HEART RATE VARIABILITY AND FENTANYL ADMINISTRATION

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ABSTRACT

This pilot study investigates the effect fentanyl has on heart rate variability (HRV) in the operating theatre. Many studies on the effect of anaesthetic agents on HRV include fentanyl in the anaesthetic mix but few studies look at the effect of fentanyl in isolation.

HRV uses changes in heart rate to indirectly observe changes in the activity of the autonomic nervous system and in particular, the relative changes in activity of the parasympathetic and sympathetic branches. Patients were studied in the 10 minutes before anaesthesia was induced with continuous ECG recording. A randomly selected dose of fentanyl was administered after 5 minutes.

Preliminary results with spectral analysis reveal a small effect on HRV with fentanyl administration. LF and HF power both decrease immediately after fentanyl administration and the LF/HF ratio slowly rises over a longer time period. This effect can be masked by application of the oxygen mask at the time of fentanyl administration.

KEY WORDS
Heart rate variability, fentanyl.

1. Introduction

Many studies have investigated the effect of anaesthetic agents on the autonomic nervous system by analysis of the HRV.[1-11] Fentanyl is one of the drugs that may be given as part of the anaesthetic package but few studies [9, 11] have looked at the effect of fentanyl on HRV in isolation from other anaesthetic agents.

Anaesthesia is bought about by using a combination of drugs to provide a balance between hypnosis (reduced neural activity, no memory), analgesia (reduced response to noxious stimuli, no pain) and neuromuscular blockade (paralysis or areflexia).[12] Fentanyl is a synthetic agent related to meperidine that is 100 times more potent than morphine.[13] It is given preoperatively and during induction of anaesthesia for its short-lived, fast-acting sedative qualities which allow patients to tolerate unpleasant procedures by relieving anxiety, discomfort, or pain. [14]

HRV measures changes in heart rate caused in part by the changing activity from the sympathetic and parasympathetic nervous system. HRV is commonly analysed using power spectral density which allows identification of the different aspects of ANS activity: the high-frequency (HF) component (0.15-0.5 Hz) is mediated by the parasympathetic nervous system, and the low-frequency (LF) component (0.04-0.15 Hz) is mediated by both the sympathetic and parasympathetic nervous systems. The low- to high-frequency (LF/HF) ratio is considered to be a useful index of cardiac sympathetic nerve activity. [15, 16]

A study on dogs in 1978 [17] showed fentanyl gave a dose-related depression of heart rate. After bilateral cervical vagotomies, the decrease caused by fentanyl was at most, 10% of the decrease in innervated dogs. This led the authors to conclude that the majority of the chronotropic action of fentanyl involved vagal efferent impulses. Fentanyl was first analysed with HRV in 1980 [18] looking at the effect of maternal fentanyl anaesthesia where it was found to give a loss of fetal HRV.

This pilot study investigates the effect fentanyl has on heart rate variability (HRV) in the operating theatre in relative isolation from other drugs used to induce anaesthesia.

2. Method

Patients were recruited if they were scheduled for minor surgical procedures, aged between 18 and 80 years, weight 40-120 kg, with a low frequency of ventricular arrhythmias (<10 premature complexes/hr), no history of cardiac-rate controlling drugs, and no clinical signs of peripheral neuropathies.
They were studied in the 10 minutes before anaesthesia was induced. Baseline ECG was recorded for 5 minutes then a standard dose of midazolam (2.5 milligram) was given, followed by a randomly selected bolus of fentanyl (50, 75, 100 or 150 microgram). A further 5 minutes of ECG was then recorded.

Oxygen was administered by facemask. The first subject had the mask and oxygen applied as the fentanyl was administered 5 minutes into the study. In order to investigate unexpected results from the first subject, the second subject had the mask and oxygen applied 5 minutes into the procedure, but no fentanyl was administered. The third subject had the oxygen mask applied at the start of the study with fentanyl administered 5 minutes into the study.

Two physiological monitors were used: one for analog ECG (Hewlett-Packard Model 78353B), the other for impedance respiration and SaO₂ (Datex-Ohmeda AS/3 Anaesthetic Monitor). Two sets of ECG electrodes were placed on the chest to give lead II configuration for both monitors. The analog ECG was digitised at 1000Hz with 12 bits resolution (National Instruments NI 6035E DAQ) and stored (LabView) for off-line analysis. Other physiological signals were collected at 300 Hz with proprietary software (Datex-Ohmeda S/5 Collect).

Analysis of the data was performed using software developed on a PC using MatLab (The MathWorks Inc., Natick, MA, USA). The ECG R-waves were identified by whichever of two methods produced the least artifacts: simple threshold or mean of backward differences.[19] Artifacts were visually identified by R-R intervals more than 30% from the mean R-R interval. The few remaining artifacts were visually identified and manually corrected. The R-R interval series (in msec) was linearly interpolated and sampled at 4 Hz to produce a data series with equally spaced intervals ready for spectral analysis.

