Effects of propofol and thiopentone, and benzodiazepine premedication on heart rate variability measured by spectral analysis†

S. J. HOWELL, V. WANIGASEKERA, J. D. YOUNG, D. GAVAGHAN, J. W. SEAR AND C. S. GARRARD

Summary

We studied the effects of temazepam premedication and induction of anaesthesia with thiopentone or propofol on the heart rate power spectrum in 47 patients undergoing elective minor surgery. Eighteen patients received temazepam 20 mg orally as premedication. There was a significant reduction in high frequency power and total power, and an increase in the ratio of low to high frequency power after induction of anaesthesia with either propofol or thiopentone. Patients who had received temazepam premedication had significantly greater low frequency, high frequency and total power than those who were not premedicated. There was no significant difference between premedicated and unpremedicated patients in the ratio of low to ventilatory frequency power. (Br. J. Anaesth. 1995; 74: 168-173)

Key words

Premedication, temazepam, Anaesthetics i.v., propofol, Anaesthetics i.v., thiopentone, Heart, heart rate. Measurement techniques, spectral analysis.

Although the normal heart rate is basically regular, its rate oscillates with time. Variation with respiration, termed sinus arrhythmia, was first described by Stephen Hales in 1733 [1]. Waves of variation with a periodicity of approximately 10 s, known as Mayer waves [2], have been identified and variation at slower rates is also thought to occur. The variability of heart rate can be resolved into its component waves by mathematical techniques such as fast Fourier transformation and autoregression. From such an analysis a graphical representation of the variation in heart rate may be produced, the heart rate power spectrum. The frequencies of the various components of heart rate variability are plotted on the X-axis and the power of these components on the Y-axis. The present study uses the fast Fourier transform to examine the effects on heart rate variability of induction doses of thiopentone or propofol in both unpremedicated patients and in those premedicated with temazepam.

Patients and methods

The study was approved by the Central Oxford Research Ethics Committee and all patients gave informed consent to participation. We studied 54 patients (25 female; ASA I and II) undergoing anaesthesia for elective surgery. Patients receiving regular intercurrent medications were excluded, as were patients with conditions known to affect the heart rate spectrum, including hypertension, cardiac disease, diabetes mellitus and renal failure. Eighteen of the patients received oral temazepam 20 mg as premedication; the remaining 36 patients received no premedication. Patients' ages ranged from 25 to 74 yr (mean 37.1 yr) and weights 54 to 100 kg. Patients in both premedicated and unpremedicated groups were allocated randomly to receive either propofol or thiopentone; 18 of the unpremedicated patients and nine premedicated patients received propofol.

In the anaesthetic room a cannula was inserted into a vein in the non-dominant hand and a pulse oximeter and automated non-invasive arterial pressure monitor were applied to the patient. Three ECG electrodes were attached to the chest to display the ECG (Hewlett-Packard monitor model No. 78203A). Ventilatory frequency was measured by impedance plethysmography performed through the same leads (Hewlett-Packard monitor model No. 78212A). ECG analogue and ventilatory impedance signals were digitized using an interface board fitted to a personal computer (Compaq 286 portable, 6 MHz, 80286 processor, 80287 maths co-processor). These signals were analysed in 256-s periods. From the ECG a tachogram of the beat-to-beat heart rate was generated. This was sampled at 4 Hz to produce a 1024-point time series. The fast Fourier transform requires a series of 2^n points and a 256-s window was chosen as being sufficiently long to allow good frequency resolution. The mean of each block was calculated and subtracted, and linear trends were

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HEART RATE VARIABILITY AND PREMEDICATION

Heart rate variability and premedication

The total power of the heart rate spectrum was taken as the variance of the heart rate signal. The heart rate power spectrum was then computed from the square of magnitude of the fast Fourier transform of the series. The ventilatory signal was analysed in a similar fashion, but without first being converted to a tachograph. The power within two frequency bands of the heart rate spectrum was determined as the area under the spectral curve within each band. The bands chosen are shown in figure 1 and correspond with the two peaks seen in the heart rate spectrum: (i) low frequency power (LP) was determined in a band lying between 0.04 and 0.1 Hz; (ii) high frequency power (HP) was determined in a band of 0.12 Hz width centred on the modal ventilatory frequency determined from the ventilatory power spectrum. The total power of the heart rate spectrum was calculated as the sum of LP and HP, and the ratio of low frequency to ventilatory frequency power was also calculated. Our method of data analysis and choice of frequency bands is similar to that used previously by other workers [3, 4].

