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Invited Commentary

This Commentary Is Based on the Recently Published Article: Tantisira KG, Systrom DM, Ginns LC. An Elevated Breathing Reserve Index at the Lactate Threshold Is a Predictor of Mortality in Patients With Cystic Fibrosis Awaiting Lung Transplantation. Am J Respir Crit Care Med 2002;165;1629–1633

Exercise testing provides useful clinical information when it can delineate the effectiveness of compensatory physiologic mechanisms that permit some degree of physical activity even in the presence of disease. In a recent retrospective study of patients with cystic fibrosis awaiting lung transplantation, Tantisira et al.[1] provided evidence that exercise testing not only delineates the degree of physiologic impairment caused by chronic disease, but might also be used to predict mortality. Their paper highlights the challenges involved when we attempt to gain nonintuitive information from the application of fundamental physiology to clinical problems.

An enigma that has been noted by a number of investigators in CF patients is that while both forced expiratory flow (e.g., forced expiratory volume in 1 sec, FEV_1) and aerobic parameters of exercise (e.g., peak $\dot{V}O_2$) are impaired, they are poorly correlated.[2] Thus, these clearly are tests of very different physiologic function. Tantisira et al.[1] reasoned that by combining the information revealed from these separate procedures, novel predictive insights into the decline of compensatory function could be gained that were more powerful than from either test alone. They chose to use the breathing reserve index (BRI) which is defined, in their paper, as the ratio of ventilation during submaximal exercise (obtained at the lactate threshold (LT) of a progressive exercise test) to maximal voluntary ventilation (MVV). The latter variable was not measured, but rather was derived from the actual measurement of FEV_1, using standard techniques ($MVV = FEV_1 \times 40$).

The authors hypothesized, and indeed found, that an *elevated* BRI at LT was predictive of mortality in the CF patients waiting for transplantation. Thus, a disproportionate elevation in $\dot{V}_E$ at LT, a disproportionate reduction in FEV_1, or a simultaneous increase in $\dot{V}_E$ at LT and decrease in FEV_1 must indicate some underlying pathophysiologic mechanisms signaling the failure of compensatory mechanisms and, ultimately, death.

But what might these novel, ratio-derived, physiological indicators be, and how might the mathematical structure of ratio and regressions influence the predictive robustness of the derived variable? First, let us consider the determinants of $\dot{V}_E$ during exercise and FEV_1. A modification of the alveolar gas equation reveals that:

$$\dot{V}_E = \left[863 \times PaCO_2^{-1} \times (1 - V_D/V_T)^{-1}\right] \times \dot{V}CO_2$$

where $\dot{V}_E$ is minute ventilation; $\dot{V}CO_2$ is CO_2 production, $PaCO_2$ is arterial CO_2 tension, and V_D/V_T is dead space to tidal volume ratio. Moreover,

$$\text{Peak Expiratory Flow} = P_{ER}/R_{US}$$

where peak expiratory flow is a major determinant of FEV_1, P_{ER} is elastic recoil pressure of the lung, and R_{US} is the upstream resistance to airflow. Combining and rearranging these equations reveals:

$$BRI \propto \left(\dot{V}CO_2 \times R_{US}\right)/(P_{ES} \times PaCO_2 \times (1 - V_D/V_T))$$

Accordingly, either $\dot{V}CO_2$ or R_{US} must have disproportionately increased, or else some combination of reduction in lung elastic recoil; lower $PaCO_2$ during exercise; or increased V_D/V_T during exercise must occur to explain the putative relationship between an elevated BRI at LT and mortality.

Among these variables, obvious candidates that could herald the onset of mortality would be upstream resistance, known to progressively increase in CF, and lung elastic recoil, known to decrease in CF. But here, clinical correlative data might help identify which of these factors played a more definitive role in. First, if only upstream resistance and lung elastic recoil were involved, then FEV_1 *alone* should have predicted mortality as well as the BRI. This was not the case, as FEV_1 was not found to be a significant predictor of mortality in this group of patients, who by definition already had very low FEV_1 values.

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Certain other factors can be excluded, based on our knowledge of their physiological determinants. For example, CO_2 production (which reflects metabolic rate during exercise) must become progressively *smaller*, not larger, as disease progresses, because subjects are increasingly unable to do external work. Indeed, peak $\dot{V}O_2$ was very low in all subjects, and even lower in those who died (818 ± 246 ml/min, compared with 987 ± 383 in the survivors).

Interestingly, high $PaCO_2$ (it is not clear whether the $PaCO_2$ was obtained at rest or during exercise) was a statistically significant, although much smaller, relative risk factor (1.29) than was BRI at LT (17.52). Elevated $PaCO_2$ indicates uncompensated hypoventilation, and is not surprising that an abnormal $PaCO_2$ is related to deterioration and mortality in these patients. However, high $PaCO_2$ levels should, by the above analysis, cause a lower, rather than higher, BRI.

This leads us, then, to V_D/V_T as a variable which, if high, would tend to increase the value of BRI. The V_D/V_T in the BRI equation represents dead space during exercise; and here we find a physiological mechanism that might be useful in explaining the predictive value of the BRI at LT. The data of Tantisira et al.[1] suggest that in a population of CF patients with a low FEV_1 (so low, in fact, that they are candidates for transplant), there is a distinct subgroup which is unable to compensate during exercise for the disease-associated anatomic and ventilation-perfusion increases in dead space. These patients have so little reserve that death is imminent.

