

## Spectral Analysis of Heart Rate Variability during Isoflurane Anesthesia

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The autonomic nervous system is an important neural control system for maintaining cardiovascular stability in humans. Analysis of heart rate variations may provide important clinical information on the influence of anesthesia on the autonomic nervous system and the central nervous system. Therefore, the effects of 1.0, 1.5, and 2.0 minimum alveolar concentrations of isoflurane anesthesia on beat-to-beat heart rate variations were studied in ten patients (ASA Physical Status 1). Spectral analysis was used to determine the intensity of the variations. For each power spectrum, the frequency components were identified as follows: 1) the parasympathetically mediated respiratory component (0.15–0.4 Hz) and 2) both parasympathetically and sympathetically mediated components (0.04–0.15 Hz). The latter was subdivided into the low-frequency component (0.04–0.09 Hz) of vasomotor origin and the mid-frequency component (0.09–0.15 Hz) of baroreceptor origin. Marked reductions in the power of heart rate variations, at all frequencies, were found during isoflurane anesthesia, indicating isoflurane decreased total autonomic nervous system activity. Isoflurane decreased the high-frequency and mid-frequency components in a concentration-dependent manner. The low-frequency component increased transiently at 1.5 minimum alveolar concentrations concomitant with the burst suppression in the electroencephalogram. The ratio of mid-frequency to high-frequency components did not change significantly during isoflurane anesthesia compared with the awake period. These frequency characteristics of heart rate variations during isoflurane anesthesia suggest there are dose-related decreases in autonomic nervous system activity in both the vagus and the cardiac sympathetic nerves. (Key words: Anesthetics, volatile: isoflurane. Monitoring, heart rate variability, measurement technique: power spectral analysis.)

ELECTROCARDIOGRAPHY IS USED to monitor electrical activity of the heart during anesthesia and surgery. However, it does not assess the autonomic nervous system (ANS) activity derived from spontaneous heart rate variations (HRVs). Several controlling systems affect the heart rate and its variation. Koizumi *et al.*<sup>1</sup> showed that, during slow wave fluctuations in heart rate (third order rhythm) and during respiratory sinus arrhythmia, both vagal and sympathetic nerve activity contribute to the

control of beat-to-beat cardiac cycle length and that the relationship of ANS activity to cardiac cycle length was linear within the physiologic range of heart rate in dogs. Therefore, regulation of short-term HRVs is mediated by the ANS. Although these variations are too small to clinically appreciate, their spectral characteristics can be shown easily using spectral analysis of HRV.<sup>2</sup> Three spectral components of HRV have been identified in dogs and humans: a low-frequency component (LF) of vasomotor origin,<sup>3,4</sup> a mid-frequency component (MF) of baroreceptor origin,<sup>5,6</sup> and a high-frequency component (HF) centered at the frequency of respiration.<sup>7,8</sup> Both LF and MF are mediated by the parasympathetic and sympathetic systems, whereas HF is mediated primarily by the parasympathetic system.<sup>3,6,9–11</sup>

The ANS is an important neural control system for maintaining cardiovascular stability in humans. Many anesthetics exert their effect on the cardiovascular system by modulating ANS activity. Power spectral analysis of HRVs may provide important clinical information on the influence of anesthesia on the ANS and the central nervous system, because a cyclic variation in heart rate is mediated via a centrally neural mechanism as well as peripheral receptors such as pressoreceptors and chemoreceptors. Using spectral analysis of HRV, Donchin *et al.*<sup>12</sup> showed that respiratory sinus arrhythmia decreases during isoflurane-nitrous oxide anesthesia (approximately 2.0 minimum alveolar concentrations [MAC]) and increases in the recovery period. They quantified variations in heart rate patterns in only one HF (0.12–0.4 Hz) to estimate vagal tone. Analysis of HRV with anesthetics should estimate sympathetic activity as well as vagal tone, since anesthetics influence both sympathetic and parasympathetic nervous activity. This can be done by quantifying the three components of HRV and examining the dose-response relationship of their frequency-specificity during anesthesia.

The purpose of this study was to compare the effect of 1.0, 1.5 and 2.0 MAC of isoflurane on the HRV in humans, using spectral analysis to separate the HRV into three frequency components.