Baseline data were recorded for two 256-s periods before induction of anaesthesia. At the beginning of the third period, anaesthesia was induced with a dose of either thiopentone or propofol sufficient to obtund the eyelash reflex while the patient breathed 100% oxygen. Ventilation was assisted if necessary until spontaneous ventilation returned. After induction, two additional periods of data were recorded. At the beginning of each of these, additional doses of thiopentone or propofol (25% of the induction dose) were given. If the patient displayed signs of clinically inadequate anaesthesia (e.g. jaw tightening) incremental doses of the induction agent were given as appropriate. Thus data were collected over five time periods in total, two before induction of anaesthesia, a period during which anaesthesia was induced and two periods after this, during which anaesthesia was maintained with the induction agent. At the end of these periods of data collection, anaesthesia and surgery proceeded as indicated by the patient's presenting condition.

STATISTICAL ANALYSIS

Data were analysed by generalized linear interactive modelling (using GLIM 3.77 update 2, copyright Royal Statistical Society, London, running on the Oxford University DEC VAX cluster). For each variable a model was generated by sequentially adding variables (premedication, time, induction agent), the most significant first. The validity of the model was then tested by removing each variable in turn. A probability value of \( P < 0.05 \) was taken as statistically significant.

RESULTS

Satisfactory heart rate recordings were obtained from 47 patients: 31 unpremedicated of whom 14 received propofol and 16 premedicated of whom eight received propofol. Period three, the induction period, has been excluded from the analysis of data for spectral power as heart rate was changing rapidly.

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in this period and the requirement for stationary data was not satisfied. Data for heart rate and ventilatory frequency are shown in figure 2 and for spectral power in figure 3. Data are shown as box and whisker plots, where the solid line is the median, the box represents the 25th and 75th percentiles, and the whiskers represent the largest and smallest values that were not outliers. Outliers are defined as values lying more than 1.5 box lengths from the 75th percentile. Statistically significant results for each variable are shown in table 1.

**HEART RATE**

Unpremedicated patients had a significantly lower heart rate than those who had received premedication ($P < 0.01, F = 16.85$ on 1 and 254 df). There was a significant increase in heart rate after induction of anaesthesia which was maintained into the post-induction periods 4 and 5 ($P < 0.01, F = 7.234$ on 4 and 233 df). There was no significant difference between drugs.

**VENTILATORY FREQUENCY**

There was an increase in ventilatory frequency with induction of anaesthesia ($0.01 < P < 0.05, F = 3.90$ on 3 and 187 df). There was no significant effect of premedication or any difference between drugs.

**HIGH FREQUENCY POWER (HP)**

Premedicated patients had a significantly greater HP than unpremedicated patients ($P < 0.01, F = 10.94$ on 1 and 187 df). There was a significant decrease in HP after induction of anaesthesia ($P < 0.01, F = 10.56$ on 3 and 186 df). No significant difference in terms of drug was seen.

**LOW FREQUENCY POWER (LP)**

LP was significantly greater in those patients who had received premedication than in those who had not ($P < 0.01, F = 11.60$ on 1 and 187 df). There was no significant effect of drug or of induction of anaesthesia.

**TOTAL POWER**

Premedicated patients had a significantly greater total power than those who received no premedication ($P < 0.01, F = 15.20$ on 1 and 187 df).

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**Figure 3** Box and whisker plots of high frequency power (HP), low frequency (LP), total power and ratio for premedicated and unpremedicated patients. Periods are labelled as follows: 1 = first preinduction period, 2 = second preinduction period, 4 = first post-induction period, 5 = second post-induction period.

