Linear and nonlinear analysis of heart rate variability during propofol anesthesia for short-duration procedures in children

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Objective: **To determine whether heart rate variability metrics provide an accurate method of monitoring depth of anesthesia, assessing the response to painful stimuli, and assessing neuroautonomic regulation of cardiac activity in children receiving propofol anesthesia for short-duration procedures.**

Design: **Prospective, case series.**

Setting: **Sixteen-bed pediatric intensive care unit, oncology unit, and endoscopy suite in a tertiary care children's hospital and ophthalmology examination rooms in an associated eye institute.**

Patients: **Thirty-three pediatric patients undergoing propofol anesthesia for short procedures.**

Interventions: **None.**

Measurements and Main Results: **Heart rate variability metrics studied included mean, SD, low- and high-frequency power, detrended fluctuation analysis (represented by correlation coefficient, α), and approximate entropy. Compared with the initial anesthetized state, we found increased heart rate SD (3.17 ± 1.31 vs. 7.05 ± 0.26 bpm, $p < .0001$), heart rate low-frequency power (3.69 ± 0.36 vs. 4.48 ± 0.41 bpm^2/Hz, $p < .0001$), heart rate low-/high-frequency ratio (1.47 ± 0.26 vs. 1.26 ± 0.24, $p = .001$), and heart rate α (1.12 ± 0.24 vs. 1.35 ± 0.21, $p < .0001$) during painful procedure. Mean heart rate (105.8 ± 13.4 vs. 101.5 ± 12.4 bpm, $p = .005$) and heart rate approximate entropy decreased with painful procedure (0.75 ± 0.19 vs. 0.53 + 0.16, $p < .001$), whereas there was no significant change in heart rate high-frequency power (3.04 ± 0.63 vs. 3.16 ± 0.71 bpm^2/Hz, $p = .26$).**

Conclusions: **We conclude that power spectral analysis of heart rate variability may be an accurate and clinically useful measure of depth of propofol anesthesia. We speculate that high-frequency heart rate power during propofol anesthesia correlates with depth of anesthesia, whereas low-frequency power allows for assessment of the patient's sympathetic response to pain. (Pediatr Crit Care Med 2003; 4:308–314)**

Administration of anesthesia for painful procedures occurs commonly in the pediatric intensive care unit. Many pediatric intensive care unit physicians also provide sedation services throughout the hospital for common pediatric procedures such as bone marrow or solid organ biopsy, vascular access, and cardioversion. However, determining the optimal anesthetic dosage for deep sedation during painful pediatric procedures is an inexact science that not infrequently results in under- or overdosage of analgesic or sedation medications. A physiologic-based method for measuring depth of anesthesia would be clinically useful in determining anesthetic dosage, optimizing analgesia and sedation effect, and minimizing adverse side effects.

Studies using both experimental models and humans have investigated the sensitivity and specificity of monitoring heart rate variability (HRV) to assess depth of anesthesia during administration of a variety of anesthetic agents (1–9). Measurements, or metrics, of HRV allow for noninvasive quantitative assessment of neuroautonomic cardiovascular regulatory mechanisms (10, 11). Not surprisingly, given the known cardiorespiratory depressant activity of most anesthetic agents (12, 13), a consistent finding has been loss of overall HRV. The main drawback to these findings, in terms of potential clinical applicability, is the relatively nonspecific nature of the decrease in HRV and insensitivity to the degree or depth of anesthesia (14, 15), particularly during deep sedation or general anesthesia when neuroautonomic cardiac efferent and afferent pathways are significantly inhibited.

