Respiratory sinus arrhythmia: comparison with EEG indices during isoflurane anaesthesia at 0.65 and 1.2 MAC

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SUMMARY

Respiratory sinus arrhythmia (RSA) is a cyclical variation in heart rate during breathing, where the heart rate increases during inspiration and decreases during expiration. RSA and the electroencephalogram (EEG) were monitored in 10 patients undergoing elective surgery with isoflurane and nitrous oxide in oxygen anaesthesia after induction with propofol. All patients were subject to controlled ventilation and recovery from competitive neuromuscular block was facilitated by neostigmine and glycopyrronium (seven patients) or atropine (three patients). Median and spectral edge (95%) frequencies of the raw EEG were derived off-line. RSA and EEG indices were obtained during preinduction (baseline), induction, incision, 0.65 and 1.2 MAC of isoflurane maintenance during surgery and recovery. Significant decreases in the level of RSA, median and spectral edge frequencies were observed during induction and significant increases in all indices were observed at recovery in all patients. Significant decreases in the median and spectral edge EEG frequencies occurred in patients treated with atropine both to counteract bradycardia after propofol induction and at antagonism of neuromuscular block (n = 3), compared with patients treated with glycopyrronium (n = 7). In contrast, the level of RSA did not decrease significantly with atropine. It is concluded that measurements of RSA could form the basis of a useful index of anaesthetic depth during isoflurane anaesthesia, even during the use of pharmacologically appropriate doses of atropine. However, any effects of atropine on the raw EEG and on indices derived from the EEG, should be characterized further so that these effects are not confused with changes in anaesthetic depth. (Br. J. Anaesth. 1994; 72: 397-402)

KEY WORDS


Respiratory sinus arrhythmia (RSA) is a non-pathological change in instantaneous heart rate under the control of a parasympathetic respiratory reflex. The level of RSA may be used as an index of vagal tone and, therefore, as a window on autonomic activity processed in the nucleus solitarius of the brainstem [1, 2]. Most research on RSA has focused on using it as a method of screening diabetics exhibiting autonomic neuropathy [3]. However, interest in RSA changes during anaesthesia began when an off-line study suggested that on-line analysis of RSA could provide a method of measuring the depth of anaesthesia in patients anaesthetized with isoflurane [4]. We have previously described changes in RSA and median EEG frequency during propofol anaesthesia [5] and RSA during propofol sedation [6]. The objective of this study was to test if RSA may be used as an index of anaesthetic depth during two standardized levels of isoflurane anaesthesia. We measured RSA in real-time and compared it with median and spectral edge frequencies of the EEG, which have been presented as indices of anaesthetic depth [7]. Some of these data have been reported briefly in conference proceedings [8].

PATIENTS AND METHODS

We studied 10 ASA I or II patients (mean age 42.5 yr, range 32-59 yr; mean weight 69.9 (SD 15.6) kg, range 45-97 kg) undergoing elective breast or gynaecological surgery; the patients gave informed consent to a study design approved by the local Ethics Committee. Anaesthesia was induced with propofol 2.5 mg kg⁻¹ and fentanyl 100 μg and maintained with 66% nitrous oxide in oxygen and alternating 10-min periods of 0.85% or 1.7% end-tidal isoflurane, measured using a calibrated anaesthetic gas analyser (Datex, Normac or Ultima; steps corresponding to 0.65 and 1.2 MAC). Vecuronium 0.1 mg kg⁻¹ was given at induction and the lungs were ventilated mechanically via a tracheal tube. Bradycardia during anaesthesia was treated with atropine 0.2-0.6 mg. Neuromuscular block was antagonized with neostigmine 2.5 mg and atropine 600 μg or glycopyrronium 0.5 mg.

Anaesthetic and surgical events were logged using a free-text database and the event data were time-locked to the appropriate ECG, EEG and RSA data files in order to facilitate off-line analysis. Additional, standard theatre monitors supplied data regarding oxygen saturation and arterial pressure.

