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EDITORIAL

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Acute respiratory failure: back to the roots!

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Hypoxic respiratory failure is one of the most commonest disorders leading to intensive care unit (ICU) admission and also a common reason for the deterioration of patients already treated in the ICU. It is a very serious condition associated with significant mortality [1, 2]. In recent decades, research and scientific attention has focused nearly exclusively on the pathophysiology and treatment of established causes of hypoxic respiratory failure such as cardiogenic pulmonary edema and the acute respiratory distress syndrome (ARDS) [1, 2]. Therefore, our diagnostic approach to patients with hypoxic respiratory failure has remained both largely unchanged and poorly validated. This is a dilemma because diagnostic uncertainty is very common. The severity of disease and the requirement for immediate ventilatory support often limit our ability to obtain a detailed patient history and physical examination. Chest X-ray is helpful but also associated with important limitations [3].

Lefebvre and colleagues are to be congratulated for shedding light on the diagnostic uncertainty associated with hypoxic respiratory failure in the ICU. In this paper they evaluate a novel approach to diagnose the cause of hypoxic respiratory failure: the measurement of B-type natriuretic peptides, specifically NT-proBNP [4]. B-type natriuretic peptides are quantitative markers of cardiac stress and heart failure (HF) summarizing the extent of systolic and diastolic left ventricular dysfunction, valvular dysfunction, and right ventricular dysfunction [5–7]. B-type natriuretic peptides have been shown to be extremely helpful in the diagnosis and prognosis of HF, particularly in the emergency department (ED). As the diagnostic dilemmas in the ICU are often as challenging as in the ED, recent studies have begun to evaluate whether the use of B-type natriuretic peptides might also be helpful in the ICU [8–12]. Major differences in patient characteristics, disease severity, comorbidity, resources available for the individual patient, and therapies applied between the ICU and the ED require that the potential clinical use of B-type natriuretic peptides in the ICU be defined by specific ICU studies.

Lefebvre and colleagues examined the use of NT-proBNP in 74 cancer patients presenting to the ICU with hypoxic respiratory failure. The rationale for focusing on cancer patients was based on the idea that rapid identification of a cardiac cause of hypoxic respiratory failure could avoid invasive procedures such as bronchoscopy and bronchoalveolar lavage in these patients. They found that NT-proBNP levels were significantly higher in patients with cardiac causes ($n = 16$) than in those with non-cardiac causes ($n = 56$). However, overall the accuracy of NT-proBNP in diagnosing HF was only moderate. NT-proBNP seemed helpful to rule out HF, but not to reliably diagnose HF [4]. The diagnostic uncertainty associated with respiratory failure in the ICU is highlighted by the fact that apparently 24 out of 74 patients received a "furosemide trial". Only 6 of these finally received a gold standard diagnosis of HF. Therefore, furo-

semide was inappropriately given to 18 patients, and appropriately to only 6 patients. On the other hand, only 6 out of 16 patients with HF received furosemide.

The following considerations might help to put these findings into perspective: First, this cohort of cancer patients differs in many aspects from unselected patients presenting with hypoxic respiratory failure [9, 10]. The patients were roughly 20 years younger and had a very low prevalence of HF as the cause of respiratory failure. Therefore, the findings of this study most likely cannot be transferred to a broader patient population. Second, the ability of an observational study to reliably quantify the diagnostic accuracy of a novel test depends on the accuracy of the gold standard diagnosis. Thus, if the gold standard is incorrect in 25% of patients, a hypothetically perfect novel test with a true accuracy of 100% would result in an accuracy of only 75%. The diagnostic uncertainty associated with hypoxic respiratory failure in the ICU is exemplified by several controversies regarding the gold standard diagnosis used in this study. The diagnosis of cardiac respiratory failure required "the absence of infection or non-infectious pulmonary involvement". This is misleading, as infection is a well-established trigger of acute HF [13]. Also, this definition neglects the clinical reality of two disorders being present and significantly contributing to respiratory failure at the same time. In addition, the gold standard diagnosis in this paper heavily relies on echocardiography. Unfortunately, the echocardiographic diagnosis of left ventricle diastolic dysfunction in critically ill patients is often challenging [14, 15]. We lack systematic studies that have validated, for example, what constitutes normal diastolic function in a 75-year-old woman with non-cardiac respiratory failure receiving positive-pressure ventilation. This limitation is further aggravated by the fact that echocardiography and NT-proBNP testing were performed at different times during ICU stay, as left ventricle diastolic function may change rapidly in response to therapy. Unfortunately, another limitation comes on top of this. As acknowledged by the authors, the detection of a cardiac dysfunction does not imply that the diagnosis of HF is the main cause of respiratory failure. For instance, a patient may have had myocardial infarction 10 years ago: his left ventricular ejection fraction is 40%, which classifies him as having systolic left ventricular dysfunction. If this patient develops respiratory failure due to pneumonia, his echo will be altered at admission but the cause of his respiratory failure is extra-cardiac.

The inherent dilemma of lack of accepted and validated gold standard diagnosis in observational studies can ultimately only be overcome by performing randomized controlled trials that apply objective measures of patient outcome as endpoints. The primary results of a large randomized controlled multicenter study (BASEL II–ICU) will soon become available and help to further elucidate the approach to ICU patients with hypoxic respiratory failure. BASEL II–ICU tests the hypothesis that the use of B-type natriuretic peptide levels in ICU patients with respiratory failure might help to more rapidly and more accurately detect the cause of respiratory failure and ultimately improve patient management and reduce total treatment cost.

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