Even so, HRV metrics may provide an independent evaluation of the integrity of the autonomic nervous system and cardiovascular control mechanisms during anesthesia (14) that cannot be detected from monitoring mean heart rate or blood pressure, thus alerting the anesthesiologist to "hidden" changes in neuroautonomic control of heart rate or blood pressure that may precede a significant clinical event. Of the various HRV metrics, respiration-related HRV (e.g., respiratory sinus arrhythmia or high-frequency heart rate power), which reflects parasympathetic nervous system activity during spontaneous ventilation while awake, has been reported to have the most potential as a clinical monitor of depth of anesthesia (1, 16, 17). A possible drawback to this method is the question of its physiologic meaning during positive pressure ventilation (18) that is often used during general anesthesia.

In contrast to general anesthesia, children undergoing deep sedation with propofol anesthesia for painful procedures breathe spontaneously and may react to painful stimuli, thus allowing an

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opportunity to reassess HRV metrics under these conditions. We hypothesized that HRV metrics may provide an accurate quantitative method of monitoring depth of anesthesia, assessment of the response to painful stimuli, and assessment of neuroautonomic regulation of cardiac activity. We studied a combination of linear and nonlinear HRV metrics including mean heart rate and heart rate SD (linear time domain metrics), power spectral density (linear frequency domain metric), and approximate entropy and detrended fluctuation analysis (nonlinear metrics) during propofol anesthesia for short-duration, painful procedures in children.

METHODS

Informed Consent. Informed consent was obtained before each study from the patient's parent or guardian. This study was reviewed and approved by the Institutional Review Board at Oregon Health Sciences University.

General Patient Management. Patients underwent the following procedures: lumbar puncture (n = 19), bone marrow biopsy (n = 4), lumbar puncture and bone marrow biopsy (n = 1), ophthalmologic exam (n = 6), percutaneous renal biopsy (n = 1), long arm intravenous catheter placement (n = 1), and intracranial pressure monitor insertion (n = 1). Data were collected before induction and throughout the procedure until the patient was awake. Procedure length ranged from 9 to 53 mins (mean = 29 ± 11 mins [SD]). The physiologic "states" were assigned solely on the temporal relationship to each procedure as follows: Awake 1 (preanesthesia), Anesthesia 1, Painful Procedure, Anesthesia 2, Emergence 1, Emergence 2, and Awake 2 (postanesthesia). Lead II or III electrocardiogram and impedance respiration analog waveforms were recorded continuously throughout the study.

Induction and Maintenance of Propofol Anesthesia. Anesthesia induction was accomplished with propofol 2–3 mg/kg via indwelling peripheral or central venous catheters and titrated to sleep while maintaining spontaneous respiration. Lidocaine up to 0.5 mg/kg was added if propofol was given through a peripheral vein. Maintenance anesthesia was achieved with bolus doses of propofol in 0.5 mg/kg amounts until the procedure was completed. Total propofol dose ranged from 0.5 to 10 mg/kg (mean = 5.3 ± 2.0 mg/kg [SD]). The range from time of induction to the last dose of propofol was 1–24 mins (mean = 7 ± 6 mins [SD]). Analgesia was accomplished by a topical anesthetic placed on or injected into the skin before the procedure.

Physiologic Signal Acquisition. Analog electrocardiogram, respiration, and blood pressure signals were recorded by using Hewlett Packard monitors 78213C and 78212D (Hewlett Packard, Palo Alto, CA) with a low-pass filter at 100 Hz. Data were collected by using a Zeos Pantera 90 MHz Pentium PC in conjunction with a PC-LMP-16 data acquisition card. Sampling rate for data collection was done at 1 kHz. Sampling at 1 kHz was determined to be sufficient to meet Nyquist sampling criteria. Signals were analyzed offline on the Zeos PC.

Time Series Analysis: Heart Rate Variability Derivation. HRView software (Boston Medical Technologies, Boston, MA) was used for digital signal (electrocardiogram and respiration) acquisition and analysis of HRV and for power spectral analysis. Electrocardiogram and respiratory signals were digitally recorded for 300–600 secs during each procedure. From these 300- to 600-sec data sets, a 128-sec time series that was artifact-free was chosen for analysis by one author (SL). Time series data were linearly detrended and analyzed by using a modification of the methodology described by Saul (19).

