The effect of remifentanil on respiratory control, assessed from resting physiological variability

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***Abstract* — We evaluated the influence of a steady state infusion of a model opioid, remifentanil, on respiratory variability during spontaneous respiration in a group of 11 healthy human volunteers. We used linear and nonlinear dynamic models to examine the effects of remifentanil upon both directions of the ventilatory loop, i.e. on the influence of natural variations in end-tidal carbon dioxide ($P_{ET}CO_2$) on ventilatory variability, and vice versa. Breath-by-breath recordings of expired CO_2 and respiration were made, for 15 minutes at estimated effect site (i.e. brain tissue) concentrations of 0, 0.7, 1.1, and 1.5 ng/ml respectively. The results revealed a decrease in the strength of the dynamic effect of $P_{ET}CO_2$ variability on V_T and an increase in the effect of V_T variability upon $P_{ET}CO_2$. Nonlinear models explained these dynamic interrelationships better than linear models. Our approach allows detailed investigation of drug effects in the resting state using non-invasive and minimally perturbing experimental protocols, which can closely represent real life clinical situations.**

I. Introduction

Respiratory depression is the most common serious side effect of opioid drugs [1]. Opioids are prescribed to millions of patients around the world every day, often in unmonitored environments; therefore, avoiding respiratory depression remains an important clinical aim. Opioids depress chemosensitive and rhythm generating centers in the brainstem [2], leading to slowing and increasing irregularity of the respiratory rhythm [3].

Much of the understanding of human respiratory control is based upon characterization of the ventilatory feedback loop, which is shown in Fig. 1 in a simplified form, supplemented by inferences from work in animals.

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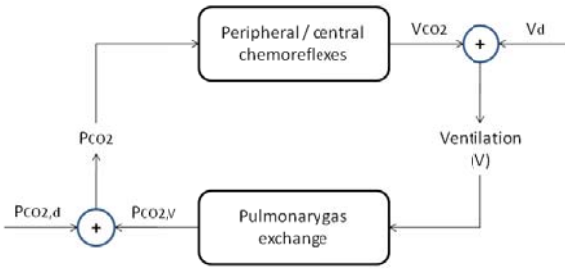

Fig. 1. Simplified diagram of the ventilatory feedback loop. Spontaneous ventilatory variability arises from a chemical component V_{CO2} that is due to variations in arterial CO_2 tension variability P_{CO2}, and a non-chemical component V_d (disturbance term, which includes sighs) that is due to all other physiological influences. Similarly, spontaneous P_{CO2} variability arises from a ventilatory related component $P_{CO2,V}$ that is due to variations in V_T and a non-ventilatory related component $P_{CO2,d}$.

Ventilatory responses are usually examined during hypoxic or hypercapnic stimulation [4]; specifically, depression of these responses by opioids has been well reported [5][6]. Moreover, it has been shown that spontaneous breath-to-breath fluctuations in end-tidal CO_2 ($P_{ET}CO_2$) are responsible for a considerable fraction of the normal variability in tidal volume (V_T) [7], and the dynamic effects of these spontaneous fluctuations have been used to derive information on ventilatory feedback [8], [9]. This breath-to-breath variability has been modulated with background hyper- and hypocapnia [10] but has not yet been applied to investigation of drug action.

In the present paper we have examined the effect of remifentanil infusion on respiratory control by quantifying the dynamic interrelationships between $P_{ET}CO_2$, V_T and breath-to-breath ventilation (V_T/T_{TOT}, where T_{TOT} is total breath time) in both causal directions of the ventilatory loop. For this purpose, we have used a nonlinear modeling approach (Laguerre expansion technique) [11]. First, we considered the dynamic influence of spontaneous $P_{ET}CO_2$ fluctuations on ventilatory variability (the forward part of the ventilatory loop), whereby the latter was assessed by tidal volume and breath-to-breath ventilation. Subsequently, we examined the influence of ventilatory variability on $P_{ET}CO_2$ (the reverse part of the ventilatory loop) by reversing the roles of input and output. We hypothesized that remifentanil, by depressing chemoreceptor responsiveness, would decrease the influence of $P_{ET}CO_2$ fluctuations on ventilatory variability. On the other hand, we were unsure whether the relationship between ventilatory variability and $P_{ET}CO_2$ variability would remain unaffected.

