Reviewer's report

Title: An increased respiratory drive accounts for the severity of dyspnea in systemic sclerosis

Version: 1 Date: 14 February 2014

Reviewer: Darcy Marciniuk

Reviewer's report:

Ninaber M, et al. An increased respiratory drive accounts for the severity of dyspnea in systemic sclerosis.

The authors prospectively assessed mouth occlusion pressure [P0.1] and dyspnea [University of California San Diego dyspnea scale] in 73 subjects with Systemic Sclerosis while breathing room air, and again during CO2 rebreathing. The P0.1 was higher in subjects with an elevated VE/P0.1, and VE/P0.1 correlated with dyspnea scores. They found that a USCSD value of 8.5 correlated with an abnormal VE/P0.1. The authors conclude that in subjects with Systemic Sclerosis and an abnormal VE/P0.1, increased central neuromuscular drive to CO2 is present and accounts for the severity of dyspnea.

Major Comments:
A. As currently described in the text, the reasons supporting the study hypothesis are not compelling. It is recognized that the sensation of dyspnea is complex, and that contributors are diverse and typically multifactorial. Additional information as to why further understanding in this population is needed should be provided.

B. Discussion – further development of the reported findings and their significance is required. In addition, statements such as [3rd paragraph, last sentence] ‘Therefore, ventilation and its components, are not considered to present an accurate output of the respiratory drive in our patients.’ require further background and explanation [and perhaps justification]. Importantly, there should be further discussion regarding the observed differences between the 2 groups ie. why did some scleroderma subjects respond different than others, and why did the majority of scleroderma subjects respond as normals, while a smaller group did not? Factors such as severity of impairment, concomitant pulmonary vascular involvement, disease duration, etc. could be noted.

C. Discussion, 4th paragraph – the finding that participants ‘… with a low VEP0.1 had an increased responsiveness to hypercapnia which indicates an increased central respiratory drive’ is not necessarily that direct, as a number of contributors could explain the enhanced sensitivity/response to hypercapnia. These factors could be briefly mentioned.

D. Summary – the conclusion that variability in the ventilatory response to hypercapnia is appropriate, and that variability seems a natural subject to further explore in the discussion. The study itself was not designed to validate mouth
occlusion pressure as an objective parallel of dyspnea (a much different study would have been designed, for example assessing dyspnea under various loads). I would suggest the authors focus on what the results truly demonstrate. Secondly, as it now stands the results lack foundation and placement; but if discussed within the larger context of this patient population, interest could be readily [and easily] increased (see B above). There is no need for further experimentation or data collection, but a broader interpretation of the results would be welcomed.

Other Comments:
1. Formatting of reference citations in the text should be uniform [Background, 3rd paragraph, line 4, 7 is superscripted].
2. Methods, Patients – the “intensive screening program …’ should be fully explained.
3. Methods, Pulmonary Function Testing – results were expressed as both absolute and % predicted (see Table 1). The specific methods for measuring lung volumes and diffusing capacity should be mentioned in the text.
4. Methods, Measuring the Hyperoxic Ventilatory Response to Hypercapnia – the techniques used to calibrate the turbine volume measuring device in the setting of hyperoxia should be described.
5. Methods, USCD Shortness of Breath Questionnaire – there is no need to justify the questionnaire, as its validation has already been undertaken and published. However, further detail regarding its administration, instructions to subjects, etc. could be provided in the text of the manuscript to assure readers its conduct was appropriate.
6. Discussion - the statement that dyspnea is increased should be revised to include under what physiologic condition ie, with CO2 re-breathing [as opposed to at rest, etc.]
7. Discussion – as noted by the authors, there are limitations to this work. The use of external values for normal ventilation has significant limitation. As also noted by the authors, the dyspnea scores were very low, providing some justification for assessing the ventilatory response to an additional load such as exercise. Although the study findings are similar in some respects, there are differences from those previously reported in interstitial Lung Disease, and potential reasons could be put forth. Conversation on these issues could be further expanded.
8. Discussion – the issues regarding hyperinflation and hypercapnia do not seem to be applicable to subjects that neither demonstrate (nor would be expected to be) hyperinflation or hypercapnia. The authors should consider deleting the paragraph.
9. PaO2 should be presented in Table 1. Units for PaCO2 should be corrected.

Declaration of competing interests:
I declare I have no conflict of interest.