Data acquisition methods have been described elsewhere [5, 6, 9]. RSA was quantified using a
modified version of a technique used for screening diabetics [3], which has been described in detail elsewhere [5, 6]. The EEG was obtained from silver-silver chloride electrodes fixed to the scalp at frontal and mastoid locations, with electrode impedance maintained at less than 7 kΩ. EEG waveforms were analogue bandpass filtered from 0.1 to 40 Hz (−3-dB points, Neurolog NL125) with a 50-Hz (mains line frequency, 20 Hz width at −3-dB points) notch filter. The EEG, ECG and respiratory waveforms were digitized (12 bits; 1 kHz) and stored using a microcomputer-based data logging system [9]. Each patient record exceeded 20 MBytes of computer storage capacity. All raw EEG waveforms were reviewed off-line in 6-s epochs to exclude artefacts and periods of burst suppression, which have been noted as adversely affecting power spectral analysis [10]. Raw EEG records were checked also for contamination by ECG waveforms, and rejected if any were seen. Failure to reject such records could have led to changes in heart rate affecting spectral analysis of the EEG.

Fast Fourier transformation (Hanning window; 2.048-s intervals, extracted from 6-s samples of EEG; 2048 points) and power spectral analysis were performed on the EEG to determine the median and spectral edge (95%) frequencies using software written for the study incorporating standard algorithms [11]. \( R \), median and spectral edge frequency time series were subjected to exponential smoothing with appropriate non-seasonal models. Intra-patient predictive autoregressive integrated moving averages (ARIMA) were determined using standard software [12]. ARIMA analysis describes disturbances or shocks in a time series and mathematically defines them within models. These models were used to forecast the future behaviour of \( R \) based on its behaviour over the preceding 15-min interval. ARIMA models were constructed at interventions in the time series caused by changes in the level of
anaesthesia and control charts were prepared showing the 99% confidence limits for a change from the predicted behaviour of R. Inter-patient grouped analysis was performed on 2-min data samples obtained from the time series of each patient, 1 min after events such as step changes in isoflurane concentration. Grouped data sets were checked for normality and equivalence of variance (Levene’s test) and inter-group comparisons were performed with Student’s two-tailed t tests and one-way analysis of variance (ANOVA). All statistical analysis was performed using standard software [12] running on an Intel 486-based PC. Groups were tested against the RSA or EEG indices seen at recovery, as avoidance of awakening during anaesthesia is the main objective of any putative monitor of anaesthetic depth.

RESULTS

All patients showed changes in the level of RSA, median and spectral edge indices as a result of anaesthesia. Figure 1 shows a typical time course for some indices in one patient. This record was of particular interest because, as a result of unexpected delay in the operating room, the patient was anaesthetized in an adjacent anaesthetic room 1 h before surgery commenced. Marked reductions in the level of RSA and both EEG indices were observed at induction of anaesthesia with propofol. Large increases were observed in both RSA and median EEG frequencies as the propofol bolus dose for induction wore off, although the patient was breathing nitrous oxide and oxygen. Isoflurane caused the level of RSA and median frequency to diminish. Step changes between 0.65 and 1.2 MAC of isoflurane resulted in step changes in the level of RSA and similar changes in median EEG frequency. Recovery from anaesthesia, in the presence of neostigmine and glycopyrronium, was accompanied by an increase in the level of RSA and increases in EEG median frequency.

Figure 2 shows the effect of administering atropine during the procedure in another patient, to antagonize bradycardia after propofol induction, and at the end of the procedure with antagonism of residual neuromuscular block with neostigmine. Levels of RSA increased progressively as a result of stimulation caused by intubation, as did the level of median EEG frequency. However, even after treatment with atropine 100 μg to counteract bradycardia associated with induction, the level of RSA changed in response to changes in levels of isoflurane. Recovery was accompanied by a marked increase in the level of RSA, occurring before a corresponding increase in median EEG frequency.