II. METHODS

A. Subjects and experimental protocol

This study was approved by the Oxfordshire Clinical Ethics research committee. Eleven healthy volunteers (age 27±5 years) were examined. The subjects wore a tight fitting facemask attached to a modified T-piece breathing system. The fresh gas flow rate was 30 litres per minute to eliminate rebreathing of expired gases. Since respiratory depression may cause hypoxemia, which causes activation of peripheral chemoreceptors in the carotid bodies and stimulates respiration, we maintained end-tidal oxygen ($P_{ET}O_2$) tension at 30 kPa. A target-controlled infusion of remifentanil was delivered via an indwelling intravenous cannula inserted into a vein in the left forearm. Stepwise ascending effect site concentrations of zero (baseline), 0.7, 1.1 and 1.5 ng/ml were maintained with a computer-controlled infusion pump (Graseby 3500 TCI). We chose relatively low doses of remifentanil to investigate the subtle changes in respiratory control seen at clinically relevant opioid analgesia, as opposed to the much higher doses used in anesthesia.

Oxygen saturations, heart rate, $P_{ET}CO_2$ and $P_{ET}O_2$ were monitored continuously using a Datex Cardiocap II (Datex Instrumentarium), respiratory volume and timing was measured with a turbine respiratory flow meter (VMM-400, Interface Associates). Following a minimum of ten minutes to adapt to the mask, the baseline recordings were taken for 15 minutes, and then for each level of remifentanil. Five minutes were allowed to reach target effect site concentration; continuous recordings were made for the following 15 minutes at that stable effect site concentration.

B. Mathematical Methods

The general Volterra model for a Q-th order nonlinear system is:

$$y(n) = \sum_{q=0}^{Q} \sum_{m_1=0}^{M} \dots \sum_{m_q=0}^{M} k_q(m_1,\dots,m_q) x(n-m_1)\dots x(n-m_q) \quad (1)$$

where $x(n)$ and $y(n)$ are the system input and output respectively (both $P_{ET}CO_2$ and V_T or V_T/T_{TOT} assume the roles of input and output), M is the system memory and $k_q(m_1,\dots,m_q)$ are the Volterra kernels of the system, which describe the linear (Q=1) and nonlinear (Q>1) dynamic effects of the input on the output. Eq. (1) reduces to the convolution sum for linear systems, with $k_1(m)$ corresponding to the impulse response of the system.

The impulse response or Volterra kernels can be estimated efficiently from the input-output data, by utilizing function expansions in terms of the orthonormal Laguerre basis:

$$k_q(m_1,\dots,m_q) = \sum_{j_1=0}^{L} \dots \sum_{j_q=j_{q-1}+1}^{L} c_{j_1\dots j_q} b_{j_1}(m_1)\dots b_{j_q}(m_q) \quad (2)$$

where $c_{j1\dots jn}$ are the expansion coefficients, $b_j(m)$ is the j-th order Laguerre function and L+1 is the total number of functions that yields an adequate system representation. In matrix form:

$$\mathbf{y}=\mathbf{V}\mathbf{c}+\boldsymbol{\varepsilon} \quad (3)$$

where $\mathbf{V}$ is a matrix that contains the convolution of $x(n)$ with the Laguerre functions $\{b_j\}$ and their second (or higher) order products. The expansion coefficients can be obtained as the least-squares solution of (3) [11]:

$$\mathbf{c}_{est}=[\mathbf{V}^T\mathbf{V}]^{-1}\mathbf{V}^T\mathbf{y} \quad (4)$$

We used the normalized mean-square error (NMSE) of the output prediction to assess model performance and determine the model complexity (i.e., L and Q) with a statistical criterion [12]. For the chemoreflex pathway ($P_{ET}CO_2 \rightarrow$ V, where V corresponds to either V_T or V_T/T_{TOT}) sighs, which were defined as breaths with values greater than 1.5 times the mean breath value were removed by linear interpolation before model estimation, as they are viewed as part of the disturbance component of V (V_d in Fig. 1). Furthermore, a pure time delay of 2 breaths was hypothesized in the effects of $P_{ET}CO_2$, in order to account for the previously described transport delays in the action of $P_{ET}CO_2$. Sighs were not removed for the reverse pathway (V $\rightarrow P_{ET}CO_2$), since they are a significant determinant of $P_{ET}CO_2$ changes. The spectral power (SP) of the first- and second-order kernels was calculated by integrating their discrete-time Fourier transforms from 0 to 0.3 cycles/breath for k_1 and from [0 0] to [0.3 0.3] cycles per breath for k_2. Changes in the steady-state values and the SP of the respiratory variables, as well as in the SP of the first and second-order kernels were assessed by using repeated measures ANOVA.

