of multiorgan failure syndrome (13). Has microcirculation become the new canary for early detection of this syndrome? Who can tell? One thing, however, is for certain. With their study, De Backer and colleagues have firmly and squarely introduced microcirculation into the clinical arena in the treatment of sepsis. They are to be congratulated on this fine study.

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DOI: 10.1164/rccm.2204033

When Ventilator and Patient's End of Inspiration Don't Coincide

What's the Matter?

During assisted mechanical ventilation, the time at which the ventilator terminates inspiration and opens the exhalation valve defines the beginning of the expiration process, for the ventilator, but also for the patient. In this issue of the *AJRCCM*, Younes and collaborators (pp. 21–30) assessed the impact of prolonging the inspiratory time of a ventilator breath beyond the end of the patient's inspiratory time (i.e., after the end of neural inspiratory time) (1). The question addressed here was therefore: what is the response of the patient's breathing controller when the onset of the natural (neural) expiration is impeded? Do the respiratory centers prolong expiratory time to defend against the risk of dynamic hyperinflation? Are expiratory muscles going to be activated to accelerate expiration? This was a difficult experiment to conduct and an important question to address.

Why is this an important question? Many attempts have been previously made to design new modes of ventilation with optimal synchrony between a patient's inspiratory effort and assistance from a ventilator. The onset of the breath has been the subject of much attention on optimizing trigger sensitivity. Also, the time elapsing before recognition of patient's effort in cases of dynamic hyperinflation and auto or intrinsic positive end-expiratory pressure has been addressed extensively (2). The criteria used for terminating the breath, also called the cycling criteria, have been much less oriented toward a specific recognition of the end of a patient's effort. Up to now, the most frequently used mode of ventilation, assist-control ventilation (3), terminates the breath on a time criterion independent of a patient's effort. What the ventilator primarily controls is flow, and insufflation time depends on the peak flow setting. The total inspiratory time can also be prolonged by the addition of a plateau at end-insufflation. Another popular mode of ventilation is pressure support ventilation. This mode proposes an original solution for terminating the breath closer to a patient's neural signal than would be achieved using a preset inspiratory time (4). Indeed, the decelerating flow signal is used to determine the time at which the ventilator switches to expiration. Because the inspiratory flow should be influenced by the patient's effort at any time of the breath, this criterion is influenced by a signal coming from the patient. It has, however, long been recognized that this off switch criterion is influenced by complex interferences: time constant of the respiratory system, the value of flow used as a threshold criterion, the level of pressure applied at the opening of the respiratory system, and the remaining inspiratory effort at the end of the breath (5). Many examples of dysynchrony occurring at the end of the breath have been described, especially for high levels of pressure support ventilation and in patients with high respiratory resistance. Therefore, for the two most popular modes of assisted ventilation, the question of inadequate timing addressed in the study by Younes and coworkers is very relevant (1). As explained previously here, this inadequacy may influence the level of dynamic hyperinflation and thus interact with the amount of patient's inspiratory effort. Could every effort made to optimize the triggering systems and the adequacy of inspiratory support be ruined by neglecting the timing of end-inspiration?

The question was difficult to address precisely because the neural inspiratory time cannot be controlled or even predicted with standard assisted modes of ventilation. Younes and coworkers (1) took advantage of the unique feature of proportional assist ventilation to terminate the inspiratory support at the exact end of patient's inspiratory neural time (or flow). They intermittently added a pause (occlusion) of variable duration at the end of inspiration, and assessed its consequences by matching the studied breaths with similar breaths without a pause. Ironically, the results of this study are very relevant for standard modes of assisted ventilation, whereas they are only of marginal interest for proportional assist ventilation, in which this situation is rather artificial.

