

Oxygen Consumption: Another Key Component in Predicting Ventilator Weaning Success

To the Editor:

I read with great interest the article by Bellani *et al.*¹ and praise their important work in the field of weaning from mechanical ventilation. More than anything, I question how the authors formed the hypothesis that oxygen consumption ($\dot{V}O_2$) increases more in patients unable to sustain decreasing ventilatory assistance. In a landmark article by Jubran *et al.*,² weaning failure was associated with increased oxygen extraction and decreased oxygen delivery. In the same article, the measured $\dot{V}O_2$ increased in both the success and failure from weaning groups, with a lower increase in the success group. In contrast, Zakyntinos *et al.*³ demonstrated that patients who cannot be weaned have one of two hemodynamic and oxygen use profiles. (1) Those who fail without increasing $\dot{V}O_2$ demonstrate increased oxygen extraction and decreased oxygen delivery. (2) In those who fail and increase their $\dot{V}O_2$, the increase mainly occurs secondary to increased oxygen extraction. Direct measures of mixed venous oxygen saturation are increased in the first group and decreased in the second group, supporting their findings. Given the complex physiologic nature of respiratory weaning and weaning failure, it is widely believed that failure to wean occurs secondary to decreased oxygen delivery and increased oxygen extraction. Given the proposal of 1870 by Fick,⁴ a decrease in cardiac output in combination with an increase in the arteriovenous oxygen content difference would yield a relatively stable $\dot{V}O_2$. Combining these data with those of Bellani *et al.*, it is clear that the weaning process is complex and highly variable between patients. Overall, this work supports previous studies demonstrating that there are patients who fail weaning in the absence of increased $\dot{V}O_2$.

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References

1. Bellani G, Foti G, Spagnoli E, Milan M, Zanella A, Greco M, Patroniti N, Pesenti A: Increase of oxygen consumption during a progressive decrease of ventilatory support is lower in patients failing the trial in comparison with those who succeed. *ANESTHESIOLOGY* 2010; 113:378–85
2. Jubran A, Mathru M, Dries D, Tobin MJ: Continuous recordings of mixed venous oxygen saturation during weaning from mechanical ventilation and the ramifications thereof. *Am J Respir Crit Care Med* 1998; 158:1763–9
3. Zakyntinos S, Routsis C, Vassilakopoulos T, Kaltsas P, Zakyntinos E, Kazi D, Roussos C: Differential cardiovascular re-

sponses during weaning failure: Effects on tissue oxygenation and lactate. *Intensive Care Med* 2005; 31:1634–42

4. Fick A: Uber die messung des blutquantams in den herzventrikeln. *Sitx Physik-Med Wurzburg* 1870; 2:16

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A High Significance Level after Analysis of Covariance in a Small-group Study?

To the Editor:

In the study by Bellani *et al.*,¹ changes of oxygen consumption ($\dot{V}O_2$) in patients, who succeeded or failed in weaning from mechanical ventilation support, were addressed. The authors rejected their original hypothesis and constructed a new theory after they analyzed their results. However, some statistical issues should first be clarified by them to better support their discussion and conclusion.

There were two main findings in their study. (1) There were no significant differences in the maximum $\dot{V}O_2$ readings between the success and the failure groups during the weaning pressure support trials. In addition, the minimum $\dot{V}O_2$ readings (when adequate pressure support was provided) in the failure group were significantly higher than in the success group ($P < 0.05$). (2) The authors further analyzed the group and pressure support effects on patients' successive $\dot{V}O_2$ data. By analysis of covariance (cited as a two-way ANOVA by the authors), significant differences were found both in the group and pressure support effects at $P < 0.001$. Accordingly, the authors concluded that the patients able to successfully complete their weaning trials were those who reacted to the decrease of ventilatory assistance with a greater increase in $\dot{V}O_2$.

A paradox exists between these two results. The statistical values increased significantly after the analysis of covariance. With an increasing P value, their analysis of covariance model probably omitted the patients' effects.² In other words, they probably treated a patient's successive $\dot{V}O_2$ data (these data were related) as independent $\dot{V}O_2$ data from different patients. Thus, their statistical values reached levels of less than 0.001 in such a small-group study (16 patients in the success group and 12 in the failure group). This criticism seems reasonable, especially after considering the diverse $\dot{V}O_2$ trend patterns in response to the withdrawal of pressure support (as shown in their second figure). The diverse patterns would add complexity to the determination of the pressure support effect and should decrease, rather than increase, the statistical significance.

Another statistical issue is that the authors used a correlation coefficient to access the reproducibility of $\dot{V}O_2$ measurements. The correlation coefficient is misleading. The Bland–Altman analysis is much more appropriate for assessing reproducibility.³

In conclusion, the authors produced an impressive and interesting study. However, after rechecking their statistics, it is clear that too many conclusions were drawn from the limited results.