Linear Metrics: Time Domain Analysis. Mean and SD heart rate were determined with HRView software.

Linear Metrics: Frequency Domain Analysis. Calculation of heart rate power spectra was done with HRView software. Total power (area underneath the curve) from 0.04 to 0.15 Hz was used to quantify low-frequency (LF) heart rate oscillations that are under joint sympathetic and parasympathetic control at rest but during periods of stress are predominantly under sympathetic regulation (10, 11, 19–22). Total power (area underneath the curve) from 0.15 to 1.00 Hz was used to quantify high-frequency (HF) heart rate oscillations that are under parasympathetic regulation related to respiratory activity, that is, the respiratory sinus arrhythmia (10, 11, 19–22). The LF/HF ratio has been used as a measure of sympathovagal balance (11).

Nonlinear Metrics: Detrended Fluctuation Analysis and Approximate Entropy. Detrended fluctuation analysis, a method for analysis of random walk-like (power-law) signals, permits detection of long-range correlations embedded in seemingly nonstationary time series and avoids detection of artifacts due to nonstationarity (23, 24). This method addresses the problem of nonstationarity and has been validated on control time series with the superposition of a nonstationary external trend. Long-range correlations are represented by α. An $\alpha = 0.5$ indicates random white noise and no long-range correlations. An α that is >0.5 and <1 indicates persistent long-range power-law correlations in HR (24). An $\alpha = 1$ indicates long-range power-law correlations of the 1/f type, a fractal relationship (24). An $\alpha = 1.5$ indicates Brownian noise (i.e., the integration of white noise or a random walk) and trivial and insignificant long-range correlations. In healthy states, α is close to 1.0. The algorithm for detrended fluctuation analysis is freely available at Physionet (http://www.physionet.org/).

Approximate entropy (ApEn) describes pattern recurrence (or regularity) in data sets. The statistic is defined as the (log) likelihood with which similar extremely short segments of data, typically two consecutive data points, remain similar when the next (e.g., third) datum is appended to the segment. This can be thought of as a measure of predictability; the less predictable, the higher the entropy. Unlike linear domain metrics, regularity statistics do not describe the data elements themselves. Rather, they provide for objective discrimination with respect to regularity between similar data sets, encapsulating specific marginal probabilities about the recurrence of short sequences. Compared with time and frequency domain metrics, these regularity statistics are especially well suited to analysis of clinical data series for three reasons. First, ApEn can be calculated reliably from data series as short as 50 elements and is especially reliable when calculated from series of 1000–1500 elements, a size for which stationarity assumptions regarding biological data sets are reasonable. Second, ApEn is highly robust to the noise that accumulates in signal streams as a result of ordinary clinical care. Third, the interpretation of ApEn is independent of the models proposed to explain the interactions among biological systems under investigation (25–27).

ApEn was calculated by using the algorithm developed by Kaplan et al. (25) implemented in MATLAB (MathWorks, Natick, MA). The software is available at http://www.macalester.edu/~kaplan. The "filter factor" used was set to be 0.2 times the SD of the segment under analysis. This filter factor provides the operational definition of "dynamically similar."

Statistical Analysis. Paired Student's *t*-test was used to compare Awake, Anesthesia, and Emergence states with a Bonferroni adjustment for multiple pairwise comparisons. The paired Student's *t*-test also was used to compare Anesthetized and Pain states. Changes over the entire study period were analyzed by using multivariate analysis of variance. The Statistical Package for the Social Sciences for Windows (SPSS, Chicago, IL) was the program used for analysis. Data are presented as mean ± SD. Significance was defined as $p < .05$.

RESULTS

We studied 33 pediatric patients undergoing propofol anesthesia. There were 15 males and 18 females. The mean age was 5.3 ± 2.5 yrs [SD]. Patients were studied in the clinical areas appropriate for their procedures including the pediatric intensive care unit, the hematology-oncology unit, and examination/procedure rooms of Doernbecher Children's Hospital and the Casey Eye Institute.