### Materials and Methods

Ten ASA Physical Status 1 patients, seven women and three men, aged  $40.4 \pm 12.5$  yr (mean  $\pm$  SD; range, 24–57 yr), scheduled for elective lower abdominal gynecologic

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( $n = 5$ ), plastic ( $n = 1$ ), orthopedic ( $n = 1$ ), or upper abdominal ( $n = 3$ ) surgery were studied. The study was approved by the institutional Human Investigation Committee, and written informed consent was obtained from all patients. All patients were free from neurologic, cardiac, and pulmonary diseases, and no patient was being treated with any chronic medication. No premedication was given. After arrival in the operating room, patients were placed supine on a padded operating table and kept warm with the blanket while a peripheral intravenous cannula was inserted under local anesthesia. Ringer's lactate solution was infused throughout the rest of the study to a total dose of 15–20 ml/kg. Oscillometric blood pressure was measured automatically every 5 min (CBM7000, Nippon Colin, Japan). The electrocardiogram (ECG), electroencephalograph (EEG), and transthoracic impedance for respiratory movement were measured continuously (Lifescope 12, Nihon Koden, Japan). Rectal temperature was monitored continuously throughout the rest of the study from immediately after the induction of anesthesia. The ECG lead representing the largest QRS amplitude at preoperative examination was chosen for recording. The EEG was recorded from stainless needle electrodes in the A1-C3 and A2-C4 position on the scalp. Throughout the study, the end-tidal concentrations of carbon dioxide and isoflurane were measured continuously by an infrared spectrometry (Capnomac, Datex, Finland) at the mask or at the distal end of the endotracheal tube and recorded. Anesthesia was induced via a mask with isoflurane in oxygen, and the trachea was intubated after infusion of intravenous vecuronium (0.2 mg/kg). The patients' lungs were mechanically ventilated with a constant volume at a rate of 18 times/min. The ventilatory volume was adjusted to maintain end-tidal  $P_{CO_2}$  at 35–40 mmHg. On-line analysis of RR intervals was made for 10 min before induction of anesthesia (the awake period) after a 15-min period of equilibration at 1, 1.5, and 2.0 MAC of isoflurane concentration in oxygen during mechanical ventilation. The three isoflurane concentrations were administered, for safety, by increasing the concentration of isoflurane step by step. One MAC of isoflurane was assumed to be 1.15 vol%.<sup>13</sup> Arterial blood gases were measured at the end of the study.

On-line analysis of RR intervals was performed using a microcomputer (NEC PC9801). The occurrence of an R wave was detected from the signal of the ECG monitor, and calculated RR intervals were stored on a floppy disc. Off-line spectral analysis was performed on 256-s segments of RR intervals. An instantaneous heart rate time series was constructed as  $1/RR$  interval length and sampled at 4 Hz. The segment chosen for analysis had the fewest sudden jumps or spikes in measured RR intervals due to artifacts such as electrical noise or arm or chest muscle contractions. To accurately describe the frequency char-

acteristics of HRV, the data must conform to the stationary assumption, *i.e.*, mean and variance independent of time. To meet the assumption of weak stationary, a 100-point moving average was stepped through 1024 segments of instantaneous heart rate time series; the template from this procedure was subtracted from the data set and provided residuals that were free of trends and slow sinusoidal changes. This procedure functioned as a high-pass filter with a cutoff frequency of approximately 0.018 Hz. Then power spectra were computed using the fast Fourier transform program. The power spectra were normalized by squared mean heart rate and, therefore, have the units of frequency<sup>-1</sup> (Hz<sup>-1</sup>). The heart rate spectra were quantified by determining the areas of the spectrum in three component widths: LF, 0.04–0.09 Hz; MF, 0.09–0.15 Hz; and HF, 0.15–0.4 Hz. Also, total power was determined as a sum of each component. The MF/HF ratio also was determined. For comparison, the mean and standard deviations of the heart rate and the mean and variance of RR intervals for each data segment were calculated.

To confirm a normal distribution, log power spectra were calculated by taking the common logarithm of the power spectra of each component and total power. Log RR interval variance also was calculated by taking the common logarithm of RR interval variance.