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References

1. Bellani G, Foti G, Spagnoli E, Milan M, Zanella A, Greco M, Patroniti N, Pesenti A: Increase of oxygen consumption during a progressive decrease of ventilatory support is lower in patients failing the trial in comparison with those who succeed. *ANESTHESIOLOGY* 2010; 113:378–85
2. Rutherford A: *Introducing ANOVA and ANCOVA: A GLM approach*. Edited by Wright DB. London, SAGE Publications, 2001, pp 43–77
3. Bland JM, Altman DG: Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; 1:307–10

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In Reply:

We thank Bloomstone for his interest in our article¹ and for his comments. We entirely agree with him when he states that the weaning process is complex, multifactorial, and highly variable; this is also outlined in the editorial that accompanied our article. Our original hypothesis was that oxygen consumption ($\dot{V}O_2$) would increase more in patients unable to sustain the weaning effort; this hypothesis was probably simplistic and did not account for some literature data, such as those published by Zakyntinos *et al.*² On the other hand, we relied on solid evidence in the literature^{3–6} showing how increased $\dot{V}O_2$ during weaning would be associated with failure. Moreover, Bloomstone wisely underlines how $\dot{V}O_2$ is linked to the complex interplay between peripheral extraction and delivery. Unfortunately, as we acknowledge in the discussion of our article, the lack of assessment of the hemodynamic changes in our patients stands as a relevant limitation of our work.

We appreciate Chen's deep attention in revising our data. In his sharp comment, he notes a paradox between the results of the Student *t* test and those of the ANOVA. However, the two tests are difficult to compare because they are performed on different sets of data. In fact, Chen neglects the fact that, although the minimum $\dot{V}O_2$ readings were compared as absolute values using the Student *t* test, the ANOVA is performed after normalization of $\dot{V}O_2$ by the minimum $\dot{V}O_2$ reading of each patient. This normalization is expected to decrease the between-patient heterogeneity in the "absolute values" of $\dot{V}O_2$, causing the observed increase in statistical significance. Moreover, at variance from figure 2 of the original article,¹ using ANOVA, the levels of pressure support are expressed as difference from the "resting" level of pressure support, rather than as absolute values; in other words, all patients are "aligned" on the x-axis, with the

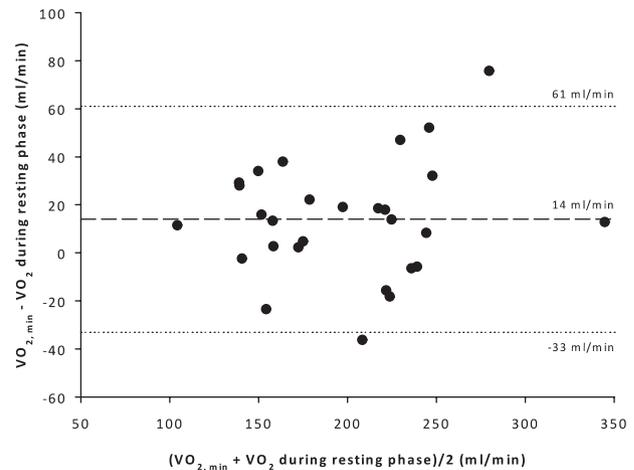


Fig. 1. Bland-Altman analysis showing the comparisons between two measurements of oxygen consumption ($\dot{V}O_2$) obtained respectively as the minimum value during the decremental pressure support trial and during the resting phase ($\dot{V}O_{2,\min}$). For further details please see the original manuscript.¹

minimum recorded $\dot{V}O_2$ corresponding to the same level of pressure support. We agree with Chen regarding the appropriateness of Bland–Altman analysis to evaluate the reproducibility of $\dot{V}O_2$ measurement. Because this was not included in our original article, we report it herein: the mean difference between the minimum $\dot{V}O_2$ value during the decremental pressure support trial and the $\dot{V}O_2$ during the resting phase was 14 ml/min (95% CI, 61 to –33 ml/min).

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References

1. Bellani G, Foti G, Spagnoli E, Milan M, Zanella A, Greco M, Patroniti N, Pesenti A: Increase of oxygen consumption during a progressive decrease of ventilatory support is lower in patients failing the trial in comparison with those who succeed. *ANESTHESIOLOGY* 2010; 113:378–85
2. Zakyntinos S, Routsis C, Vassilakopoulos T, Kaltsas P, Zakyntinos E, Kazi D, Roussos C: Differential cardiovascular responses during weaning failure: Effects on tissue oxygenation and lactate. *Intensive Care Med* 2005; 31:1634–42
3. Shikora SA, Benotti PN, Johannigman JA: The oxygen cost of breathing may predict weaning from mechanical ventilation better than the respiratory rate to tidal volume ratio. *Arch Surg* 1994; 129:269–74
4. Shikora SA, Bistrrian BR, Borlase BC, Blackburn GL, Stone MD, Benotti PN: Work of breathing: Reliable predictor of weaning and extubation. *Crit Care Med* 1990; 18:157–62
5. Mitsuoka M, Kinninger KH, Johnson FW, Burns DM: Utility of measurements of oxygen cost of breathing in predicting success or failure in trials of reduced mechanical ventilatory support. *Respir Care* 2001; 46:902–10
6. Miwa K, Mitsuoka M, Takamori S, Hayashi A, Shirouzu K: Continuous monitoring of oxygen consumption in patients undergoing weaning from mechanical ventilation. *Respiration* 2003; 70:623–30

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