III. RESULTS

The effects of remifentanil on the respiratory variables are shown in Table I. We observed a dose-dependent decrease in respiratory rate that was due to increases in duration of expiratory time (T_E). V_T initially decreased but increased at higher levels towards baseline values. $P_{ET}CO_2$ increased and became more variable. The SP of $P_{ET}CO_2$ and V_T between 0 and 0.3 cycles/ breath revealed an increase over the entire frequency range for $P_{ET}CO_2$ and a less pronounced increase for V_T above 0.02 cycles/ breath.

The prediction NMSEs obtained by linear and nonlinear models (Q=1, 2) for both pathways of the ventilatory loop are given in Table II. Nonlinear models improved model performance in both pathways. For the forward part of the loop ($P_{ET}CO_2 \rightarrow$ V) we also observed a dose-dependent reduction in the NMSE values during remifentanil (nonlinear models), which suggests that a larger fraction of the respiratory variability is caused by $P_{ET}CO_2$ changes. Similar results were obtained for V_T/T_{TOT}.

TABLE I
RESPIRATORY PARAMETERS

	Baseline	0.7 ng/ml	1.1 ng/ml	1.5 ng/ml
$P_{ET}CO_2$ (kPa)	5.4 (0.3)	5.8 (0.4)**	5.9 (0.4)**	6.2 (0.6)**
SP $P_{ET}CO_2$	1.2 (1.1)	2.6 (1.5)**	3.3 (2.9)	4.0 (2.6)**
$P_{ET}O_2$ (kPa)	30 (1)	30 (1)	30 (2)	29 (2)
V_T (ml)	412 (134)	348 (128) *	360 (114)	384 (144)
SP V_T	$1.7\cdot10^5$ (1.3)	$1.8\cdot10^5$ (1.7)	$3.2\cdot10^5$ (3.3)	$2.5\cdot10^5$ (2.3)
T_I (s)	1.5 (0.3)	1.6 (0.4)	1.6 (0.5)	1.6 (0.5)
T_E (s)	2.7 (0.4)	3.8 (0.8)**	4.7 (1.6)**	5.2 (2.1)**
V_T/T_{TOT} (ml/s)	100.2 (23.3)	64.0 (23.6) **	60.8 (20.6) **	61.5 (22.3) **
SP V_T/T_{TOT}	436.0 (233.9)	494.2 (323.7)	658.9 (430.2)	989.4 (1274.5)
HR	56.8 (7.8)	55.8 (7.1)	54.8 (9.3)	55.9 (8.3)

Values are mean (SD). * P<0.05 ** P<0.01 with respect to baseline.

TABLE II
PREDICTION NMSES FOR THE FORWARD AND REVERSE PATHWAYS OF THE VENTILATORY LOOP

	NMSE [%] Mean (SE)			
	$PETCO_2$->V_T		V_T ->$PETCO_2$	
Baseline	87.6 (2.0)	71.0 (2.9)	71.1 (5.0)	53.3 (4.6)
0.7 ng/ml	87.3 (3.0)	62.6 (3.6)	67.5 (5.5)	46.6 (4.6)
1.1 ng/ml	89.4 (1.6)	62.1 (3.9)	79.7 (1.6)	58.8 (3.8)
1.5 ng/ml	87.1 (2.5)	57.9 (3.7)	78.6 (4.4)	54.3 (4.5)

Representative data sets used for model estimation (baseline) are shown in Fig. 2, along with the corresponding linear and nonlinear model predictions. $PETCO_2$ variations mainly account for the V_T post-sigh response, as sighs are clearly correlated with sharp $PETCO_2$ drops, which in turn influence V_T. These sharp drops are accounted by the V_T → $PETCO_2$ model. In the frequency domain, the incorporation of nonlinear model terms improved performance over a wide range of frequencies below 0.03 cycles/breath.

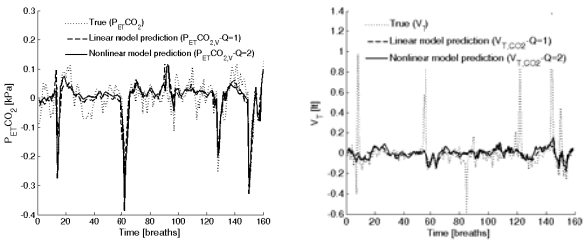

Fig. 2. $PETCO_2$ and V_T time series (dotted lines) during baseline, used for model estimation in both pathways of the ventilatory loop, and corresponding model predictions ($PETCO_{2,V}$ and $V_{T,CO2}$ respectively, solid lines). The large drops in $PETCO_2$ induced by sighs are clearly accounted by the V_T → $PETCO_2$ model (left), while $PETCO_2$ changes account mainly for the post-sigh V_T response (right).

The averaged impulse responses (Q=1 in (1)) for the forward part of the ventilatory loop are displayed in Fig. 3, when both V_T (blue) and V_T/T_{TOT} (black) were used to assess ventilatory variability. The form of the averaged impulse response during baseline suggests that an increase in $PETCO_2$ will cause an increase in V_T (or V_T/T_{TOT}), with the maximum instantaneous effects occurring at 4 and 8 breaths after the $PETCO_2$ increase. The impulse response values generally decreased during remifentanil infusion, with the decrease being more evident for the second peak.

The impulses responses of Fig. 3 in the frequency domain during baseline exhibit a main resonant peak occurring between 0.04 and 0.08 cycles/ breath. These characteristics were less consistent during remifentanil infusion, with the main resonant peak being shifted to lower frequencies. The averaged impulse response for the reverse branch of the ventilatory loop (V → $PETCO_2$) is shown in Fig. 4 for both V_T (blue) and V_T/T_{TOT} (black). Its form suggests that an increase in ventilation will lead to a decrease in $PETCO_2$, with the maximum effects occurring within the first 2 breaths. The dynamic effects of these changes cease before 20 breaths. Remifentanil did not alter these characteristics; however, the impulse response values increased at all levels, suggesting a stronger dynamic effect of ventilatory variability on $PETCO_2$.

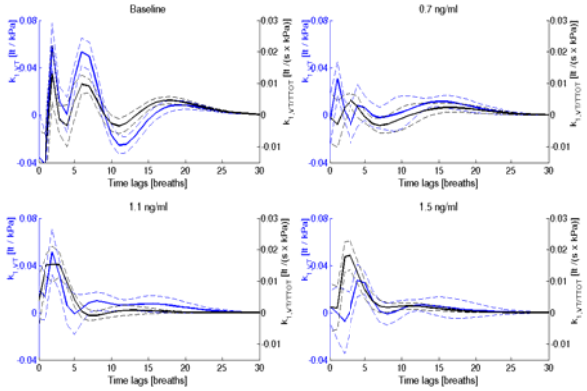

Fig. 3. Averaged impulse response for the chemoreflex pathway, whereby both VT (blue) and VT/T_{TOT} (black) were used to assess ventilation. Remifentanil decreased the impulse response values.

The above observations are quantified by the SP of the first- and second-order kernels for both pathways shown in Fig. 5. For the chemoreflex branch (left), a decrease was observed in the SP of k_1 and k_2. This decrease was statistically significant only during the lowest level of remifentanil infusion for V_T; however, more pronounced differences were observed when V_T/T_{TOT} was used as the model output. For the reverse pathway (right), the SP of k_1 increased significantly (P<0.01 during all remifentanil levels for V_T). The SP of the second-order model components k_2 increased as well (P<0.05 at 0.7 ng/ml).

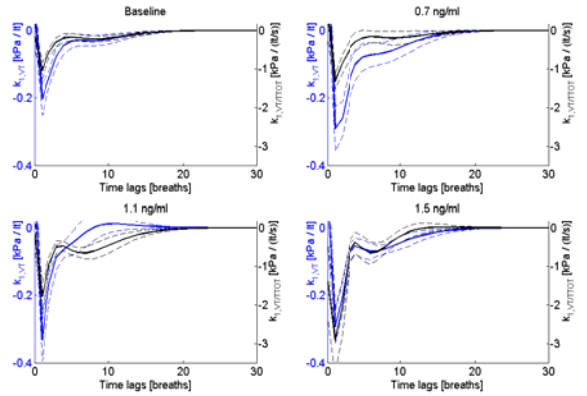

Fig. 4. Averaged impulse response for the V → $PETCO_2$ pathway when both V_T (blue) and V_T/T_{TOT} (black) were used as measures of ventilatory variability. A main negative peak is observed at 1 breath. The impulse response drops to zero before 20 breaths in all cases. The impulse response values increased considerably at all infusion levels.

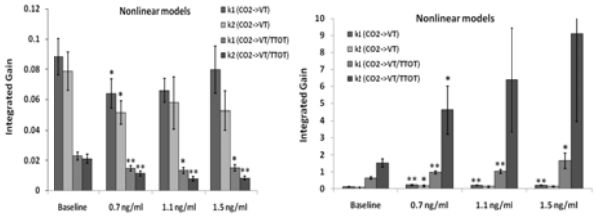

Fig. 5. Spectral power of the first and second-order Volterra kernels for the chemoreflex (left) and reverse (right) pathways. The spectral power of both the linear and nonlinear chemoreflex components between 0 and 0.3 cycles/ breath decreased during remifentanil infusion. * P<0.05, ** P<0.01 compared to baseline.