Data are presented as means  $\pm$  SD. Log power, the MF/HF ratio, mean blood pressure, heart rate, RR intervals, RR interval variance, and log RR interval variance were analyzed using repeated measures of analysis of variance followed by Bonferroni modification of the *t* test for multiple comparisons. Differences were considered significant at  $P < 0.05$ .

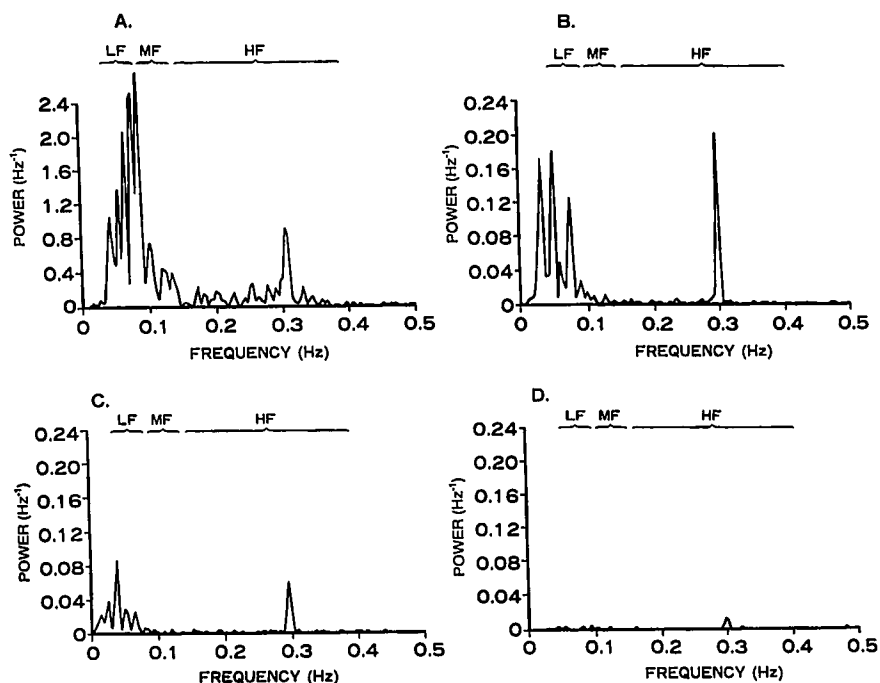
Regression analysis was used to test the effects of age on RR interval variance during the awake period.

## Results

Figure 1 is an example of power spectrum change during isoflurane anesthesia from one patient. The high-frequency component distributed to a wide frequency range during the awake period, but it peaked sharply at about 0.3 Hz during anesthesia due to mechanical ventilation of 18 times/min. Both HF and MF decreased stepwise as the depth of anesthesia increased. Although LF decreased significantly during isoflurane anesthesia compared with those during the awake period, it did not show a linear decrease.

Effects of 1.0, 1.5, and 2.0 MAC of isoflurane on log power of each component and total power are shown in figure 2. Total power and LF decreased significantly during isoflurane anesthesia compared with those during the awake period. Both power spectra showed transient increases at 1.5 MAC. Isoflurane produced dose-dependent decreases in MF and HF. The MF/HF ratio did not

FIG. 1. An example in one patient of the influence of isoflurane anesthesia on power spectrum of heart rate variations. LF = low frequency component (0.04–0.09 Hz); MF = mid frequency component (0.09–0.15 Hz); HF = high frequency component (0.15–0.4 Hz). A: AWAKE. Before the induction of anesthesia, there were three major spectral components, i.e., LF component, MF component, and HF component. B: 1.0 minimum alveolar concentration (MAC). Three components decreased. C: 1.5 MAC. While MF and HF components decreased further, LF component increased. D: 2.0 MAC. Very small LF and HF components were observed, whereas MF component was not observed. (Power spectrum units are  $\text{Hz}^{-1}$  because the units  $\text{beat}^2 \text{min}^{-2} \text{Hz}^{-1}$  are normalized by the square mean of the heart rate.)



change during isoflurane anesthesia compared with the awake value (table 1).

Close examination of individual instantaneous heart rate and EEG revealed that the former increased at the onset of burst in EEG and decreased during the period of suppression (fig. 3). Nine of ten patients showed burst suppression in EEG at 1.5 MAC of isoflurane.