Figure 1 shows changes in time series analysis measurements of heart rate and

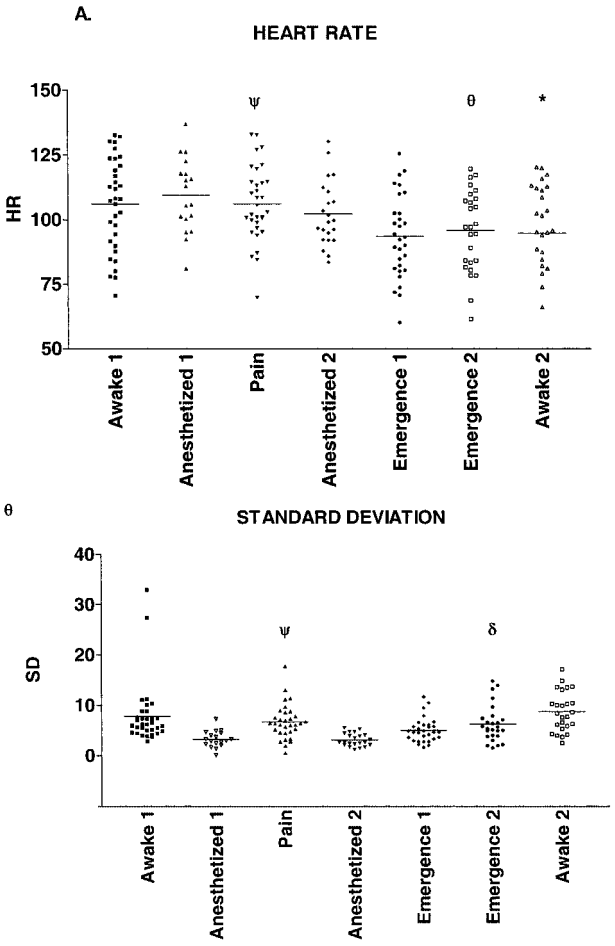

Figure 1. Changes in time series analysis measurements of heart rate (*HR*) variability during propofol anesthesia. *A*, time domain plots of mean heart rate and SD of heart rate. *B*, frequency domain plots of power spectral values in heart rate low-frequency power (*HRLFP*; 0.04–0.15 Hz), heart rate high-frequency power (*HRHFP*; 0.15–1.0 Hz), and low-/high-frequency ratio (*L/H*). *C*, nonlinear plots of approximate entropy (*ApEn*) and detrended fluctuation analysis (*DFA*) showing the scaling exponent, α. Ψ$p < .05$ compared with Anesthesia 1 state; δ$p < .05$ compared with Emergence 1 state; θ$p < .05$ compared with Awake 1 state (multivariate analysis of variance); *$p < .05$ compared with Awake 1 state.

heart rate variability during propofol anesthesia.

Comparisons Between Like States. We found no significant differences between Awake 1 and Awake 2 states for heart rate HF power, heart rate LF power, or heart rate SD. There were decreases in mean heart rate (105.6 ± 17.9 vs. 94.5 ± 23.8 bpm, $p = .04$), heart rate LF/HF ratio (1.18 ± 0.14 vs. 1.11 ± 0.11, $p = .13$), heart rate ApEn (0.77 ± 0.22 vs. 0.63 ± 0.18, $p = .02$), and heart rate α (1.13 ± 0.18 vs. 1.05 ± 0.21, $p = .05$) between Awake 1 and Awake 2 states.

We found no significant differences between Anesthesia 1 and Anesthesia 2 states for mean heart rate, heart rate SD, heart rate HF power, heart rate LF power, heart rate LF/HF ratio, heart rate α, or heart rate ApEn.