IV. Discussion

We have demonstrated that infusion of remifentanil leads to increased irregularity of the respiratory pattern during spontaneous respiration. Moreover, it decreased the strength of the dynamic effect of natural $P_{ET}CO_2$ variability on tidal volume and breath-to-breath ventilation, but increased the reverse relationship, i.e., the effect of ventilatory variability on $P_{ET}CO_2$. Nonlinear, rather than linear, models best described these dynamic relationships. Collectively, these findings suggest the potential use of data-driven approaches to identify drug-induced changes on respiratory control on a systems level, employing minimally invasive protocols.

The influence of the spontaneous variability of $P_{ET}CO_2$ on fluctuations of breath-to-breath V_T variability has been demonstrated by application of a $P_{ET}CO_2$ buffering technique [7]. Moreover, coherent oscillations between $PETCO_2$ and mean inspiratory flow V_I/T_I in the frequency domain, in agreement with a closed-loop model of the chemoreflex feedback, have been reported [9]. In order to quantify these correlations, we have employed a nonlinear approach that extends the aforementioned observations to both pathways of the ventilatory loop.

The high NMSE values for both pathways reflect the fact that the resting variability of $P_{ET}CO_2$ and V is determined by many factors. Significant influences that are part of the disturbance signal (non-chemical respiratory drive) V_d are exerted by cortical centres (behavioural, volitional modulation), the reticular activating system during wakefulness, as well as changes in cardiovascular parameters (e.g. cardiac output, cerebral blood flow oscillations) [13]. Our results (nonlinear models) suggest an increase in the chemical drive of ventilation during remifentanil infusion. Since the magnitude of the $P_{ET}CO_2 \rightarrow$ V model dynamics decreased, this increase was due to the increased $P_{ET}CO_2$ variability. Likewise, the $P_{ET}CO_2$ disturbance signal is influenced by the aforementioned and other factors, such as metabolism, level of arousal, sleep state and PaO_2 level [14].

The presence of nonlinear dynamics in spontaneous respiratory volume variability has been reported [15]. The steady-state chemoreflex response, i.e. the relation between the mean values of $P_{ET}CO_2$ and ventilation has been shown to be relatively linear; however, in the present study we are examining the dynamic relation between spontaneous fluctuations around the mean values. Regarding the reverse branch, it has been suggested that the influence of V_T on CO_2 exhibits nonlinear characteristics in the case of large V_T variations [9]. The Laguerre expansion technique was used in [16] to obtain the loop gain in normal subjects and patients with obstructive sleep apnea. However, the ventilatory impulse response was estimated as a whole, whereas we have examined the two branches separately.

The form of the impulse response between $P_{ET}CO_2$ and V agrees qualitatively with the previously described effects of $P_{ET}CO_2$ on ventilation, i.e., an increase in $P_{ET}CO_2$ results in an increase in ventilation some breaths later. The spectral peaks of the $P_{ET}CO_2 \rightarrow$ V dynamic models during baseline agree with the results of [9], where coherent oscillations between $P_{ET}CO_2$ and V_I/T_I below 0.15 cycles/breath with a peak at 0.08 cycles/breath were reported. The multi-phasic characteristic observed during baseline possibly reflects the closed loop nature of respiratory control, as an initial perturbation in $P_{ET}CO_2$ will cause a change in tidal volume that has an opposite effect on $P_{ET}CO_2$. The spectral power of the $P_{ET}CO_2 \rightarrow$ V system dynamics decreased during remifentanil administration, suggesting decreased chemosensitivity. We speculate that the increased $P_{ET}CO_2$ variability seen in the present study may help maintain ventilation during opioid-induced respiratory depression.

The waveforms of the V $\rightarrow$ $P_{ET}CO_2$ impulse responses correspond to the well-known effects of respiratory changes, i.e., an abrupt increase in V_T (or V_T/T_{TOT}) results in a rapid decrease in $P_{ET}CO_2$. Remifentanil infusion did not have a profound effect upon the timing of the V $\rightarrow$ $P_{ET}CO_2$ impulse responses; however, its increased values suggest increased $P_{ET}CO_2$ sensitivity to ventilatory changes. Hypercapnia may contribute to this increased, due to greater CO_2 excretion per breath as a simple mass effect, as similar observations have been reported during sleep, which also induces hypercapnia.

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