

# Loop gain in severely obese women with obstructive sleep apnoea



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## ABSTRACT

Our objective was to assess whether obstructive sleep apnoea (OSA) patients were characterised by a reduced central CO<sub>2</sub> controller gain (CG) and an enhanced plant gain (PG). We matched three groups of women ( $n = 10$  per group) enrolled in a previous study (Essalhi et al., J. Asthma. 50: 565–572, 2013): obese women with a respiratory disturbance index (RDI)  $\geq 15$ /h and with a RDI  $< 15$ , and lean women without OSA (RDI  $< 5$ ). Tidal ventilation recordings during wakefulness with end-tidal PCO<sub>2</sub> monitoring allowed the assessment of loop gain (LG) and its components (PG and CG).

LG were similar for the three groups ( $p = 0.844$ ) while both PG and CG depicted significant differences ( $p = 0.046$  and  $p = 0.011$ , respectively). Obese women with OSA were characterised by an increased PG and a reduced CG as compared to obese women without OSA. A negative relationship between CG and RDI ( $\rho = -0.46$ ,  $p = 0.008$ ) was evidenced.

In conclusion, OSA in women is associated with a reduced central CO<sub>2</sub> controller gain and an enhanced plant gain.

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## 1. Introduction

It has been recently debated whether elevated loop gain is a consequence or a cause of obstructive sleep apnoea (OSA) (Younes, 2014). As stated by Younes (2014), in a closed loop system, such as the breathing system, a perturbation in the controlled loop component (the respiratory apparatus, or ‘plant’) elicits changes in the feedback (blood gas tensions) received by the controller (respiratory centres), which in turn effects a compensatory response in the plant. Loop gain is the ratio of the initial response to the initial perturbation. Loop gain is determined by: (a) how much blood gas tensions deteriorate before the controller can reverse the trend (maximal changes), and (b) how much the controller will respond to these maximal changes (‘controller gain’). Maximal changes are determined by the time course of changes in gas tensions after the onset of hypopnoea and the time it takes to elicit a ventilatory response (‘delay’). The longer the delay, the greater the maximal changes and the higher the plant gain.

When respiratory mechanical impedance is fairly constant, such as in patients with a stable upper airway, delay is strictly a func-

tion of the lung–carotid circulatory delay. Under such conditions recurrent apnoeas or hypopnoeas occur when circulatory delay is abnormally long (heart failure), plant gain is high (low lung volume, etc.) and/or high ventilatory responses to CO<sub>2</sub> and hypoxia. Loop gain under such conditions predominantly reflects the behaviour of chemoreceptor-mediated feedback loops (chemical loop gain concept). On the opposite, in OSA patients with unstable upper airways during night, the increased loop gain is mainly the result of the obstructive event itself (increased delay related to event duration).

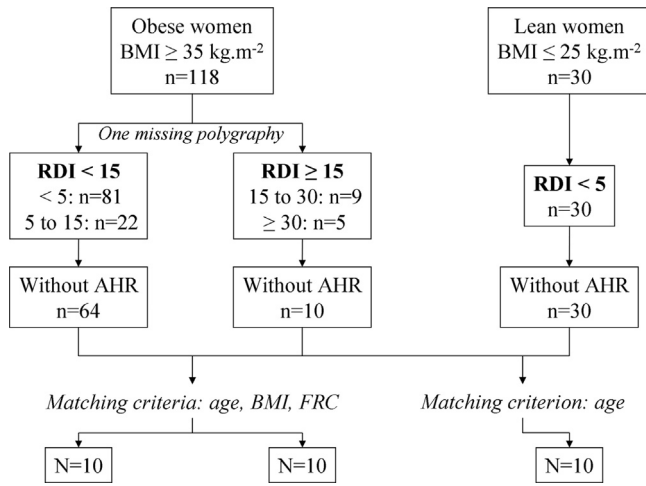
In OSA the chemical challenge is brief stimulation by a mixture of hypoxia and hypercapnia (asphyxia), which further makes harder its evaluation (both O<sub>2</sub> and CO<sub>2</sub> loop gains are involved). Finally, CO<sub>2</sub> loop gain depends on the responsiveness of both peripheral and central chemoreceptors, which may be oppositely regulated (Loewen et al., 2009). Our objective was to assess whether OSA patients were characterised by a reduced central CO<sub>2</sub> controller gain, as suggested by Loewen et al. (2009) and an enhanced plant gain, as suggested by Hudgel and colleagues (Hudgel et al., 1998).