Figure 3 shows the results from analysis of grouped data from all 10 patients. One 2-min sample (four, 30-s data points) was taken from the time series data, with a 1-min delay (two, 30-s data points) after a change in anaesthetic level, to allow the anaesthetic to take effect. The grouped data show that RSA and the EEG indices were reduced during increasing levels of anaesthesia. RSA decreased significantly after propofol induction (P < 0.05) and during isoflurane anaesthesia (0.65 MAC, P < 0.05, 1.2 MAC, P < 0.01). The level of RSA increased during incision and was not significantly different from the level seen at recovery. The EEG spectral edge frequency before anaesthesia was significantly different from that after recovery (P < 0.01). Spectral edge frequency was not significantly different from that at recovery after propofol induction or incision, but was significantly different during isoflurane anaesthesia (P < 0.001). The median frequency of the EEG was significantly different from that at recovery after propofol induction (P < 0.05), during incision (P < 0.01) and isoflurane anaesthesia (P < 0.001). Neither the EEG median frequency nor the spectral edge frequency increased during incision.

Figure 4 shows the mean data for the three patients given atropine after propofol induction and at antagonism of competitive neuromuscular block.
compared with the seven patients given glycopyrronium only at antagonism. There was no significant difference (ANOVA, $P = 0.47$) between grouped levels of RSA on treatment with glycopyrronium or atropine. However, both median and spectral edge frequencies were significantly lower after treatment with atropine ($P < 0.01$) compared with glycopyrronium.

ARIMA intervention analysis at changes in the level of isoflurane maintenance showed that increasing isoflurane decreased the level of RSA and vice versa. Figure 5 shows the effect of decreasing the level of isoflurane in one patient. Within 5 min of decreasing isoflurane from 1.2 to 0.65 MAC, the level of RSA increased significantly ($P < 0.01$) and remained high.

**DISCUSSION**

Measurements of vagal tone using studies of heart rate variability have been described as an important window into the activity of the nervous system [2]. Anaesthesia suppresses activity progressively in the central nervous system and it has been proposed that indices of heart rate variability reflect the depth of anaesthesia [4, 5]. However, in common with the EEG, vagal tone is prone to several confounding influences which may not result from the level of anaesthetic depth. It is important, therefore, to isolate specific components from both the EEG and heart rate variability which minimize these artefacts. However, regardless of the number of data processing steps, the raw EEG, and any spectral frequency derived from it, represents the summed potential from only the upper 2 mm of cerebral cortex. Only evoked potentials represent activity from deeper centres, transmitted to the scalp by volume conduction. The cerebral cortex can reflect cognitive awareness under anaesthesia, but may not reflect the first signs of wakening, if those signs originate from deeper centres of the brain with an influence on the brainstem, or from the brainstem itself. RSA is an ideal method of detecting waking arousal in the central nervous system, as it is a component of heart rate variability which reflects parasympathetic activity originating in the brainstem.

Several groups, using fundamentally different methods compared with the present study, have reported that changes in the level of RSA mirror changes in anaesthetic level. One study [13] demonstrated a marked reduction in high frequency power of the cardiac spectral distribution on increasing the level of isoflurane anaesthesia progressively from no anaesthesia to 1.0, 1.5 and 2.0 MAC. The high
frequency component of the cardiac spectral distribution was attributed to RSA and the results showed the same trend as we have observed. However, the previous study was off-line and was performed on 256-s epochs of ECG R-wave timings. This implies that a temporal resolution of only approximately 4.5 min could be obtained. In addition, the fast Fourier transform (FFT) based spectral analysis used in the previous study depends on an epoch being a representative sample of a theoretically infinite data continuum. This implies that artefacts in the ECG record are not rejected easily on-line. This contrasts with the circular statistical analysis which we have used in this study, which is particularly selective and robust against contamination from cardiac artefacts other than RSA, such as ectopic beats and changes in heart rate [3]. We are also able to resolve changes in the RSA characteristics within 30 s, making our technique very suitable for incorporation into a usable patient monitor.