Data, processed in 256 point segments (64 sec), was linearly detrended to remove its contribution to low frequency power, and then smoothed with a Hanning window that is commonly used in cardiovascular data analysis. Classical spectral estimation was performed using a standard fast Fourier transform algorithm. These segments were plotted on a 3 dimensional spectrum.

The spectral power was assessed over the range 0.03 Hz to 0.5 Hz. The spectral power was evaluated quantitatively and the data expressed in m²/Hz. Two frequency ranges were examined: low-frequency (LF) at 0.04 - 0.15 Hz, and high-frequency (HF) at 0.15 - 0.4 Hz.

Figure 1 Subject 1: Fentanyl administration at 5 minutes with oxygen mask application (arrow). a) 3D spectrum of complete protocol. b) LF, HF power and LF/HF ratio.

3 Results

Selected subjects were respectively 2 females and a male, aged 41, 43 & 54 years, weighing 61, 68 & 97 kg and received fentanyl doses of 75, 0 & 100 µg (i.e. 1.23, 0 and 1.01 µg/kg).

The first subject (Figure 1) who received 75 micrograms of fentanyl showed a definite change in the peak HF after the fentanyl was administered 5 minutes into the study. This can be viewed in the 3D spectrum as a shift in the frequency at which the peaks occur from ~0.2 Hz to ~0.15 Hz. There was no apparent difference in the LF or HF power, or in the LF/HF ratio.

The second subject (Figure 2) who received no fentanyl showed an increase in LF and HF power after mask and oxygen application.

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The third (Figure 3, 100 micrograms of fentanyl) and subsequent subjects had the mask and oxygen applied at the start of the study. The results show a decrease in both LF and HF power immediately after fentanyl administration and a slow increase in LF/HF ratio over a longer time period.
Figure 2 Subject 2: Application of mask and oxygen at arrow, no fentanyl administered. a) 3D spectra, b) LF & HF power and LF/HF ratio

4 Discussion

Most studies investigating HRV of anaesthetic agents analysed data before and after induction of anaesthesia and found decreased total autonomic nervous system activity and a shift of the balance between parasympathetic and sympathetic activities. [1-11]

The first subject in this pilot study did not show the expected decrease in autonomic nervous activity and led us to investigate further.

Table 1 Anaesthetic agents studied with HRV

<table>
<thead>
<tr>
<th>First Author</th>
<th>Anaesthetic agents</th>
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</thead>
<tbody>
<tr>
<td>Latson [1]</td>
<td>Sufentanol</td>
</tr>
<tr>
<td>Galletly [2]</td>
<td>Propofol</td>
</tr>
<tr>
<td>Deutschman [5]</td>
<td>Fentanyl or alfentanil, succinylcholine or vecuronium, &amp; propofol</td>
</tr>
<tr>
<td>Galletly [6]</td>
<td>Fentanyl, propofol, halothane or isoflurane</td>
</tr>
<tr>
<td>Pomfrett [7]</td>
<td>Propofol, fentanyl, nitrous-oxide in oxygen, isoflurane</td>
</tr>
<tr>
<td>Howell [8]</td>
<td>Temazepam &amp; thiopentone or propofol</td>
</tr>
<tr>
<td>Michaloudis [10]</td>
<td>Midazolam, morphine, and clonidine</td>
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</table>

Our results are different to that of Michaloudis et al [10] who noticed that premedication with morphine and clonidine depressed the LF component more than the HF component and the LF/HF ratio was decreased, suggesting parasympathetic dominance. However, their study used much larger doses than ours (e.g. morphine 0.15 milligram/kg).

Galletly et al [6] found HRV in those patients receiving fentanyl to decrease in all frequency bands and saw a shift
in power to <0.15 Hz but there was no major difference in HRV spectral response. They theorised, fentanyl should exert a parasympathomimetic effect on HRV but found no greater increase in HF (absolute or proportional) power or decrease in LF/HF ratio in the fentanyl groups as one might expect if there was a change in the balance of autonomic tone towards parasympathetic predominance.

Galletly et al [6] proposed that when studying patients who were breathing spontaneously it is probable that any respiratory depressant effect of the opioids might have offset the expected increase in HF power, as ventilators drive correlates with HF power [20, 21] and any carbon dioxide retention caused by the opioids would have altered the balance towards increased sympathetic tone. The observation of Galletly and colleagues are in line with our results.

5. Conclusion

Preliminary results with spectral analysis reveal a small effect on HRV with fentanyl administration. LF and HF power both decrease immediately after fentanyl administration and the LF/HF ratio slowly rises over a longer time period. This effect can be masked by application of the oxygen mask at the time of fentanyl administration.

References: