Effects of Pain and Audiovisual Stimulation on the Hypoxic Ventilatory Response


1. Introduction

The non-chemoreflex drive to breathe is complex and influenced by the cortical, limbic and reticular activating systems. This reflex can be facilitatory or inhibitory and may have different modulating effects on normoxic ventilation and the acute hypoxic response (AHR). This interaction can be particularly important when considering the effects of the non-chemoreflex drive on anesthetic induced ventilatory depression.1–5 This study clarifies the effects of pain and audiovisual stimulation (AVS) on ventilation and on the AHR.

2. Methods

We enrolled 25 (11 male; age 23.4 ± 5.8 yr., mean ± SD) healthy volunteers to complete a stimulation-randomized (tests: AVS, Pain, Rest) protocol during the measurement of their AHR. Subjects visited the lab prior to the experiment in order to acclimate to the apparatus. All breathing experiments were performed with subjects breathing into an oronasal facemask in a semi-reclining position.

AVS was a computer game entitled “You Don’t Know Jack® The Ride” (Berkeley Systems®, Jellyvision Inc., 1998) that entailed the subjects’ answering trivia questions by typing into a game controller. Pain (Visual Analog Scale of 3–6) was caused by a thermode (Precision Pain Source (PPS-3), Cygnus, Paterson, N.J.) applied to the ventral forearm skin following pre-sensitization with capsaicin cream6 (Tmax = 47°C). Rest implies that the subject had closed eyes with headphones (no noise) on the ears.
The acute hypoxic response was determined by utilizing a step into five minutes of hypoxia (saturation = 81.4 ± 1.3) after five minutes of normoxia. A computer-controlled gas-mixing system, using the dynamic end-tidal forcing technique, controlled the inspired gas concentration on a breath-by-breath basis in order to achieve the desired end-tidal concentrations of CO\(_2\) and O\(_2\). The control AHR was determined at a PETCO\(_2\) level slightly above resting levels to ensure that ventilation had significant chemoreceptor input. The PETCO\(_2\) used in a particular subject was selected by a prior period of breathing 1% inspired CO\(_2\) and measuring the average PETCO\(_2\) over five minutes after steady-state was reached.

Minute ventilation (\(V_m\)) can be expressed either as the product of tidal volume and breathing frequency or mean inspiratory flow and inspiratory time duty cycle, see equation (1). Mean inspiratory flow rate is a good indication of central neural ‘output’, and duty cycle indicates features such as bulbopontine control and pulmonary and somatic afferent influences. Together, these measures provide a more fundamental indication of the control process than tidal volume and frequency.

Since the acute hypoxic ventilatory response, AHR, is conveniently expressed as the ratio of the change in ventilation to the change in saturation (sat), there results four terms when the AHR is separated into its components, equations (2) and (3).

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V_m = V_T \cdot f = \left( \frac{V_i}{T_i} \right) \cdot \left( \frac{T_i}{T_{tot}} \right)
\]

(1)

\[
\frac{\Delta V_m}{\Delta sat} = f \cdot \left( \frac{\Delta V_T}{\Delta sat} \right) + V_T \cdot \left( \frac{\Delta f}{\Delta sat} \right)
\]

(2)

\[
\frac{\Delta V_m}{\Delta sat} = \left( \frac{T_i}{T_{tot}} \right) \cdot \left( \frac{\Delta \left( \frac{V_i}{T_i} \right)}{\Delta sat} \right) + \left( \frac{V_i}{T_i} \right) \cdot \left( \frac{\Delta \left( \frac{T_i}{T_{tot}} \right)}{\Delta sat} \right)
\]

(3)

Data is reported as mean ± standard deviation except as noted. Statistical analysis (STATA statistical package, Stata Corp., College Station, TX) was performed by analysis of variance with these factors: gender, subject nested within gender, test, and test by gender interaction. When a significant test effect was found, post hoc Wald test was used to isolate the differences. When the distributions were skewed, a log transformation was used. P values without correction for multiple comparisons are reported. One-sided t-test was used to test the differences of the sensitivities from zero. P values greater than 0.05 are reported as not significant.

3. Results

The table shows the values of the AHR and its components. PETCO\(_2\) was well controlled across tests and across normoxia (39.4 ± 3.8 mmHg) and hypoxia (39.4 ± 3.6 mmHg). The calculated sensitivities for the components of ventilation were significantly different from zero, except for the frequency sensitivity during pain (the frequency sensitivity at rest showed marginal statistical significance). When a significant test effect is indicated, post hoc pair-wise analysis always showed a difference between AVS and Pain with the values for Rest in between.