Heart rate variability in patients recovering from general anaesthesia

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Summary
We studied heart rate variability (HRV) using spectral analysis techniques in 58 adult patients recovering from general anaesthesia. The aim was to discover how HRV was affected by a variety of common preoperative, intraoperative and postoperative factors. ECG, respiration, level of consciousness, nausea, pain and arterial pressure were recorded during the first hour of recovery from general anaesthesia. HRV was found to decrease with increased weight, age, complexity of operation, use of reversal agents for neuromuscular block and preoperative beta-block. These effects were not mediated by changes in respiration. HRV was unaffected by administration of morphine. The level of nausea or pain had no effect on HRV except that pain decreased the relative ratio of high frequency to low frequency power within the power spectrum. In the group of patients that did not receive reversal agents, there was an abrupt increase in HRV when patients became responsive to verbal command. (Br. J. Anaesth. 1996; 76: 657–662)

Key words

Analysis of heart rate variability (HRV) has been used widely as a measure of activity in the sympathetic and parasympathetic components of the autonomic nervous system [1–3]. From oscillations in instantaneous heart rate, some information may be obtained on the status of the cardiovascular controlling systems. Spectral analysis of the R-R intervals is used commonly to quantify the components of beat-to-beat variability. The area under the power spectral curve in a particular frequency band is considered to be a measure of the variation in heart rate at that frequency.

From a variety of physiological experiments it has been demonstrated that inspiratory inhibition of vagal parasympathetic tone causes “high” frequency (HF) fluctuations in heart rate which are related to respiration. This effect seems to be mediated centrally via pathways between medullary respiratory and cardiovascular centres, and is well known as “respiratory sinus arrhythmia”. The frequency of these oscillations depends on the breathing frequency but is usually 0.15–0.5 Hz. The origins of oscillations in the mid frequency (MF) (0.05–0.15 Hz) range are less well known but are thought to be caused mainly by the vasomotor part of the baroreflex arc [1]. Low frequency (LF) (<0.05 Hz) fluctuations are believed to be largely the result of thermoregulatory changes in peripheral vascular resistance [1]. However, when HRV is measured in patients undergoing general or regional anaesthesia, the explanation of the observed changes is more difficult to interpret. It is certainly open to debate as to whether HRV is a reliable indicator of autonomic balance [4, 5], and how it is affected by respiration, anaesthetic drugs, illness and surgery [6–8].

Induction and maintenance of general anaesthesia cause a marked reduction in HRV [9, 10], and it has been proposed that monitoring HRV may provide a useful indicator of depth of anaesthesia [11]. All components of the HRV power spectra decrease with general anaesthesia and increase during the recovery period [9]. However, published studies have involved small numbers of patients who were not suffering from chronic diseases and were not receiving long-term medication. These factors have major effects on HRV and therefore may seriously limit its widespread application. With this in mind, an observational study was performed with the aim of understanding the clinical significance of the HRV power spectrum by recording sequential changes in HRV in a cross-section of patients awakening from general anaesthesia. Apart from documenting the changes in HRV that occur as the patient is awakening in the early recovery period, we hoped to identify factors that influence HRV, and study the associations of HRV data with adverse effects experienced during recovery from general anaesthesia. From this we also hoped to gain information on factors that influence the reliability of using HRV as an indicator of arousal and, possibly, awareness.

Patients and methods

DATA COLLECTION

After obtaining regional Ethics Committee approval and written informed consent, we studied 60 randomly selected hospital inpatients undergoing general anaesthesia...
anaesthesia for a wide range of surgical procedures. Patients with known arrhythmias and those less than 16 yr of age were excluded. Information was recorded on clinical factors that were thought to possibly influence HRV. These included: preoperative data such as patient age, sex and weight, preoperative medications and significant clinical disease; intraoperative data such as type of surgery and anaesthetic drugs administered. The end of operation was defined as either the time when neuromuscular block was antagonized or when the anaesthetic vapour stopped if spontaneous respiration had been used. An attempt was made to grade the magnitude of surgery using the Resource Utilization System (RUS) score. This is a system that is used routinely in our hospital to grade the complexity of a particular operation for statistical purposes. It classifies operations on an ordinal scale of 1 (minor) to 4 (multiple major); postoperative data, including when the patient entered the recovery room, ECG, respiration and the patient’s clinical state for the length of time that the patient was in the recovery room (minimum of 30 min) or until 1 h had elapsed.