This analysis suggests, then, a possible physiologic mechanism that might explain why the ratio of two distinct physiological functions ($\dot{V}_E$ during exercise and FEV_1) might be a more powerful a predictor of mortality than either variable alone (N.B. that it would have been useful had the authors analyzed $\dot{V}_E$ at LT by itself as a predictor of mortality, but the relative risk of FEV_1 was 0.26, of V_D/V_T was 1.04, and of BRI at LT was 9.82). One could envision the following scenario: the (unfortunately relentless) disease processes involved in CF lead progressively to increased upstream resistance and reduced lung elastic recoil. FEV_1 consequently worsens with lung disease, but because the determinants of FEV_1 are not the same as those of $\dot{V}_E$ during submaximal exercise, there is a range of disease severity in which a nadir of FEV_1 has been reached but where compensatory mechanisms still exist, so that during exercise, V_D/V_T remains below some critical level. Eventually, deterioration of lung function reaches some point where this compensation fails, and V_D/V_T remains high even during exercise. This then signals some point where all of the inflammatory, metabolic, and cardiorespiratory impairments associated with CF are no longer amenable to known interventions.

The work of Tantisira et al.[1] is provocative and challenging. But as a retrospective study, it does not yet provide enough evidence to unequivocally support the BRI at LT as a definitive predictive procedure that ought to be adopted clinically to predict mortality in sick CF patients. Prospective studies need to be done, and other issues need to be addressed. When working with ratios of regressions, one must be careful not to interpret algebraic phenomena as indicators of real physiology. For example, in Figure 1, two theoretical regressions of physiological variables ($\dot{V}_E$ at LT and FEV_1) are shown as a function of disease severity. As suggested by Tantisira et al.,[1] $\dot{V}_E$ is likely to increase with disease severity, while FEV_1 decreases. The ratio of these two regressions forms a new variable which defines an asymptotic hyperbola. The hyperbolic nature of the derived curve can easily be misconstrued as a threshold of a real physiological marker. In this case, the predictive value of BRI at LT may simply reflect the fact that the ratio of these two variables becomes nonlinearly increased in the sicker patients, the very ones more likely to die.

The work of Tantisira et al.[1] should stimulate clinical researchers to probe new ways to use clinical exercise

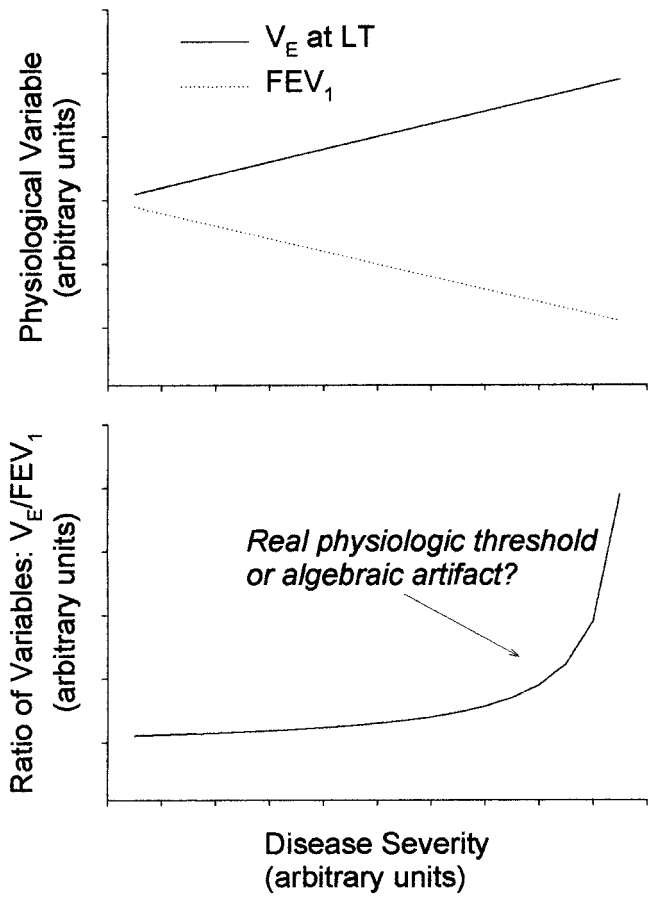

Fig. 1. BRI is calculated from ratio of $\dot{V}_E$ at LT and FEV_1. These variables are likely to change as a function of disease severity in manner depicted at top. Ratio of these two lines will form an asymptotic hyperbola, and the change point might be confused with a true physiologic threshold.

testing in other chronic diseases. As the authors point out, by focusing on submaximal exercise, the test itself is ''kinder and gentler,'' and perhaps more acceptable to sicker patients and less stressful for the clinician and exercise technician than is traditional, maximal exercise testing. Indeed, further work may show that finding the precise LT is less critical than defining a range of submaximal data where exercise testing yields reproducible and robust data. Finally, the clinical value of exercise testing will ultimately rest on research that links the richness of these minimally invasive and less intrusive procedures to specific pathophysiologic mechanisms caused by the underlying disease.

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Editor's Note: This is the first of what I hope will be many invited commentaries on what are perceived to be ''hot'' new papers in the broad field of pediatric pulmonology. Such papers may be clinically oriented or else more basic science-oriented. I invite feedback from the readership.

—Victor Chernick
Editor-in-Chief