Influence of the vagus nerve on changes in heart rate during sleep apnoea in man

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Summary

1. The changes in heart rate surrounding a period of apnoeic asphyxia, produced by either central or obstructive sleep apnoea, are characteristically a progressive bradycardia during the apnoeic period followed by an abrupt reversal to tachycardia with resumption of lung inflation.

2. In a subject who had undergone bilateral pulmonary vagotomy with sparing of the cardiac branches on the left side, the bradycardia is still present during the apnoeic period; however, there is no abrupt response to lung inflation.

3. A subject who had undergone unilateral right-sided pulmonary vagotomy demonstrated a normal response, the increase in heart rate coinciding with resumption of airflow.

4. These findings are consistent with the hypothesis that the bradycardia of sleep apnoea is a hypoxia-induced chemoreflex and that reversal to tachycardia with resumption of lung inflation is a reflex with afferent fibres in the pulmonary vagus nerves.

Key words: asphyxia, chemoreceptor, heart rate, pulmonary inflation reflex, sleep apnoea, vagotomy, vagus.

Introduction

In recent years polygraphic monitoring has revealed many different populations who have arterial oxygen desaturation associated with periods of apnoea or disordered breathing during sleep [1]. This includes ostensibly normal people [2] and patients with obstructive airways disease [3, 4]. During an apnoeic period there is progressive asphyxia and, depending on the duration of the apnoea, in a given subject can be associated with profound levels of hypoxia [5]. Accompanying the hypoxia, in most cases, is a progressive slowing of the heart during the apnoeic period with an abrupt quickening coincident with the resumption of lung inflation [6, 7] (Fig. 1).

Recent animal studies have provided convincing evidence that the carotid body chemoreceptors play an important role in the responses of apnoeic bradycardia [8, 9] and that their reflex effects can be reversed by lung inflation [10]. From work on subjects who underwent carotid body resection for asthma, it is known that the bradycardia of breath holding in man is dependent upon the presence of the carotid body chemoreceptors [11]. From animal work [12] and other breath holding experiments, where normal subjects were taken to their 'breaking point' and then allowed to inhale a mixture of 10.5% O₂ and 6.5% CO₂, it is clear that mechanical lung inflation alone without altering blood gas tensions will reverse the heart rate response [10]. It is, however, not possible to deduce from these experiments whether the response of heart rate to lung inflation in man is due to respiratory centre activity, afferent nerve activity from receptors in the chest wall or a pulmonary vagal inflation reflex, which in terms of a Hering–Breuer reflex is generally considered to be weak in man [13].

This study makes observations in two subjects with obstructive airways disease and partial or
complete pulmonary vagotomy, together with control comparisons. Both these subjects underwent vagotomy for dyspnoea [14]. One had a right-sided vagotomy performed in the neck. The other had undergone bilateral pulmonary vagotomy with sparing of the left cardiac branches. Both subjects were studied overnight and experienced short periods of sleep apnoea.

Methods

Subjects

Details of age and lung function for both subjects and the controls are represented in Table 1.

Both subjects had severe emphysema, but were both well at the time of the study.

Subject no. 1 had undergone vagotomy 3 years previously, followed by left pulmonary vagotomy 2 years previously.

Subject no. 2 had undergone right vagotomy 6 years previously by division in the posterior triangle of the neck. Ventilation perfusion scanning had revealed that effective lung function was confined to the posterior segments of each lower lobe.

Subject no. 1 took 5 mg of nitrazepam as night sedation and 40 mg of frusemide daily for mild oedema. Neither subject suffered from any other relevant illness. Subject no. 1 was studied over 2 nights, subject no. 2 for 1 night.

Four control subjects all had obstructive airways disease (Table 1).

Sleep study

The following variables were monitored: electroencephalogram (C4-A1 from the international 10-20 placement system), left and right electrocugulogram. These three channels indicated the patients' alertness and allowed sleep staging. Respiration was monitored by impedance pneumography (Hewlett-Packard 78202B) and two thermocouples indicating airflow at the nose and mouth. The impedance pneumogram used the left arm and right arm ECG chest electrodes. Owing to the proximity of the electrodes this gave an indication of chest wall movement only and no real information of lung volume. No abdominal movement was measured. Oxygen saturation was measured continuously with an ear oximeter (Hewlett-Packard 47201A); ECG lead 2 was also recorded. These data were recorded on paper at 7-5 mm/2 via the spare channels of the EEG machine (Officine Galileo E14a) and recorded on half-inch tape with a Racal Thermionics recorder.

Subsequently selected parts of the data were played back from tape via rate computers (Hewlett-Packard) producing instantaneous cardiac rate, and amplifying the oximeter signal (Hewlett-Packard medium gain amplifier). These data were recorder simultaneously on a Gould Accuchart Brush recorder at 5 mm/s (Figs. 1-3).

Results

In the four control subjects nine apnoeic episodes were observed.

Fig. 1 shows a typical event occurring in a control subject and demonstrates an obstructive apnoeic episode of approximately 28 s duration. This episode is associated with a desaturation of 9% and it may be seen that during the apnoea there is a progressive bradycardia, which rapidly reversed to sustained tachycardia coincident with resumption of airflow, as indicated by nasal and oral flow signals. This change in heart rate is acknowledged as typical [16, 71]. The event shown in Fig. 1 is taken from non-rapid eye movement (non-REM).