ECG and respiratory data were recorded continuously, in serial “runs” of 300 R-R intervals. At the end of each run, the following clinical data were determined: (1) patient’s level of consciousness (LOC) using the scale, 1 = alert and orientated, 2 = drowsy but rouses spontaneously, 3 = drowsy, arouses only to verbal command, 4 = asleep, arousable to stimulation, unarousable to verbal command and 5 = anaesthetized, unarousable to pain; (2) level of pain and nausea using the scale, 0 = none, 1 = mild, 2 = moderate and 3 = severe; (3) time of the patient’s first response to a verbal command (the patient was requested to give a single hand squeeze) [12]; (4) medications administered and vital signs.

**SIGNAL PROCESSING**

The patient’s ECG was obtained from lead II of a standard ECG monitor. This was fed to a 386DX computer fitted with a 12-bit Keithley DAS-1200 analogue/digital I/O board (Keithley, Taunton, MA, USA), where it was digitized using a sampling rate of 200 Hz. The signal was filtered digitally and processed to extract QRS peaks which determine the R-R intervals [13]. These peaks were then edited semi-manually to remove and interpolate ectopic beat artefacts. Spectral density was then determined by applying Welch’s method to 100-s overlapping data segments which were weighted using the Bartlett window and fast Fourier transformed and averaged. Areas under the spectral density curve up to 0.50 Hz were determined by the trapezium rule. Low frequency (LF) (0.02–0.05 Hz), mid frequency (MF) (0.05–0.15 Hz) and high frequency (HF) (0.15–0.50 Hz) bandwidth powers were determined for each 300 R-R interval series.

The respiratory signal was obtained from a respiratory inductance plethysmograph (Respitrace, Studley Data Systems, Oxford). Data were sampled at 20 Hz by the Keithley board (12-bit) and stored on hard disk. The respiratory power spectrum was obtained in a manner identical to that of heart rate.

The Respitrace was calibrated using a Wright’s respirometer to obtain concurrent tidal volume readings of the first five breaths of the patient. We used the AC output from the Respitrace, without automatic resetting.

The influence of the lung volume signal on the HRV signal was estimated by multiplying the coherence function of the two spectra by the heart rate spectrum. This technique enables HRV power to be partitioned into a proportion that may be attributed to the lung volume signal and a component that is independent of the lung volume signal.

**STATISTICAL ANALYSIS**

We attempted to discover associations between the dependent HRV indices and the various explanatory “clinical” variables. These explanatory variables comprised preoperative, intraoperative and postoperative data, as described above.

HRV indices consisted of: (i) natural logarithms of absolute LF, MF, HF and total power (LFP, MFP, HFP, TotP); (ii) ratio of HF to LF and MF power (HF/LFMF); (iii) percentage power in each frequency band that could be attributed to respiration (%RHF, %RMF, %RLF, %RTot).

Because power spectral data commonly have a skewed distribution, we followed the example of Kato and colleagues [10] and performed a natural logarithmic transformation on the raw data. After checking for normality using Agostino’s Omnibus-K2 test [14], this allowed the use of parametric statistics for inter-individual comparison and Pearson’s statistic for quantifying correlations between HRV indices. All HRV values in this article are therefore reported in lnBPM² units.