The authors found that most patients (45 of 50) lengthened their expiratory time because of the delayed onset of expiration. In other words, their respiratory centers activated the inspiratory muscles with a slight delay compared with a nonoccluded breath. This time compensation, however, represented a highly variable and often very limited fraction of the delay imposed by the occlusion. Patients with chronic obstructive pulmonary disorder and expiratory flow limitation, who are more prone to develop hyperinflation, had a very poor compensatory response. Lastly, the authors did not observe any substantial expiratory muscle activation, at least as far as they could measure it.

The study has limitations. We do not know how, for instance, the acute response to delayed expiration gets modified over a more prolonged period of time. After a change in ventilator settings, it may take more than a few breaths to find a new equilibrium, because many different stimuli can be progressively involved (6). This study tells us, however, that delayed expiration, as frequently observed with inadequate settings during assisted ventilation, may influence the level of dynamic hyperinflation and worsen patient-ventilator interaction.

It always takes time to explain to students why obstructive lung diseases, which are primarily defined as an expiratory problem, cause enormous problems to patients during inspiration. This study by Younes and coworkers (1) illustrates the same kind of relationship between expiration and inspiration. It shows that failing to detect precisely the correct onset of expiration may interact with the next inspiration and put the patient at much higher stress to inspire.

Finally, to determine the true onset of inspiratory effort, one of the investigators analyzed each breath by looking for the abrupt deflection observed on the flow and airway pressure tracings. In most patients, this clearly occurred before the ventilator was able to detect patient's effort, because of the presence of dynamic hyperinflation. This well-known phenomenon has prompted other investigators to design complex electromyographic recording systems to trigger the ventilator (7). It is striking to see that the same information is conveyed by a careful examination of flow and airway pressure tracing signals available in every ventilator. To move from readings performed by an investigator with the skill, experience, and background of Younes to an automatic recognition of these signals by a specially designed algorithm is not simple. This study shows, however, that this important information is available noninvasively at the bedside in most ventilated patients.

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DOI: 10.1164/rccm.2205008

Studies of the Early Bactericidal Activity of New Drugs for Tuberculosis

A Help or a Hindrance to Antituberculosis Drug Development?

During the past several years there has been renewed interest in the development of new antituberculosis drugs (1), and the newly established Global Alliance for Tuberculosis Drug Development (available online at www.tballiance.org) is providing needed leadership in this long-neglected area. One of the many impediments to progress has been the long and costly process of clinical development. Thus, methods to more efficiently assess drug activity and clinical efficacy, including studies of the early bactericidal activity (EBA) of new drugs, are receiving greater attention. In EBA studies, newly diagnosed patients with acid-fast bacillus (AFB)-positive, pulmonary tuberculosis are treated for periods ranging from 2 to 14 days with single drugs or drug combinations. During this period, quantitative counts of viable tubercle bacilli from carefully collected sputum specimens are made, with the EBA traditionally expressed as log-decrease in colony forming units/ml sputum/day over the first 48 hours.

In this issue of the *AJRCCM*, Gillespie and colleagues (pp. 31–35) describe a novel method for the analysis of data from EBA studies (2). Gillespie proposes that daily measurements be made for the first 5 days and that the data be fitted to a regression curve with the results expressed as the time to achieve a 50 percent reduction in cultivatable bacilli. By incorporating a larger number of data points and providing for exclusion of outlier data that may arise from both intrinsic and extrinsic factors, Gillespie suggests that this method may both reduce the inherent variability commonly found in these studies and increase the precision of the measurement. Investigators in the United States have also suggested that EBA studies are optimally conducted over 5 days (3).

The first EBA study was conducted in Kenya over 20 years ago, demonstrating the feasibility of the methodology (4). Subsequently, a series of studies have been reported, most commonly from countries in sub-Saharan Africa. The few EBA studies conducted elsewhere were often plagued with greatly variable results of the kind that Gillespie seeks to address. To explain these findings, it has been suggested that the success of an EBA study is largely determined by the type of patient evaluated (5). African patients with acute, far advanced pulmonary tuberculosis seem to have a more uniform and predictable EBA response, as contrasted to Asian or North American patients who may have more chronic forms of the disease.