We found no significant differences between Emergence 1 and Emergence 2 states for mean heart rate, heart rate LF/HF ratio, heart rate α, or heart rate ApEn. There were increases in heart rate SD (4.62 ± 2.04 vs. 6.50 ± 3.61 bpm, $p = .002$), heart rate HF power (3.55 ± 0.74 vs. 3.80 ± 0.69 bpm^2/Hz, $p = .002$), and heart rate LF power (4.01 ± 0.30 vs. 4.25 ± 0.53 bpm^2/Hz, $p = .008$) between Emergence 1 and Emergence 2 states.

Comparisons to Awake 1 State. Mean HR trended down during the study period and was significantly decreased during Emergence 2. Heart rate SD diminished with Anesthesia 1, increased near Awake 1 levels with Painful Procedure, returned to low levels with Anesthesia 2, and gradually increased back toward Awake levels. This pattern also was observed with heart rate LF power. The inverse pattern was seen with heart rate ApEn. Heart rate HF power remained low following Anesthesia, was unaffected by Painful Procedure, and then increased back to Awake 1 levels during Emergence and Awake 2 states. Heart rate α and heart rate LF/HF ratio showed increases in levels during Anesthesia, a further increase with Painful Procedure, and then return toward Awake 1 levels with Emergence and Awake 2 states.

Comparisons Between Anesthetized and Pain States. Compared with Anesthetized 1 state, we found increased heart rate SD (3.17 ± 1.31 vs. 7.05 ± 0.26 bpm, $p < .0001$), heart rate LF power (3.69 ± 0.36 vs. 4.48 ± 0.41 bpm^2/Hz, $p < .0001$), heart rate LF/HF ratio (1.26 ± 0.24 vs. 1.47 ± 0.26, bpm, $p = .001$), and heart rate α (1.12 ± 0.24 vs. 1.35 ± 0.21, $p < .0001$) during Pain. Mean heart rate (105.8 ± 13.4 vs. 101.5 ± 12.4 bpm, $p = .005$) and heart rate ApEn decreased with Painful Procedure (0.75 ± 0.19 vs. 0.53 ± 0.16, $p < .001$), whereas there was no significant change in heart rate HF power (3.04 ± 0.63 vs. 3.16 ± 0.71 bpm^2/Hz, $p = .26$).

DISCUSSION

It has long been recognized that beat-to-beat variations exist in hemodynamic signals such as heart rate. A variety of metrics, including linear and nonlinear analysis techniques, have been applied in quantifying the role of autonomic regulation of cardiovascular function during various physiologic and pathophysiologic states (10, 11, 19, 21, 28). One potential application of this methodology is in monitoring the effect of anesthetic agents on sympathetic and parasympathetic nervous regulation of heart rate (13). Current clinically based methods of assessing depth of anesthesia, such as movement, pupillary light reflex, diaphoresis, increased blood pressure, pulse, and frequency of respiration, are problematic because they all may be attenuated or absent by neuromuscular blocking drugs or opioid analgesics (7, 29). The Ramsay Scale is the most widely used subjective scale for assessing anesthetic effect; however, this scale is inconsistent (30–32). In addition, clinically based scores such as the Ramsay Scale or the Aldrete Score (33) are not designed to detect subtle physiologic changes that occur during deep sedation or upon emergence. We routinely prospectively recorded the