To evaluate chemical loop gain in OSA patients it is necessary to measure it when upper airway is stable, for example by measuring ventilatory responses during wakefulness. We previously conducted a trial designed for the description of airway responsiveness/asthma and dyspnoea in severely obese women as compared to lean women (Essalhi et al., 2013a,b). During wakefulness Tidal ventilation and end-tidal PCO<sub>2</sub> were obtained in order to describe the variability of resting ventilation. We thus matched three groups

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**Fig. 1.** Flow-chart describing the selection process of the 30 included women. RDI denotes respiratory disturbance index evaluated during overnight polygraphy, while AHR denotes airway hyperresponsiveness determined by metacholine challenge test (dose-response slope  $\geq 2.39\%$  decrease/ $\mu\text{mol}$ ).

of women, obese with OSA, obese without and OSA and lean healthy women, and analysed Tidal ventilation recordings to assess  $\text{CO}_2$  loop gain and its components, namely plant and central controller gains.

## 2. Methods

### 2.1. Patients and control subjects

We previously conducted a prospective study involving both obese women (referred for bariatric surgery) and healthy lean women (Essalhi et al., 2013a, 2013b). The selection process of the thirty women included in the present study is described in a flow-chart (Fig. 1). It has been demonstrated that loop gain decreases with age (Edwards et al., 2014) and based on theoretical grounds, FRC (and BMI) would affect plant gain (Plataki et al., 2013). Consequently, matching criteria were age for the three groups, and BMI and FRC% predicted for the two obese groups. Airway hyperresponsiveness was a non inclusion criterion since we recently showed that plant gain is modified in patients with hyperventilation (manuscript submitted), a disorder frequently associated with asthma. Ten obese women with moderate to severe OSA (respiratory disturbance index  $\geq 15$ , see below) were available. These 10 women were then matched with 10/30 lean women and with 10/64 obese women without OSA or with mild OSA. Due to lower age and BMI, we were unable to find 10 women without OSA satisfying the matching criteria with obese women with moderate to severe OSA (older women), thus women with moderate to severe OSA were compared to women with no OSA or mild OSA (age non significantly different).

### 2.2. Tidal ventilation assessment

Breathing pattern at rest was measured by a pneumotachograph placed at the outlet of a full-face mask as previously described (Essalhi et al., 2013a,b). End-tidal  $\text{PCO}_2$  ( $\text{PET}_{\text{CO}_2}$ ) was continuously monitored and flow and  $\text{PET}_{\text{CO}_2}$  signals were digitised. Tidal ventilation parameters were automatically analysed and stored.

#### 2.2.1. Variability of resting ventilation

The variability of  $V_T$  often depicts a non-normal distribution; as a consequence, the coefficient of variation of  $V_T$  is a crude indicator. We thus described  $V_T$  variability using the slope of the linear

regression through the long tail of the probability density distribution on a log-log graph as previously described (Essalhi et al., 2013a,b).

