Reply: Selection Bias in Study Participants with Acute Hypercapnic Respiratory Failure

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Abstract

We reexamined the efficacy of the clinically effective anticonvulsant drug phenytoin in the kindling model. We investigated the effects of varying doses of intravenous phenytoin on serum concentrations and on several indexes of stimulation-evoked kindled seizures. Intravenous phenytoin produced a dose-dependent increase in serum phenytoin concentration and powerfully suppressed both limbic and clonic motor seizures. Although focal afterdischarge threshold was elevated to some extent, the most profound effect of phenytoin was limitation of seizure propagation. Variable and low serum concentrations of intraperitoneal or oral phenytoin may explain previous findings that phenytoin is only partly effective or ineffective against kindled seizures. Together with previous results with other drugs, the excellent correlation among drugs effective against human and kindled seizures strengthens the validity of this model. We suggest that the efficacy of experimental anticonvulsant drugs be established in the kindling model before initiation of clinical trials for partial and secondarily generalized seizures.

Reference


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Reply

From the Authors:

We thank Dr. Chertoff for his interest in our work. Our study showed that acute hypercapnic respiratory failure (AHRF) requiring intensive care unit (ICU) admission resulted primarily from chronic obstructive pulmonary disease or obesity, and we suggest that AHRF survival should be an opportunity for clinicians to systematically evaluate lung, heart, and sleep functions to improve poor outcomes (1) [this issue, pp. 200–207]. Dr. Chertoff raises concerns about possible selection bias related to inclusion/exclusion criteria. We concur that the results of a cohort study should always be interpreted within the frame of inclusion/exclusion criteria. This is an important rule to avoid major bias in the interpretation of results and to allow a proper generalization. Dr. Chertoff’s letter is therefore an important reminder that all observational studies should comply with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (2).

The following is our point-by-point rebuttal that addresses his comments and concerns.

Although we understand Dr. Chertoff’s concerns about the fact that we did not include all patients with AHRF admitted in the ICU, we did this on purpose. Indeed, our goal was to capture one group of frequent patients who are often not well characterized and managed after an ICU admission. We tried to make it very clear in the article from the first paragraph of the introduction, which was:

Patients with an episode of severe acute hypercapnic respiratory failure (AHRF) suggestive of an acute exacerbation of chronic obstructive pulmonary disease (COPD) or an obesity hypoventilation syndrome are admitted to the intensive care unit (ICU) to receive noninvasive ventilation (NIV). In most patients, NIV is successful, and ICU mortality is now consistently reported to be as low as 5–10%. However, hospital and ICU readmissions are frequently observed in specific at-risk COPD phenotypes or due to the underdiagnosis and lack of integrated care for associated comorbidities in other patient categories. The correct assessment of comorbidities after AHRF needs to be better defined to improve the long-term care of these patients. (1)

Therefore, we believed that inclusion of other groups of patients with rare or transient conditions or conditions with very different pathophysiology would distract from our goals. In addition, there were other specific reasons for the different groups excluded, as follows.

First, “iatrogenic respiratory failure” does refer to drug-induced AHRF. Although opiates and benzodiazepines are well-known contributors to AHRF and ICU admission, we consider that such a dramatic event is frequently an isolated occurrence and does not reflect any other specific comorbid condition. We also decided to exclude patients with major psychiatric disease for the same reason and because valid consent might be difficult to obtain.

Second, we believed it unethical to plan an in-laboratory full-night sleep study 3 months after ICU discharge in patients with life expectancy less than 3 months. These patients were managed focusing on symptoms and goals/preferences for care planning.

Third, patients with neuromuscular diseases and amyotrophic lateral sclerosis are rare in the ICU, as they are monitored very closely in specialized consultations in our institution and do not represent a significant burden for ICU physicians. Close monitoring of symptoms and respiratory parameters of patients with neuromuscular disease has been associated with a dramatic reduction of ICU admission for AHRF.

The aim of our study was therefore not to investigate the innumerable causes of AHRF in the general population but to provide an objective and methodical assessment of the lung, cardiac, and sleep function in a selected group of patients surviving AHRF and looking like (clinical phenotype) acute exacerbations of chronic respiratory failure. We believe that our findings contribute to a change in our current understanding of AHRF and encourage clinicians not to be reassured by a “single-disease tag” when caring for AHRF but to shift thinking toward a more complex and realistic picture of “treatable traits” (Figure 1). Only such a shift can pave the way for the development and testing of post-ICU discharge care bundles (3) to impact readmission and mortality.

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On behalf of all the authors
To the Editor:

We read with interest the article by Thamrin and colleagues (1), which discussed systems biology approaches to study the respiratory system, as a complex system, within the context of diagnosis and monitoring of diseases. A section of the article described previous studies that characterized the complex behavior of the lung in respiratory diseases using nonlinear analysis of the fluctuations of physiologic variables over time. Chronic lung diseases have variable clinical symptoms and represent complex behavior, which may be associated with a shift in dynamics of the respiratory system toward either too regular or too irregular (2). Analyzing such nonlinear fluctuations not only may improve traditional assessments in diagnosing the onset of illness and its severity and prognosis (1) but also could provide new insights into the different pathophysiological characteristics of respiratory diseases (2). In addition to studies described by Thamrin and colleagues (1), our recent report (2) showed that both respiratory rhythm and volume fluctuations continuously under a delicate equilibrium to maintain adaptability to external or internal stimuli. These fluctuations showed decreased long-range correlation, increased regularity, and reduced sensitivity to initial conditions in patients with asthma, particularly in the uncontrolled state. More importantly, receiver operating characteristic curve analysis showed that respiratory variability analysis can be useful not only to aid in asthma diagnosis and in differentiating uncontrolled from controlled asthma but also for discriminating between nonatopic and atopic asthma (2). We found decreased long-range correlation, irregularity, and a chaotic nature of respiratory dynamics in nonatopic asthma as compared with atopic asthma, possibly reflecting different pathophysiological mechanisms and maybe justifying a higher degree of disease severity in patients with...

Figure 1. Illustration of treatable traits of acute hypercapnic respiratory failure. COPD = chronic obstructive pulmonary disease; ICU = intensive care unit.