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Respir Physiol Neurobiol. Author manuscript; available in PMC 2011 January 31.

Published in final edited form as:

Respir Physiol Neurobiol. 2010 January 31; 170(1): 1–4. doi:10.1016/j.resp.2009.11.001.

Response to Hemmingsson, Horn and Linnarsson article "Measuring Exhaled Nitric Oxide at High Altitude"

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The Hemmingsson, Horn and Linnarsson article (Hemmingsson et al., 2009) *Measuring Exhaled Nitric Oxide at High Altitude* highlights methodological and technical considerations for data collection and interpretation of exhaled nitric oxide (NO) (ATS/ERS, 2005) at high altitude. The discussion centers on technical issues with analyzers used to measure NO using the online technique for FeNO (fraction of exhaled nitric oxide) and comparing FeNO at sea level to results obtained at various altitudes. The data suggest that Aerocrine NO analyzers performance characteristics vary from sea level to high altitude (ambient barometric pressure was varied using a hyperbaric chamber) as a result of the change in barometric pressure and this in turn affects the internal mass flow controller accuracy in adapting to the pressure changes (Hemmingsson et al., 2009).

Hemmingsson et al. discuss our published measures of NO at altitude in the context of correct and incorrect methodology. However, the technical issues addressed in the Hemmingsson article do not pertain to: (i) The GE Analytical Instruments Sievers NOA 280 (Boulder, CO) that was used in our studies and which was available years prior to the Aerocrine system (Duplain et al., 2000) or; (ii) the technique that we used for measurement of exhaled NO (Beall et al., 2001; Dweik et al., 2001; Brown et al., 2006). Since the development and FDA-approval of the Aerocrine device for clinical use, it has become readily available for research. Hemmingsson et al. raise valid cautionary points regarding the Aerocrine system; however our findings using the GE NO analyzer at altitude are not impacted by their findings (Duplain et al., 2000).

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1. NO analyzers: online and offline techniques for exhaled NO measure

Our published NO data was collected using the GE Analytical Instruments Sievers NOA 280 (Boulder, CO), which is significantly different in design and response than the Aerocrine device (Duplain et al., 2000). As opposed to the Aerocrine device, the GE system allows the measure of NO in breath directly during the active exhalation of an individual, *i.e.* online, or sampled from a collection bag, *i.e.* offline. The joint European Respiratory Society and American Thoracic Society Guidelines for NO measurement describe the online and offline technique (2005). We used the offline measure for many of our original studies (Beall et al., 2001; Dweik et al., 2001), not the online technique discussed by Hemmingsson et al. Briefly, in our 2001 study (Beall et al., 2001), offline refers to the study participant inhaling to total lung capacity, holding the breath for 15 s, then completely exhaling through a mouthpiece into an inert non-permeable gas collection bag. Subsequently, the gas is sampled from the bag by the analyzer for measure of NO in the entire exhaled breath volume. Offline and online techniques are valid and accurate for comparison of NO among populations, although values measured offline are different than those measured online. The difference in instrumentation and methods is critically important because the Hemmingsson et al. article reaches the erroneous conclusion that our first published data on NO at altitude are invalid (Beall et al., 2001). To the contrary, our original data revealing high exhaled NO among Tibetans has been confirmed by subsequent measurement of whole body NO metabolites in blood, urine and saliva (Erzurum et al., 2007).

2. Flow dependence: methodological implications

NO levels in the exhaled breath are dependent on flow, the slower the flow the higher the NO (Silkoff et al., 1997; Kissoon et al., 2000). The 50 ml/s flow is recommended for clinical online measures of NO based on the discrimination amongst asthma and healthy controls using this flow rate (2005). When controlling flow, it is possible to have subjects' target airway opening (which with a fixed resistance determines a fixed flow) or flow itself. The Aerocrine analyzer controls flow using an internal flow controller as part of the breathing circuit during the online measurement; the Hemmingsson article concludes that the Aerocrine inline flow-control devices are pressure-dependent. Hence, the instrument may not be valid for use at altitude. The GE analyzer does not rely on an internal flow controller, but rather targets airway opening. For the offline measures with the GE analyzer, the equipment designed for offline collection of exhaled gases uses a mechanical, spring-based gauge incorporated into the mouthpiece to control exhalation at a constant rate into the collection bag; this spring-based system is barometric pressure independent. The orifice and spring-based system results in a steady flow of 350 ml/s. For the online measures with the GE analyzer, the flow is controlled by the subject exhaling against a fixed resistance, which determines a fixed flow (Silkoff et al., 1997; Duplain et al., 2000; Kissoon et al., 2000; Hoit et al., 2005). We used multiple fixed resistances (mouthpieces containing needle resistors of diameters that resulted in flow rates of 17 ml/s and 50 ml/s) in our later studies at altitude with the GE device (Hoit et al., 2005).

3. Gas sampling from a collection bag in the offline method

Careful attention to calibration is required for valid measures at altitude. In our studies, we calibrated daily at sea level and high altitude as acknowledged in the Hemmingsson article to account for any effect of barometric pressure on the inlet sample flow rate or response of the GE instrument. We did report data in ppb (ppbV). The volume of NO and the volume of air change by equal amounts as a function of pressure. Given that the partial pressure of a gas is independent of the pressures of the other gases in the mixture (*Dalton's Law*), the partial pressure of a gas is simply the concentration of the gas (ppbV) times the total pressure. Volume/volume mixing ratios (ppbV) and partial pressures are identical in physical systems. Thus, ppb can be compared across altitude. Nevertheless, values in nm Hg can be calculated from published values using the measured barometric pressure at morning calibrations of 467 Torr in the Tibet Autonomous Region, 484 Torr in Bolivia and 742 Torr in Cleveland, Ohio.

Although a direct comparison of the Aerocrine system to the GE Sievers NOA was not considered in the Hemmingsson article, studies using the GE Analytical Sievers model 280 indicate that its measures of NO do not change in response to barometric pressure (Duplain et al., 2000; Beall et al., 2001; Hoit et al., 2005). The conclusions by Hemmingsson et al. about Aerocrine analyzers/flow controllers should not be extended to studies using the GE Analytical System analyzer, or measurements made with external resistor techniques. Our studies using the latter methods provide results independent of atmospheric pressure that have been confirmed by a diverse numbers of methods of measuring NO production in human beings (Hoit et al., 2005; Erzurum et al., 2007).

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