Statistical analyses were performed using the NCSS computer package (NCSS 5.01, Kaysville Utah). Initially, we performed an exploratory analysis of the data set looking for associations. The HRV indices were compared pairwise with the various clinical factors; visually using scatterplots and numerically using the Spearman rank correlation measure. Because three HRV power bands are compared with each explanatory variable, $P < 0.02$ was considered significant (giving an overall experimental type I error of $P = 0.056$). Using the NCSS package, it was possible to allow for the effect of other variables (so-called “partial” variables) on the correlation. This is similar to the use of covariates in ANCOVA models. The residual correlation between two variables is determined after a multiple linear regression has subtracted the effect of the partial variables. If the correlation coefficient is unchanged before and after the linear influence of the partial variables is removed, it is suggested that the partial variables are not confounding factors.

For those variables with a binary structure (such as whether or not the patient was receiving preoperative beta-blocker treatment), groups were compared using the $t$ test.

From these results it was possible to build a multivariate model to attempt to account for the observed HRV using general linear model (GLM) multiple linear robust regression. The explanatory
variables were the various clinical factors. This was done in a “forward stepwise selection” manner by sequentially adding variables to the model. To assess the potential power of HRV to predict wakefulness, a post hoc logistic regression was performed and the results presented as area under the receiver operating characteristic curve.

Results

We obtained 420 technically acceptable data records from 58 patients (table 1). Significant correlations between clinical variables and HRV indices are shown in table 2. It can be seen that the correlation coefficients were similar when respiratory-related HRV power was subtracted. This strongly suggests that the mechanisms by which the explanatory variables alter HRV are not mediated via respiratory changes. There was no single variable that was strongly correlated with any of the HRV indices.

The amount of HRV that could be accounted for by changes in lung volume was less than has been found in healthy volunteers, but varied widely between patients. The mean percentage of total power (%RMF) that was correlated with respiration was 46% (interquartile range 30–60%). In the low frequency band (%RLF) it was 43% (interquartile range 24–58%), in the medium frequency band (%RMF) 41% (28–51%) and in the high frequency band (%RHF) 56% (36–74%). The percentage of total power influenced by respiration did not change with increasing time from reversal ($P = 0.9121$).

There were no significant differences between male and female groups for any of the HRV indices, but our results confirmed the well known negative correlation of HRV with increasing patient age. Of interest, there was a significant, and previously unreported, negative correlation of patient weight with all HRV indices. It appeared to be an independent factor. We repeated the correlation using other factors (age, beta-block, complexity of operation, use of reversal agents, LOC, pain and nausea) as partial correlates, but were unable to identify any confounding factors that might explain this observation. There was also a consistent negative correlation of all HRV indices with the complexity of operation, as estimated by the RUS score. Again, this was unaffected by age, beta-block, reversal agents, LOC, pain or nausea as partial correlates. Patients with diabetes had HRV indices that were low but not statistically different from non-diabetics. Patients who had a combined extradural–general anaesthetic technique had a higher mean TotP than those who received only general anaesthesia ($P = 0.042$).

**Table 1** Patient data (mean (range) or number)

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>54 (16–65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>25/33</td>
</tr>
<tr>
<td>Preoperative disease</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>4</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>3</td>
</tr>
<tr>
<td>Preoperative medication</td>
<td></td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>11</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>8</td>
</tr>
<tr>
<td>Thyroxine</td>
<td>5</td>
</tr>
<tr>
<td>Anaesthetic technique</td>
<td></td>
</tr>
<tr>
<td>IPPV</td>
<td>33</td>
</tr>
<tr>
<td>Combined extradural–general anaesthesia</td>
<td>4</td>
</tr>
<tr>
<td>Propofol/thiopentone</td>
<td>40/18</td>
</tr>
<tr>
<td>Isoflurane/halothane</td>
<td>5/3</td>
</tr>
<tr>
<td>Suxamethonium/vecuronium/pancuronium</td>
<td>2/22/5</td>
</tr>
<tr>
<td>Atracurium</td>
<td>6</td>
</tr>
<tr>
<td>Operation type</td>
<td></td>
</tr>
<tr>
<td>Laparotomy</td>
<td>15</td>
</tr>
<tr>
<td>Thoracic</td>
<td>3</td>
</tr>
<tr>
<td>Urological</td>
<td>5</td>
</tr>
<tr>
<td>Vascular</td>
<td>4</td>
</tr>
<tr>
<td>Body surface</td>
<td>31</td>
</tr>
</tbody>
</table>