Subject no. 1 (bilateral pulmonary vagotomy) slept for 5.8 h on night 1 and 4.7 h on night 2 and experienced a total number of 13 desaturations of more than 5% saturation. Of these 13 desaturations seven were apnoeic and six hypopnoeic. Fig. 2 shows an obstructive apnoea in the bilateral vagotomized subject associated with desaturation. It may be seen that the sustained increase in heart rate is not coincident with resumption of airflow as in Fig. 1 but is delayed by approximately 5-5 s.

Subject no. 2 (unilateral right vagotomy) slept for 4-3 h and experienced eight periods of desaturation of more than 5% and was apnoeic rather than hypopnoeic in four of these.

The alterations in oxygen saturation, heart rate and the time between the resumption of airflow
Heart rate and sleep apnoea

Fig. 1. Obstructive apnoea in a control subject. (a) Respiration (inspiration upwards); (b) nasal airflow (the arrow indicates the point taken as representing resumption of airflow); (c) oral airflow; (d) instantaneous heart rate; (e) amplified oximeter signal (the oximeter has a 2-3 s, 67% response time). Note decrease in heart rate with decrease in oxygen saturation, and rapid increase coincident with resumption of airflow. The diagram in the bottom right-hand corner represents the normal thoracic vagal anatomy present in this subject, with left vagus (LV) and right vagus (RV) dividing into branches to the heart (H) and right and left lungs (RL, LL).

Fig. 2. Obstructive apnoea in a bilaterally pulmonary vagotomized subject. Results are presented as described in Fig. 1. The diagram (bottom right) represents the left cardiac branches (H) of the left vagus (LV), left intact in this subject. Note the overall decrease in heart rate during apnoea with no immediate response in heart rate to the resumption in airflow. A gradual increase in heart rate occurs approximately 5 s after the resumption of regular airflow.

and the increase in heart rate are summarized in Table 2. It may be seen that the mean delay between the resumption of airflow and the increase in heart rate is 1.4 ± 0.2 s in control subjects and 4.8 ± 1.0 s in bilaterally vagotomized subjects, which gives a significant difference at the 5% level with Student’s t-test. There is no significant difference between control
and unilaterally vagotomized subjects, either in terms of the delay between airflow and the increase in heart rate (mean 1.1 ± 0.1) or the rate of increase of heart rate.

**Discussion**

The most likely explanation for the observed heart rate changes coincident with an apnoeic period (cardiac slowing during apnoea with quickening on resumption of lung inflation) is provided by the work of Angell-James & Daly [12]. In this work on dogs they showed that the primary response to combined carotid and aortic chemoreceptor stimulation was bradycardia. Furthermore they showed that this response can be completely over-ridden by an inflation reflex arising in the lungs. They concluded therefore
that, in the intact animal, chemoreceptor stimulation produces different effects depending upon other variables, the final response of chemoreceptor stimulation being the result of a number of other mechanisms [10]. In man the cardiac slowing during apnoea, which is known to be vagally mediated [6], would appear to be the pure primary chemoreceptor response to apnoeic asphyxia, as this response is absent in subjects who have undergone carotid body resection [11]. This bradycardia is reversed on resumption of lung inflation. Despite considerable intrathoracic volume changes occurring during obstructive apnoea this is known to cause only minimal stretch receptor discharge [15], and lung inflation with airflow is required to reverse the bradycardia. Tilkian et al. [6] argue that this characteristic pattern of heart rate change (Fig. 1) is an extreme form of sinus arrhythmia. This may be misleading because the centrally produced component of sinus arrhythmia is commonly seen to persist throughout an obstructive apnoeic period with bradycardia, coincident with the attempts at inspiration (Fig. 3), and also because this implies that there is some central mechanism which causes the respiratory and cardiac disturbance. That at least the early part of the cardioacceleration after bradycardia is a reflex effect of lung inflation is substantiated by the fact that the cardiac response occurs in less than 1.5 s after the commencement of the increase in lung volume, whereas any central or chemoreceptor reaction to an alteration of blood gases secondary to lung inflation would probably not be manifested for approximately 5 s as this is the lung–carotid body circulation time in man [16]. The absence of the rapid increase in heart rate in the pulmonary vagotomized subject, presented here, also supports the argument that the increase in heart rate is reflex in origin with the afferent pathway lying in the pulmonary vagus nerves, rather than a result of central or chest wall effects.

In the subject with bilateral pulmonary vagotomy the time lag between the onset of regular breathing and the increase in heart rate is approximately 5 s (similar to the lung–carotid body circulation time), suggesting that the withdrawal of chemoreceptor stimulation from apnoeic asphyxia is responsible for the increase in heart rate in this case. This finding is in agreement with the work of Drysdale, who showed that the primary effect of withdrawal of arterial chemoreceptor stimulation by hypercapnic hypoxia in man is tachycardia [16].

The only other subject known to have had bilateral pulmonary vagotomy was studied over 2 nights but unfortunately experienced no apnoeic episodes; however, the results in this subject strongly suggest that a pulmonary vagal inflation reflex is responsible for the over-riding effect of lung inflation over chemoreceptor effects after apnoea.

References