Mean RR interval was significantly less during 2.0 MAC than the awake value (table 1). RR interval variance during isoflurane anesthesia was significantly less than the awake value, and log RR variance decreased in a dose-dependent manner (table 1).

Linear regression analysis showed that the total power of HRV was not correlated with age during the awake period (total power =  $-0.604 \times \text{age} + 73.119$ ;  $n = 10$ ;  $r = 0.19$ ;  $P > 0.05$ ).

Mean blood pressure decreased as end-tidal isoflurane concentration increased (77.3% of the awake value at 1.0 MAC, 64.9% at 1.5 MAC, 58.7% at 2.0 MAC) (table 1). Heart rate did not increase up to 1.5 MAC but increased significantly at 2.0 MAC (101.0% at 1.0, 102.6% at 1.5, and 110.6% at 2.0 MAC) (table 1).

Results of arterial blood gas analysis performed at the end of the study were as follows:  $p\text{H}$ ,  $7.39 \pm 0.04$ ;  $P_{\text{O}_2}$ ,  $573 \pm 62 \text{ mmHg}$ ;  $P_{\text{CO}_2}$ ,  $39 \pm 3.0 \text{ mmHg}$ ; and base excess,  $-1.1 \pm 1.7 \text{ mM/L}$ .

There were no significant changes in mean rectal temperature from the time immediately after induction of anesthesia ( $36.7 \pm 0.3^\circ\text{C}$ ) to the end of the study ( $36.8 \pm 0.3^\circ\text{C}$ ).

Mean spontaneous breathing rate was  $16.4 \pm 2.5$  breaths/min during the awake period.

FIG. 2. Changes in log total power (A), log low frequency component (LOG LF) (0.04–0.09 Hz) (B), log mid frequency component (LOG MF) (0.09–0.15 Hz) (C), and log high frequency component (LOG HF) (0.15–0.4 Hz) (D) in patients exposed to three concentrations of isoflurane. a =  $P < .05$  versus value at AWAKE; b =  $P < .05$  versus value at 1.0 MAC of isoflurane; c =  $P < .05$  versus value at 1.5 MAC of isoflurane.

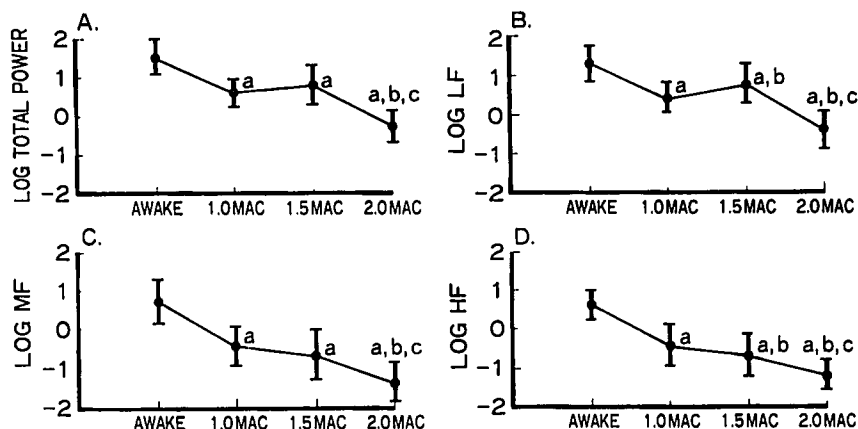


TABLE 1. The Effects of Isoflurane on HR, MBP, RR Variability, and MF/HF Ratio

	Awake	1.0 MAC	1.5 MAC	2.0 MAC
HR (beats/min)	75 ± 12	75 ± 7	76 ± 9	82 ± 12*†‡
MBP (mmHg)	97 ± 15	75 ± 9*	63 ± 7*†	57 ± 8*†‡
RR interval (ms)	818 ± 130	810 ± 74	808 ± 86	742 ± 103*†‡
RR variance (ms <sup>2</sup> )	1,195 ± 580	231 ± 158*	556 ± 897*	35 ± 15*†
Log RR variance (log ms <sup>2</sup> )	3.02 ± .22	2.27 ± .30*	2.45 ± .48*	1.49 ± .22*†‡
MF/HF ratio	1.7 ± 1.6	1.6 ± 1.8	1.6 ± 1.5	0.7 ± 0.3

Mean ± SD.

n = 10.

