and respiration (9). Vaschillo *et al*. found that heart beat is highly synchronized with respiration only at a BF of approximately 0.1 Hz (low frequency band), which implies maximum gain with zero phase lag (35). The current study also demonstrated that as BF decreased to 0.1 Hz, the cardio-respiratory coherence also increased. The yawning group had more significantly increased coh-LF than the no-yawning group. The above finding may partly be explained by the fact that the effect of cardio-respiratory synchronization can improve pulmonary gas exchange *via* efficient ventilation/perfusion matching and maintain cerebral perfusion (5, 12, 13, 38).

One of limitations of our study is the lack of baroreflex sensitivity estimation. Baroreflex sensitivity may be an independent factor in the coordination between RR and respiration (8). Secondly, the pre-operation psychologic status of the patients was not been evaluated. Mental status may confound the study results (22). Lastly, further investigation of the effects of respiration parameters on cardio-respiratory dynamics should be considered (30).

This study has successfully developed a time-frequency coherence to disclose the short-term dynamics of cardio-respiratory interaction at different frequency bands during propofol-induced yawning. It demonstrated altered cardio-respiratory dynamics with more significant bi-directional changes at different frequency bands during yawning.

Acknowledgments

The authors thank the National Science Council of Taiwan for its grant support (NSC97-3114-E-241-001).

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