**Table 1** Variables identified by generalized linear interactive modelling as contributing significantly to the variability in heart rate, ventilatory frequency and high, low and total power or ratio. All other interactions between the heart rate variables and the three variables (time, premedication, induction agent) were not statistically significant.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Variable</th>
<th>&quot;F&quot;</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>Premedication</td>
<td>$F = 16.85$ on 1 and 234 df</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td></td>
<td>Time</td>
<td>$F = 7.234$ on 4 and 233 df</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Ventilatory frequency</td>
<td>Time</td>
<td>$F = 3.90$ on 3 and 187 df</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>High frequency power</td>
<td>Premedication</td>
<td>$F = 10.94$ on 1 and 187 df</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td></td>
<td>Time</td>
<td>$F = 10.56$ on 3 and 186 df</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Low frequency power</td>
<td>Premedication</td>
<td>$F = 11.60$ on 1 and 187 df</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Total power</td>
<td>Premedication</td>
<td>$F = 15.20$ on 1 and 187 df</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td></td>
<td>Time</td>
<td>$F = 4.745$ on 1 and 186 df</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Ratio</td>
<td>Time</td>
<td>$F = 2.992$ on 3 and 187 df</td>
<td>0.01 &lt; P &lt; 0.05</td>
</tr>
</tbody>
</table>
There was a significant decrease in total power after induction of anaesthesia ($P < 0.01$, $F = 4.745$ on 1 and 186 df). No effect of drug was demonstrated.

**RATIO (LP/HP)**

There was a significant increase in the ratio of low frequency to ventilatory frequency power with induction of anaesthesia ($0.01 < P < 0.05$, $F = 3.90$ on 3 and 187 df). No other significant effects were demonstrated.

**Discussion**

The normal heart rate spectrum displays two peaks, a low frequency peak between 0.04 and 0.1 Hz and a ventilatory frequency peak centred on the ventilatory frequency (fig. 1). In the present study the low frequency band has been taken to lie between 0.04 and 0.12 Hz and the ventilatory frequency component to lie in a band 0.12 Hz wide centred on the modal ventilatory frequency. Heart rate variability is thought to be mediated by the autonomic nervous system. This interpretation of the heart rate spectrum is based on pharmacological studies using propranolol and atropine to block the effects of sympathetic and parasympathetic activity. The high frequency component of the spectrum is thought to be controlled by the parasympathetic nervous system, and reductions in this component of the heart rate spectrum can be attributed to reductions in parasympathetic activity. On the other hand the low frequency band of the spectrum is said to be controlled in part by the sympathetic and in part by the parasympathetic nervous system. A change in the ratio of the low frequency to the high frequency area is taken to indicate a change in the balance of sympathetic to parasympathetic activity [3-5]. Thus overall changes in the heart rate spectrum are taken to represent changes in autonomic activity.

We observed an increase in heart rate after induction of anaesthesia, but were unable to distinguish between the effects of thiopentone and propofol. Thiopentone is known to cause an increase in heart rate at induction [6] while propofol has been variously reported as causing little change in heart rate or tachycardia [7-9].

With induction of anaesthesia, we observed a decrease in the power of both the low and the high frequency bands of the heart rate spectrum. There was also a significant increase in the ratio of low frequency to ventilatory frequency power. In the presence of nitrous oxide, thiopentone has previously been reported to cause a reduction in the power of the heart rate spectrum with a greater reduction in high than low frequency power [6]. In contrast, propofol induction followed by maintenance with nitrous oxide and isoflurane has been reported to cause a decrease in the total power of the heart rate spectrum with a relatively greater reduction in the power of the components of the spectrum with frequencies less than 0.12 Hz [10]. Nitrous oxide has been shown to cause a reduction in high frequency power and an increase in the ratio of low to high frequency power [11]. This complicates the interpretation of studies in which nitrous oxide and another agent or agents were administered. Induction and maintenance of anaesthesia with propofol alone has been reported to cause a reduction in the total power of the heart rate spectrum with relative preservation of frequencies in the range 0.02–0.08 Hz [12]. Thus our findings of an increase in heart rate and a reduction in the total power of the heart rate spectrum with induction of anaesthesia are consistent with other observations on the effects of propofol. We were unable to demonstrate any significant difference between the effects of thiopentone and those of propofol.

Other studies, for example Robinson, Buyck and Galletly, have investigated the beat-to-beat changes in heart rate during induction of anaesthesia with propofol 0.2 ml kg$^{-1}$ followed by an infusion of 1 mg kg$^{-1}$ h$^{-1}$ [13]. Onset of action caused a reduction in total power and in both mid and high frequency ranges (0.08–0.15 Hz and 0.15–0.45 Hz, respectively). There was a significant increase in the percentage of power in the low frequency band (0.02–0.08 Hz). These results are broadly in agreement with our own with respect to the low and high frequency bands of the heart rate spectrum, but while Robinson observed a non-significant decrease in his "high power ratio", we observed a significant increase in the low:high power ratio with time. The differences may be related to differences in methodology (infusion vs bolus dosing) or spectral array analysis.