MAC = minimum alveolar concentration; HR = heart rate; MBP = mean blood pressure; RR = electrocardiographic RR interval; MF/HF ratio = mid frequency (0.09–0.15 Hz) to high-frequency (0.15–0.4 Hz) components ratio.

\* *P* < .05 versus AWAKE.† *P* < .05 versus 1.0 MAC.‡ *P* < .05 versus 1.5 MAC.

### Discussion

This study demonstrated that HRV power spectra in all frequency components were reduced markedly by isoflurane anesthesia. The decrease in HF and MF linearly correlated with increases in isoflurane concentration, whereas LF and total power exhibited a biphasic response downward overall and with a secondary peak at 1.5 MAC, corresponding with the onset of burst suppression on the simultaneously recorded EEG. These results indicate progressive depression of ANS activity with isoflurane anesthesia.

The magnitude of HF provides a quantitative and specific index of vagal cardiac function.<sup>8,10</sup> Donchin *et al.*,<sup>12</sup> examining the effect of isoflurane-nitrous oxide anesthesia on high-frequency parasympathetic spectral components, found a decrease in vagal activity during maintenance of anesthesia, and during the recovery period, vagal tone increased to the conscious level. However, they did not examine the dose response of HF with isoflurane. Our

observation of a dose-related decrease in HF during isoflurane anesthesia indicates that depression of vagal activity was concentration related.

The mid-frequency component of HRV is related to the carotid baroreceptor reflex.<sup>5,6,14</sup> The spectral power of MF probably reflects sympathetic efferent activation;<sup>6,11</sup> our results showed that isoflurane decreased MF in a dose-related manner, implying the dose-related depression of the baroreceptor reflex. Consistent with the current study, Kotrly *et al.*<sup>15</sup> reported that increasing concentrations of isoflurane caused further depression of the baroreflex control of heart rate.

Akselrod *et al.*<sup>3</sup> and Kitney *et al.*<sup>14</sup> suggested that LF also was related to cyclic fluctuations in peripheral vasomotor tone associated with thermoregulation. Reduced power in LF was found during isoflurane anesthesia, implying less fluctuations in the vasomotor tone, and is probably due to 1) reduced sympathetic output from the central nervous system and 2) influence of isoflurane on the resistance of vessels. Previous studies have shown that drug-induced vasodilation and vasoconstriction<sup>3,10</sup> can affect LF fluctuations. One could therefore conclude that decrease of vascular tone by isoflurane affects LF. An additional explanation for reduced power in LF that cannot be ruled out is that it could be due to a decrease in fluctuations in stroke volume and cardiac output. The diminished modulation of stroke volume and cardiac output would occur from the interdependency of several factors, such as negative inotropic effect on myocardium and changes in preload or afterload by isoflurane anesthesia.

The low-frequency component increased transiently during 1.5 MAC of isoflurane associated with a burst suppression in EEG. Yli-Hankala and Jantti<sup>16</sup> reported heart rate and EEG changes during isoflurane anesthesia and suggested that the heart rate changes were due to central inhibition mediated by the vagus nerve during EEG suppression.

Akselrod *et al.*<sup>10</sup> and Pomeranz *et al.*<sup>9</sup> studied the principal branches of autonomic cardiovascular control and their frequency-specific contribution to the HRV. They

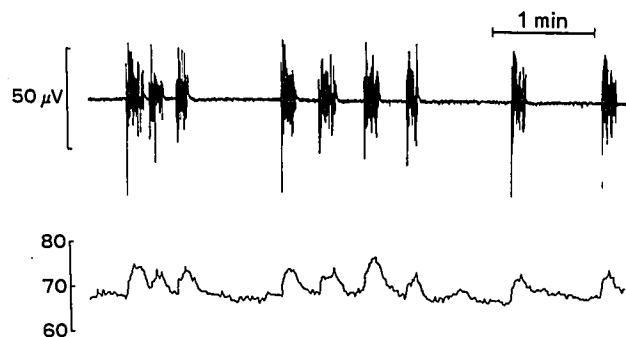


FIG. 3. Typical tracings showing electroencephalogram (EEG) at 1.5 minimum alveolar concentration (MAC) of isoflurane and the instantaneous heart rate (IHR) ( $\text{min}^{-1}$ ). Heart rate fluctuates synchronously with EEG burst-suppression. (Note the rises in IHR coinciding with bursts and the decreases in IHR coinciding with suppression). The small fluctuation was caused by the mechanical ventilation (18 times/min). The IHR is interpolated at 0.25-s intervals from the electrocardiographic RR intervals as described in the Methods section of the text.