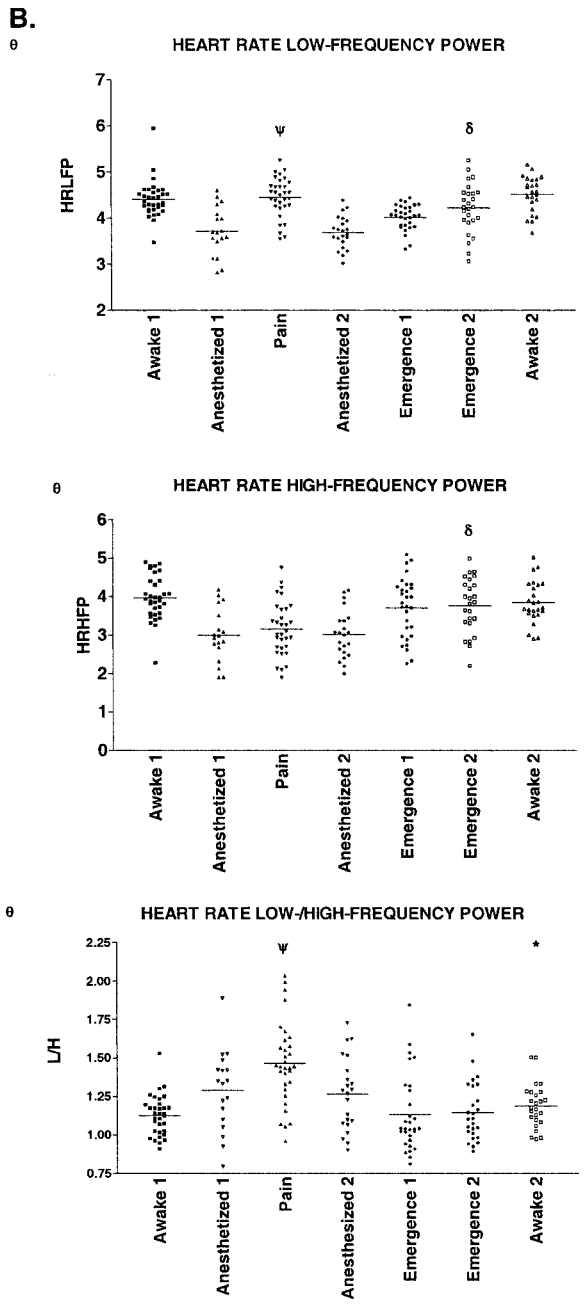

Figure 1. (Continued)

Ramsay Scale score for the first ten patients in our study, but the score always ranged from 5 to 6 during deep sedation (i.e., sluggish to no response to stimulation), thus providing no information about underlying cardiovascular changes. A reliable, physiologically based scale that could be incorporated into real-time bedside monitoring would be of great clinical utility in determining proper dosage of anesthetic agents required to provide effective anesthesia while minimizing the risk of side effects.

Several investigators have evaluated the effects of propofol anesthesia on the autonomic nervous system, as measured by changes in HRV and blood pressure variability (9, 29, 34–40). Together, the main findings were that HRV, especially HF power, decreased during anesthesia states and increased with recovery. Our study uses both linear and nonlinear HRV metrics to investigate the effects of propofol anesthesia on autonomic cardiac regulation in children during all physiologic states from awake through emergence from deep anesthesia. This assessment has significant clinical relevance as propofol, because of its pharmacokinetic characteristics which allow a rapid recovery with early return of psychomotor function (41), is well suited for use with children undergoing brief procedures, such as bone marrow biopsy, lumbar puncture, or ophthalmologic examination.

In our study, the changes in HRV, as measured by SD, LF power, HF power, and heart rate α, as well as the changes in heart rate complexity, as measured by heart rate ApEn, are all consistent with a decrease in autonomic modulation of heart rate following administration of anesthesia. Our findings are in agreement with previous reports (34, 38–40). We found that these measures return toward baseline values (e.g., Awake 1) during emergence from anesthesia. Thus, these measures may have clinical use in monitoring depth of anesthesia. By contrast, mean heart rate did not return to baseline values with emergence. We conclude that the use of linear analysis techniques in time and frequency domain, as well as nonlinear analysis methods, may be of use in revealing information contained in commonly measured physiologic signals that is not apparent with the variables generally monitored at bedside, such as mean heart rate averaged over 3- to 5-sec intervals.