The changes which we observed in the heart rate spectrum are consistent with an overall reduction in autonomic activity, but with a greater reduction of parasympathetic compared with sympathetic activity. Both propofol and thiopentone have been shown to reduce directly measured sympathetic nerve activity [14-16]. There is also evidence that these drugs depress parasympathetic activity. Several studies have shown that thiopentone depresses the vagally mediated pressor baroreflex and causes a resetting of the reflex to allow a faster heart rate at a given arterial pressure [15, 17]. In subjects who had received propofol and vecuronium Ebert and co-workers observed moderate depression of the pressor reflex and more marked depression of the depressor reflex [8]. This would be consistent with attenuation of the increase in vagal tone in response to hypertension and a failure to decrease vagal tone and increase sympathetic tone in response to hypertension. However, studies on the effect of propofol on cardiovascular autoregulation have shown varied findings. For example, Samain and co-workers were unable to demonstrate a significant effect of propofol on pressor or depressor reflexes or on plasma concentrations of noradrenaline [18].

Relating autonomic activity directly to the power of the heart rate spectrum may be an oversimplification. Our understanding of the heart rate spectrum is based to a large extent on the reductions in spectral power caused by block with atropine and propranolol. Recent work has demonstrated that reduction in high frequency power may also result from an increase in parasympathetic tone [19]. These
authors suggest that control of vagal tone, and hence heart rate and modulation of this vagal tone by respiration, are separate phenomena.

Heart rate variability has also been correlated with the frequency and depth of inspiration with no relation to heart rate [20]. Blocking the effects of the vagus on the heart with atropine eliminates both the effects of vagal tone and its modulation by respiration. We observed a significant increase in ventilatory frequency with induction of anaesthesia, which might be expected to cause an increase in high frequency power, but there was an opposite effect. This could be explained by propofol and thiopentone interfering with the modulation of vagal tone by respiration.

We observed a marked effect of temazepam premedication on heart rate variability. In the models generated by GLIM for heart rate, low frequency power and total power, the effect of premedication was more significant than the other variables (table 1). We observed faster heart rates and greater low frequency, high frequency and total power in those patients who had received premedication. There was no difference in the ratio of low to ventilatory frequency power between the two groups. The effects of temazepam on heart rate variability have not been well documented to date. In a study comparing premedication with oral diazepam or i.m. midazolam, heart rate variability was reduced by midazolam but unaffected by diazepam [21]. Based on the usual interpretation of the heart rate spectrum, the increase in spectral power which we observed represents an increase in both sympathetic and parasympathetic autonomic activity. This is not consistent however, with other data examining the effects of benzodiazepines on autonomic activity. A study comparing the effects of induction of anaesthesia with diazepam or midazolam showed a reduction in the pressor baroreflex with both drugs. Diazepam depressed plasma noradrenaline concentrations, while midazolam decreased both plasma adrenaline and noradrenaline concentrations, and thus the authors concluded that both diazepam and midazolam cause a sustained reduction in sympathovagal activity [22].

As already discussed, it may be an oversimplification to interpret the heart rate power spectrum as a direct reflection of autonomic activity.

A decrease in high frequency power may indicate that temazepam interferes with modulation of vagal tone by respiration. The mechanism of low frequency heart rate variability is not fully understood. Thermoregulatory fluctuations in vascular tone and local autoregulation of blood flow and vascular tone are suggested to have a role in its production. The reduction in low frequency power produced by propranolol indicates that the sympathetic nervous system is important in low frequency modulation of heart rate, but this is only one of its many activities. It may be incorrect to interpret an effect of temazepam on low frequency heart rate variability as a manifestation of an overall reduction in sympathovagal activity. The benzodiazepines are thought to facilitate GABA-mediated inhibitory transmission, and it has been suggested that general anaesthetics affect the function of GABA-activated chloride channels [23]. While producing depression of the higher centres, the benzodiazepines may have more specific effects on the sympathetic control of cardiovascular function by facilitating GABA-mediated transmission in the brain stem or elsewhere. Further research into the effects of temazepam and the other benzodiazepines on specific indices of sympathetic activity, such as muscle sympathetic nerve activity, would therefore be interesting.

References