**Table 2** Spearman correlation coefficients for respiratory and non-respiratory related HRV spectral power indices. Only correlations for $P < 0.02$ are shown. LF, MF and HF refer to the frequency bands 0.02–0.05, 0.05–0.15 and 0.15–0.5 Hz, respectively. The numbers in parentheses are the correlations after subtraction of the power that is correlated with changes in lung volume and thus is a measure of HRV power independent of respiration

<table>
<thead>
<tr>
<th></th>
<th>LFP</th>
<th>MFP</th>
<th>HFP</th>
<th>HF/LF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>$-0.25$</td>
<td>$-0.20$</td>
<td>$-0.22$</td>
<td>$-0.21$</td>
</tr>
<tr>
<td>Weight</td>
<td>$-0.24$</td>
<td>$-0.23$</td>
<td>$-0.26$</td>
<td>$-0.28$</td>
</tr>
<tr>
<td>Beta-block</td>
<td>$-0.16$</td>
<td>$-0.16$</td>
<td>$-0.26$</td>
<td>$-0.26$</td>
</tr>
<tr>
<td>Reversal</td>
<td>$-0.22$</td>
<td>$-0.19$</td>
<td>$-0.35$</td>
<td>$-0.33$</td>
</tr>
<tr>
<td>LOC</td>
<td>$-0.17$</td>
<td>$-0.17$</td>
<td>$-0.17$</td>
<td>$-0.16$</td>
</tr>
<tr>
<td>SAP</td>
<td>$-0.23$</td>
<td>$-0.23$</td>
<td>$-0.12$</td>
<td>$-0.12$</td>
</tr>
<tr>
<td>Heart rate</td>
<td>$-0.22$</td>
<td>$-0.29$</td>
<td>$-0.13$</td>
<td>$-0.20$</td>
</tr>
<tr>
<td>RUS score</td>
<td>$-0.17$</td>
<td>$-0.17$</td>
<td>$-0.19$</td>
<td>$-0.24$</td>
</tr>
</tbody>
</table>

**DRI effects**

Beta-blocker use ($n = 11$) was associated with a significantly reduced TotP from a mean of 2.15 to 1.40 (SEM 0.12, $P = 0.0001$). This decrease was noted in all frequency bands, but was particularly marked in the MF band. This band also had the strongest negative correlation with beta-blocker use (table 2). Angiotensin converting enzyme (ACE) inhibitor use ($n = 6$) was associated with a slight increase in MFP from $-0.10$ to 0.58 (SEM 0.31, $P = 0.0197$), and a positive correlation between ACE inhibitor use and HF/LFMMF ($r = 0.27$, $P = 0.0006$). There were no differences in HRV attributable to the different induction agents, volatile agents or neuromuscular blocking drugs. The use of reversal agents (neostigmine 2.5 mg and atropine 1.2 mg, $n = 33$) was associated with a significant decrease in HRV (TotP) from a mean of 2.43 to 1.70 (SEM 0.09, $P = 0.0001$). The difference was similar in all frequency bands. It was not possible to separate the effects of reversal
agents from the use of neuromuscular blockers, or positive pressure ventilation, but it seemed likely that the observed effect was largely attributable to atropine.

There were no changes in HRV indices associated with morphine or metoclopramide administration during the recovery period.

**PHYSIOLOGICAL CHANGES DURING RECOVERY**

As shown in table 2, LOC had a significant negative correlation with LFP and MFP. This effect is shown in figure 1, which also demonstrates that the use of reversal agents eliminated the change in HRV power with LOC. In the group that did not receive reversal agents, there was a large increase in HRV power between LOC grades 3 and 4. This phenomenon occurred before and after patients became responsive to verbal command. If this is taken as a threshold level for consciousness, the area under the receiver operating characteristic curve was 0.91 in the non-reversed and 0.63 in the reversed group. We compared the predictive power of LFP with heart rate (HR) and systolic arterial pressure (SAP) alone, and in combination, using a logistic regression. Only LFP had values significantly different from zero. HR and SAP, either alone or in combination, could not distinguish between awake and asleep groups.