Frequency domain metrics, specifically power spectral analysis, provide additional information compared with time domain metrics including a means to assess the relative degrees of sympathetic and parasympathetic neuroautonomic modulation of cardiovascular activity. Indeed, the principal finding in this study was that the heart rate HF power value (an indicator of parasympathetic modulation) did not change significantly during painful stimuli, whereas other indicators of HRV or complexity, including heart rate SD, α, and LF power (an indicator of sympathetic modulation), did change significantly. The other measures returned back to Anesthesia 1 levels following the cessation of painful stimuli. Just as importantly, both LF and HF power differentiated between emergence states, whereas others, except heart rate SD, did not. Thus, it appears that heart rate LF power may indicate the patient's sympathetic response to pain, whereas HF power is indicative of the effects of the anesthetic agent on parasympathetic regulation of heart rate. Lending further support for this conclusion is a study by

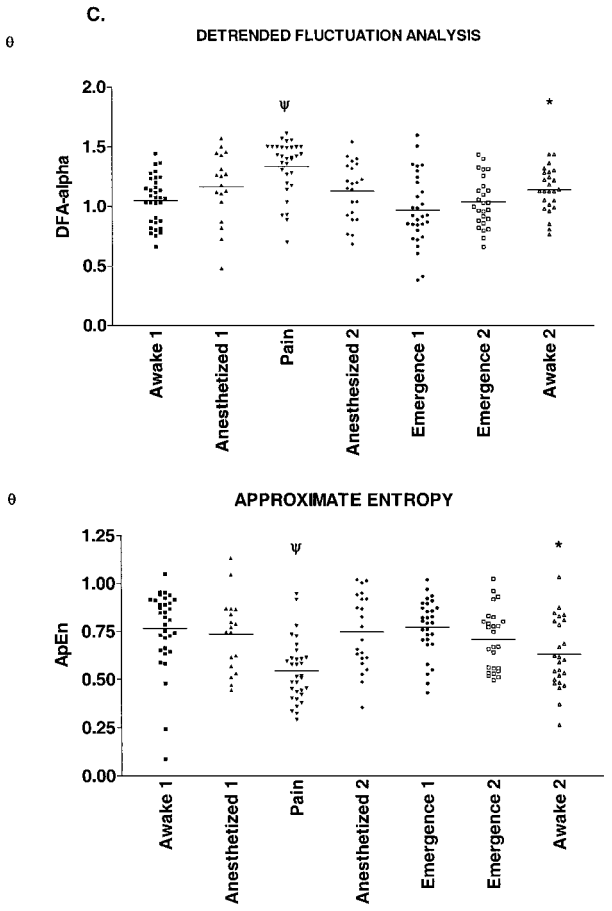

Figure 1. (Continued)

Wang et al. (36), who concluded that LF mean arterial pressure changes may reflect a sympathetic response to noxious stimuli in adult patients undergoing propofol and vecuronium general anesthesia, and Sato et al. (40), who reported increased sympathetic cardiac activity with insufflated pneumoperitoneum. We suggest that HRV metrics may prove to be a clinically useful physiologic monitor of propofol anesthesia that could be used to determine both depth of anesthesia (HF power) while ensuring a sustained sympathetic response to pain (LF power and ApEn) and assess emergence from anesthesia. This may be a unique situation compared with general anesthesia in that, as would be expected, there is no measurable change in cardiovascular regulation.

The calculated LF/HF ratio may reflect sympathovagal balance (10, 11). It is known that changes in sympathovagal balance, either increased sympathetic or decreased parasympathetic activity, may increase the susceptibility of the adult heart to ventricular fibrillation (42, 43). The use of anesthetic agents that preserve cardiac vagal tone coupled with an accurate method to assess cardiac sympathetic activity may reduce the risks of cardiac dysrhythmias and cardiovascular compromise (44) during surgery, particularly in children with congenital heart disease. Further study is required to assess the sensitivity and specificity of frequency domain metrics to assess physiologic status during anesthesia.