concluded that in humans, LF and MF of HRV are both sympathetically and parasympathetically mediated, whereas HF is primarily mediated by parasympathetic nervous system activity in the supine position. Pagani *et al.*<sup>11</sup> reported that the LF/HF ratio provides an index of sympathovagal interaction. In our previous study, the LF/HF ratio provided a convenient index of such interaction during anesthesia.<sup>8</sup> In this study we calculated the MF/HF ratio to examine the balance of the autonomic nervous system, because LF apparently does not contribute to the HRV, as seen during 1.5 MAC of isoflurane. As previously reported, while isoflurane appears to directly depress vagal and sympathetic nervous activity in a dose-related manner,<sup>17</sup> the direct depression is compensated for by reflex increases in sympathetic tone due to the hypotension accompanying the anesthesia.<sup>18</sup> Therefore, we could predict an increase in the MF/HF ratio during isoflurane anesthesia. However, the results of this study showed that the MF/HF ratio did not change significantly during isoflurane anesthesia, while all frequency components decreased. Several possible other factors as well as anesthesia may contribute to the overall attenuation of autonomic nervous activity indicated by the individual component of HRV. First, patients' apprehension was greater than usual since no premedication was given. The decrease in sympathetic component effectively will be larger than the parasympathetic component during isoflurane anesthesia because of the high sympathetic tone of starting points, as indicated by a high MF/HF ratio in the awake period. Second, we did not investigate the effects of mechanical ventilation on HF. It might be influenced by marked changes in the respiratory waveform,<sup>19</sup> either through the stimulation of lung receptors<sup>20</sup> or through fluctuations induced by arterial pressures.<sup>21,22</sup> In either case, vagal tone is enhanced, resulting in HF increase of HRV during controlled ventilation. Therefore, mechanical ventilation alone can lead to an increase in HF but also to a reduction in LF, as shown previously by Pagani *et al.*<sup>11</sup>

Vecuronium was administered to all patients in this study. Although vecuronium is known to have few grossly observable autonomic effects,<sup>23</sup> its influence on HRV is unknown. The potential effects of vecuronium on HRV need to be considered as well. However, isoflurane decreased HRV in the patient of the current study and depression was dose related. Isoflurane seems to have played a more important role in modifying HRV than vecuronium in this study.

To date, the depth of anesthesia is determined only by such clinical parameters as assessment of body movement,

changes in blood pressure, pulse rate, frequency of respiration, pupil size, and diaphoresis. None of these are reliable, because all may be blocked or attenuated by nonanesthetic drugs, *e.g.*, muscle relaxants, calcium-blockers, beta-blockers, and anticholinergics. Autonomic nervous system activity assessed by the frequency of spontaneous lower esophageal contractions is one alternative.<sup>24</sup> Heart rate spectral analysis is a powerful noninvasive tool for quantifying ANS activity.<sup>9</sup> Komatsu *et al.*<sup>8</sup> investigated the changes in HRV during high-dose fentanyl and diazepam anesthesia and noted a diminution of both vagal and sympathetic components with a shift toward sympathetic suppression. They further suggested that changes in HRV might correlate to a certain extent with depth of anesthesia with fentanyl and diazepam. In this study we also found consistent frequency-specific HRV decreases with isoflurane MAC. The changes in HRV could not be detected by visual inspection of ECG. By means of spectral analysis, the pattern of HRV was well characterized by oscillations at specific frequencies, even in patients whose amplitude decreased significantly during isoflurane anesthesia in this study.

Despite the anesthesiologists' enthusiasm for monitoring physiologic functions during anesthesia, there has been little success in arriving at an objective method for assessing ANS and adequacy of anesthesia. Spectral analysis of HRV may be such a technique.

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