#### 2.2.2. Loop gain assessment

The influence of chemoreflexes on respiratory variability in healthy subjects (Tidal ventilation in room-air breathing) has previously been demonstrated (Van den Aardweg and Karamaker, 2002). The model used quantifies the inter-relationships among spontaneous fluctuations in breath-to-breath values of ventilation and end-tidal  $\text{CO}_2$  by characterising the “transfer path” between each pair of variables, and has recently been described (Gederi et al., 2014; Nemati et al., 2011). The transfer path between  $\text{CO}_2$  and ventilation defines the controller gain for  $\text{CO}_2$ . Likewise, the  $\text{CO}_2$  plant gain is equal to the transfer path function between ventilation and  $\text{CO}_2$ . The product of controller and plant gains for  $\text{CO}_2$  is the loop gain. Loop gain is a frequency dependent quantity. Values of gains were given for the low (0.005–0.017 Hz), medium (0.017–0.05 Hz) and high frequencies ranges (0.05–0.125 Hz) as previously done (Nemati et al., 2011). Nevertheless, unless stated, gain refers to that of low frequencies range because this range is similar to that of respiratory disturbance index (0.0064–0.0139 Hz, see Table 1).

Preprocessing and bivariate autoregressive modeling were performed accordingly to Nemati et al. (2011). Controller, plant, and loop gain for  $\text{CO}_2$  were calculated.

Briefly, the start and end of inspiration were determined by detecting local maxima and minima of the tidal volume signal and were confirmed visually. Minute ventilation ( $\dot{V}_E$ ) was calculated for each breath as  $V_T/T_T$  (total time of respiratory cycle).  $\text{PET}_{\text{CO}_2}$  was calculated by taking the maximum value of  $\text{PCO}_2$  signal during an expiratory phase. In order to obtain perfect match between the each set ( $V_T$ ;  $\text{PET}_{\text{CO}_2}$ ) a dead volume was fixed for each subject, which valued typically 170 ml.

Bivariate autoregressive modeling: Our model represents the two key variables ( $\text{PET}_{\text{CO}_2}$ ) as linear functions of their history and random fluctuations. A bivariate model with maximal lag (or memory) of  $p$  breaths that describes the interactions between the ventilation and  $\text{PET}_{\text{CO}_2}$  can be represented by the following vector autoregressive process (VAR) of order  $p$ :

$$y_t = \nu + A_1 y_{t-1} + \dots + A_p y_{t-p} + u_t$$

where

$$y_t = \begin{pmatrix} \dot{V}_E(t) \\ \text{PET}_{\text{CO}_2}(t) \end{pmatrix}$$

$$A_k = \begin{pmatrix} a_{\dot{V}_E, \dot{V}_E}^{(k)} & a_{\dot{V}_E, \text{PET}_{\text{CO}_2}}^{(k)} \\ a_{\text{PET}_{\text{CO}_2}, \dot{V}_E}^{(k)} & a_{\text{PET}_{\text{CO}_2}, \text{PET}_{\text{CO}_2}}^{(k)} \end{pmatrix}$$

$$\nu = \begin{pmatrix} \bar{\dot{V}_E} \\ \bar{\text{PET}_{\text{CO}_2}} \end{pmatrix}$$

$$u_t = \begin{pmatrix} u_{\dot{V}_E}(t) \\ u_{\text{PET}_{\text{CO}_2}}(t) \end{pmatrix}$$

The vector  $y_t$  comprises,  $\dot{V}_E$  and  $\text{PET}_{\text{CO}_2}$  at breath  $t$ ; the matrices  $A_k$  for  $k = 1, \dots, p$  represent the static gains that relate  $y_{t-k}$  to  $y_t$ ;  $\nu$  is the mean value of the ventilation and  $\text{PET}_{\text{CO}_2}$  over the time series (1, ...,  $t$ ) and  $u_t$  represents the variations in  $\dot{V}_E$  and  $\text{PET}_{\text{CO}_2}$  that are not explained by the chemical control system properties and are therefore considered to be the result of external stochastic disturbances to the system, i.e. noise.

In this work, the orders of the autoregressive terms associated with the dynamics of the plant ( $a_{\text{PET}_{\text{CO}_2}, \dot{V}_E}$  and  $a_{\text{PET}_{\text{CO}_2}, \text{PET}_{\text{CO}_2}}$ ) were set

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