Nonlinear analysis techniques, such as ApEn and detrended fluctuation analysis, although less well studied than the time and frequency domain statistics, may offer some advantages over more traditional methods (45). ApEn is relatively robust to noise and error in subject data (25), and because it is scale-invariant it is well-suited for intra- and interpatient comparisons (46). It has been suggested that ApEn is a sensitive marker of changes in neuroautonomic modulation during disease states, and changes in ApEn were found to occur earlier than other measures of HRV in an experimental model of human endotoxemia (46). Our findings were similar to those of Landry et al. (8), in that ApEn decreased with administration of anesthesia, indicating a decrease in heart rate complexity or an increase in heart rate regularity. ApEn and heart rate α both changed significantly following painful stimulus. We suggest that ApEn, heart rate α, or some other nonlinear metric may provide a simpler means to monitor physiologic state during anesthesia, including the prediction of impending cardiovascular collapse or arrhythmias, compared with frequency domain metrics.

Limitations of the Study. Both respiratory rate and tidal volume may influence the amplitude of respiratory sinus arrhythmia and thus HF heart rate power (16, 47, 48). Neither respiratory rate nor tidal volume was controlled in this study, so it is possible that changes in heart rate HF power or sympathovagal balance (LF/HF ratio) could occur, at least in part, from changes in respiration (1). If the respiratory rate was not significantly altered between awake and anesthetic states, such as in this study, it is safe to assume that changes in respiratory rate did not affect our results. However, changes in tidal volume could have influenced the results. The amplitude of the respiratory sinus arrhythmia has been demonstrated to change in concert with tidal volume (48). Other investigators have noted an inverse relationship between respiratory sinus arrhythmia and tidal volume under conditions in which a decrease in tidal volume resulted in an increase in end-expired P_{CO_2} and hypoxia (49). Thus, it appears that an anesthesia-induced reduction in tidal volume, if accompanied by an increase in arterial P_{CO_2} and an increase in end-expired P_{CO_2}, would be expected to cause increases in parasympathetic modulation rather than the decreases seen in the our study (1).

It is important to consider that other compounding factors exist that may alter the degree of HRV beyond those due to the administration of anesthesia. Storella et al. (44) evaluated characteristics of HRV during cardiac surgery. They found that measures of HRV decreased with anesthesia and that some measures recovered with consciousness in the postsurgical period whereas others remained depressed following surgery. They suggested that some measures of HRV are more specific to the effects of anesthesia whereas others are more global indicators of cardiovascular compromise. This would not be expected to influence the

We conclude that power spectral analysis of heart rate variability may be an accurate and clinically useful measure of depth of propofol anesthesia and, if a real-time clinical monitoring system could be developed, may provide complementary information when combined with clinical examination, standard clinical sedation scoring systems, or newer methods, such as Bispectral Index monitoring of cerebral electrical activity.

results of the present study of patients who underwent brief procedures, but it does suggest that additional work is needed in evaluating the application of these techniques in a broad range of clinical settings. Finally, there were differences in mean HR and most HRV metrics between Awake 1 and Awake 2 states. This may have been due to either preprocedure anxiety or residual postanesthetic effect. Future studies should consider control populations not experiencing imminent surgical or other procedures.

We conclude that power spectral analysis of HRV may be an accurate and clinically useful measure of depth of propofol anesthesia and, if a real-time clinical monitoring system could be developed, may provide complementary information when combined with clinical examination, standard clinical sedation scoring systems, or newer methods, such as Bispectral Index monitoring of cerebral electrical activity (50–52). We speculate that heart rate HF power during propofol anesthesia correlates with depth of anesthesia whereas LF power allows for assessment of the patient's sympathetic response to pain. Other nonlinear measures of HR variability may prove to have clinical value in assessing depth of anesthesia as well. Further study is warranted to evaluate the effectiveness of HRV metrics during propofol and other types and combinations of anesthesia.

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