Pain had no significant effect on HRV indices, except for the HF/LFMF ratio which was decreased significantly ($r = -0.18$, $P = 0.02$). Nausea did not appear to have consistent effects on any of the HRV indices except to decrease HFP in the group that had not received reversal agents ($r = 0.21$, $P = 0.0007$).

**CORRELATIONS WITHIN HRV INDICES**

The matrix of correlations between the various HRV indices is shown in table 3. In general the indices demonstrated strong linear correlations. However, as shown by the numbers in parentheses in table 3, the use of beta-blocking drugs appeared to be associated with a reduction in the correlation between the various indices. The use of reversal agents, ACE inhibitors, RUS score, LOC and pain or nausea score resulted in non-significant changes in the correlation coefficients.

**MULTIVARIATE MODEL**

Eight explanatory variables (age, weight, beta-block, RUS score, reversal, LOC, SAP and beta-block/SAP interaction term) were found to contribute significantly in a robust multiple linear regression model. This model achieved $r^2$ values of 56% for TotP, 52% for LFP, 63% for MFP and 43% for HFP. If the overall spectral power was partitioned by subtracting the power that was correlated with respiration (%Rtot) from TotP it was possible to derive the amount of spectral power that was independent of lung volume (NR-Tot). When a similar regression was performed, $r^2$ values of 47% were obtained for NR-Tot, and only 10% for %Rtot. Thus about half of the variation in HRV can be accounted for using these predictor variables, none of which appears to act significantly via changes in respiration.

**Discussion**

This was a descriptive study and therefore interpretation of possible effects is difficult because of the problem of unknown confounding factors which may cause spurious correlations. Notwithstanding, there appeared to be several consistent observations. In this study, approximately 50% of this variability could be explained by a linear multivariate model using clinical variables. Presumably the rest of the interindividual variation was a result of other microscopic and biochemical changes that are not easy to measure. It is difficult to disentangle the relative effects of preoperative morbidity, residual effects of anaesthetic agents and activation of the
surgical stress response. However, clearly HRV is correlated negatively with the complexity of the operation and weight of the patient. There is circumstantial evidence that stress hormonal activation may be an important modulator of HRV. Most studies have concentrated on the effects of the autonomic nervous system on HRV, but have ignored the fact that in situations of high sympathetic tone there are commonly coexisting elevations in vasopressin, renin, angiotensin II, corticosteroids and a number of autacoids controlling vasomotor tone [15, 16]. These hormones may act in at least two ways. Vasopressin is known to modulate directly the autonomic outflow from the brain stem by inhibiting vagal tone. Other substances may change peripheral resistance, thus affecting the oscillations in the HR feedback loops that manifest as LFP.

Pain (or nausea) does not appear to be associated with a marked increase in sympathetic power, as shown by an increase in the LFP and MFP bands. There are major problems with the common interpretation of MFP (or LFP) as being an indicator of sympathetic nervous system “tone” [17]. This explanation is based on changes in MFP induced by tilt or negative pressure studies in volunteers. In other hyper-adrenergic states (cardiac failure, exercise and high altitude hypoxia) there is a characteristic pattern in the HR response, consisting of a decrease in LFP, increase in HR and a relative “switching off” of parasympathetic tone, as evidenced by a decrease in the HF/MFLF ratio. Saul and colleagues [18] compared HRV indices with sympathetic activity, as measured directly from the peroneal nerve, and by plasma noradrenaline concentrations. They found a marked heterogeneity in response. In 50% of their subjects there was a close association with LFP and muscle sympathetic nerve activity, but for the remainder there was no correlation.