We were particularly interested in assessing the effect of pharmacologically suitable doses of atropine on RSA, as the abolition of RSA with high-dose atropine is a demonstration of its parasympathetic origin. Previous work in unanaesthetized subjects [14] and the results shown here during isoflurane anaesthesia, suggest that RSA is attenuated, but not abolished, by standard doses of atropine, as used during clinical anaesthesia. The three atropine-treated patients demonstrated visually obvious increases in the level of RSA on recovery, but these changes did not achieve statistical significance because of the small sample size ($n=3$). We feel that our findings are not in conflict with established literature, as our technique is capable of determining RSA at very low levels, certainly below the classic definitions of RSA, for example as a variation in the ECG P-P interval of greater than 120 ms or variation in sinus cycle length of 10% or more [15, 16]. We observed that RSA, median and spectral edge EEG frequencies did not change markedly in the grouped data when atropine-treated patients were subjected to isoflurane concentrations of 0.65–1.2 MAC, although individual records still showed that the responses did change (fig. 2). We suggest that atropine in pharmacologically relevant doses serves to attenuate, but not abolish, changes in RSA and EEG indices in response to changing anaesthetic depth.

We observed significant reductions in both median and spectral edge frequencies of the EEG in patients treated with atropine (figs 2, 4). This reduction may explain the reason why the EEG median frequencies of many of our patients in both this and an earlier study [5] were generally greater than the 5 Hz empirical guideline for adequate surgical anaesthesia adopted by Schwidlen and co-workers [7, 10]. Future studies may show that atropine reduces median and spectral edge frequencies in a dose-dependent manner. Few previous studies have mentioned any effect of atropine on the EEG. Atropine 0.5 mg in two awake subjects did not show large changes in the compressed spectral array (CSA) of the EEG [17]. That study did not, however, measure median or spectral edge frequencies and close visual inspection of both the CSA and raw EEG does indeed show some differences before and after administration of atropine. A subsequent study of EEG indices in volunteers treated with atropine for protection against the effects of cholinesterase-inhibiting nerve agents, showed significant increases in delta power, decreases in alpha power and reductions in beta and theta frequency after treatment with atropine [18]. We suggest, therefore, that further studies on the effect of atropine and other premedicants on the EEG must be performed so that any changes in the spontaneous EEG, or derived indices such as the auditory evoked response, caused by these drugs may be differentiated from changes in EEG frequency as a result of the depth of anaesthesia. It is also important that potential contamination of the EEG by ECG artefacts is eliminated before spectral analysis, otherwise changes in heart rate during recovery may falsely raise the median and, to a lesser extent, the spectral edge frequency of the EEG.

There are several advantages to using RSA analysis to determine the depth of anaesthesia. These include the use of standard ECG and respiratory signals and the inherently fast, artefact-free signal analysis. RSA also shows a more marked response to surgical stimulation than either of the EEG indices examined. This is a potentially useful feature, giving the anaesthetist the ability to increase the level of anaesthesia for a short period of severe surgical stimulation, which would otherwise not affect EEG indices due to their relatively long latency of response to lightening anaesthesia. The only potential exclusion criteria for the use of RSA are severe autonomic neuropathy and after heart transplantation. In both of these instances, components of the parasympathetic reflex loop governing RSA are disrupted.

In conclusion, we suggest that RSA can be used to stage the level of anaesthesia during isoflurane maintenance. In addition, RSA is responsive to surgical stimulation during anaesthesia, allowing the anaesthetist to gauge anaesthesia not only by the need for an empirical baseline, but also on the needs of the patient for increased anaesthesia based on the physiological response to noxious stimuli, even during competitive neuromuscular block.

REFERENCES

6. Wang DY, Pomfrett CJD, Healy TEJ. Respiratory sinus