Berger, Saul and Cohen [19] performed a canine study in which the cardiac sympathetic nerves were stimulated directly causing some increase in LFP but without effect on MFP. Furthermore, they demonstrated a decrease in LFP with increasing stimulation frequency. Malliani and colleagues [20] found that fluctuations in arterial pressure preceded variations in heart rate. We therefore conclude that it is more accurate to interpret MFP as an index of phasic (not tonic) sympathetic nervous system activity, principally mediated by oscillations in the baroreflex arc. The possible confounding effects of other stress hormones, such as angiotensin and vasopressin, are not mentioned in any of these studies. However, it is of interest to note that ACE inhibitors tend to increase HRV, particularly in the HF band. Hopf and colleagues [21] have compared HRV before and after preganglionic cardiac block using thoracic extradural local anaesthesia. They reasoned that if LFP was dependent on sympathetic activity, then block should result in a decrease in LFP. However, they found that absolute LFP did not decrease when the block was commenced but that HF/LF ratio did decrease with tilt, particularly if the cardiac nerves were not blocked. Interestingly, they reported an increase in vasopressin plasma concentrations in the presence of sympathetic block and tilt.

The effects of beta-block observed were depressant on all frequencies of HRV, but particularly inhibitory on phasic baroreflex activity (MFP). We also showed that beta-block appeared to have the effect of “uncoupling” the usually strong correlations between the different frequency bands in the HRV power spectrum. Beta-blockers have a number of pre- and postsynaptic actions that could affect HRV. Central beta-receptors are known to directly modulate vagal tone, in addition to causing dissociation of sympathetic neural traffic between different organs.

Our findings that LF and HF power are reduced with increasing depth of anaesthesia are consistent with similar studies [9, 10, 11, 22]. Kato and co-workers [10] made the important observation that the reduction in LF power is not related linearly to depth of anaesthesia, as measured by end-tidal volatile anaesthetic concentrations. We have obtained similar results using a relatively coarse clinical scale of arousal. As shown in figure 1, LFP (and HFP) increased abruptly in a stepwise manner at the point at which the patient became responsive to verbal command. This particular end-point may be an important clinical indicator of the possibility of awareness, or at least recall. Dutton, Smith and Smith [12] have studied patients recovering from general anaesthesia. They found that response to command was a useful indicator of anaesthetic depth, as evaluated by memory formation. In their study none of 22 patients who had a brief wakeful response to verbal command had memory formation. In contrast, 13 of 28 patients who could sustain wakefulness long enough to complete four hand squeezes on command had memory formation. On the scale that we used in our study, the transition from LOC grade 4 to 3 would correspond to Dutton’s brief wakefulness level. Loss of amnesia starts to occur regularly at the transition from LOC grades 3 to 2. In our study HRV increased markedly when the patient moved from LOC grades 4 to 3. HRV is therefore a conservative marker of consciousness, increasing at the point at which there is a coordinated response to command, but relatively unrelated to the presence or absence of amnesia. We may conclude that a low HRV strongly suggests unawareness and furthermore an increase in HRV is a relatively early warning sign of conscious recall, the patient probably still being amnesic.

Our data tentatively suggest that HRV power may be a useful adjunct in monitoring depth of anaesthesia, but the findings need to be confirmed. In our post hoc analysis, if the patient had not received atropine, the LFP correctly categorized wakefulness in 92% of patients in our study. However, this result was biased because most of the patients were rousable by the time they were taken to the recovery area and therefore classified as being “awake”.

Further work needs to be done to establish accurately the true positive predictive value and appropriate threshold level of HRV. Nevertheless, even if it is not completely reliable, the use of HRV would seem to be a great improvement on the common clinical
indicators of awareness. The discriminatory power to detect awareness was not improved if heart rate and systolic arterial pressure were included in the prediction. The predictive power also appeared to be relatively robust to many common medications and illness (ACE inhibition and opioids), but allowances in TotP of about \(-0.1\, (\ln\text{BPM}^2)\) per decade must be made for age and approximately \(-1\, (\ln\text{BPM}^2)\) for the use of beta-block. It was completely obtunded by the use of atropine.

Acknowledgement

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References


