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Increases in B-type natriuretic peptide for detecting weaning-induced heart failure: hidden biases and methodologic flaws in an observational study

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Dear Editor,

We read with interest the observational study by Zapata et al. [1] showing that changes in B-type natriuretic peptide (BNP) levels (ΔBNP >48 ng/l) during a spontaneous breathing trial (SBT) can predict cardiac origin of SBT failure with an acceptable accuracy (88.9%). Despite its potential value, this study had some design and methodologic flaws worth mentioning.

First, the postextubation application of noninvasive ventilation in high-risk patients was associated with a significant reduction in the rate of reintubation, resulting in a reduction of the risk of intensive care unit mortality [2]. Therefore, the lack of noninvasive ventilation after extubation would overestimate the rate of reintubation, and bias the study. A further selection bias may be present since the SBT failure rate in this study (32%) was higher than those reported previously [3].

Second, as pointed out by the authors (page 482 on the left), it is the extubation failure rather than SBT failure that is associated with a higher mortality rate. Indeed, there is no real need to predict SBT outcome, since a carefully monitored SBT is safe with rare occurrence of major complications [4]. We do agree that patients failing the SBT due to heart failure (HF) would benefit from preventive measures such as vasoactive drugs and diuresis, if the failure could be anticipated. However, the study by Zapata et al. [1] could not address this question because the ΔBNP, which was not measured until the patient had already failed the SBT, was determined too late. As demonstrated in the study by Anguel et al. [5], the identification of initial SBT failure due to HF would prompt the use of diuretics and/or vasodilators, which resulted in none of these patients experiencing recurrent weaning-induced pulmonary edema during their next SBT. We would wish to know whether and to what extent the patients failing their initial SBT due to HF would benefit from supportive therapy such as vasoactive drugs or diuresis in their next SBT.

Last but not least, in this study "disease" (D+) was defined as a patient failing the SBT due to HF, whereas "disease absent" (D−) was defined as patients in the other three

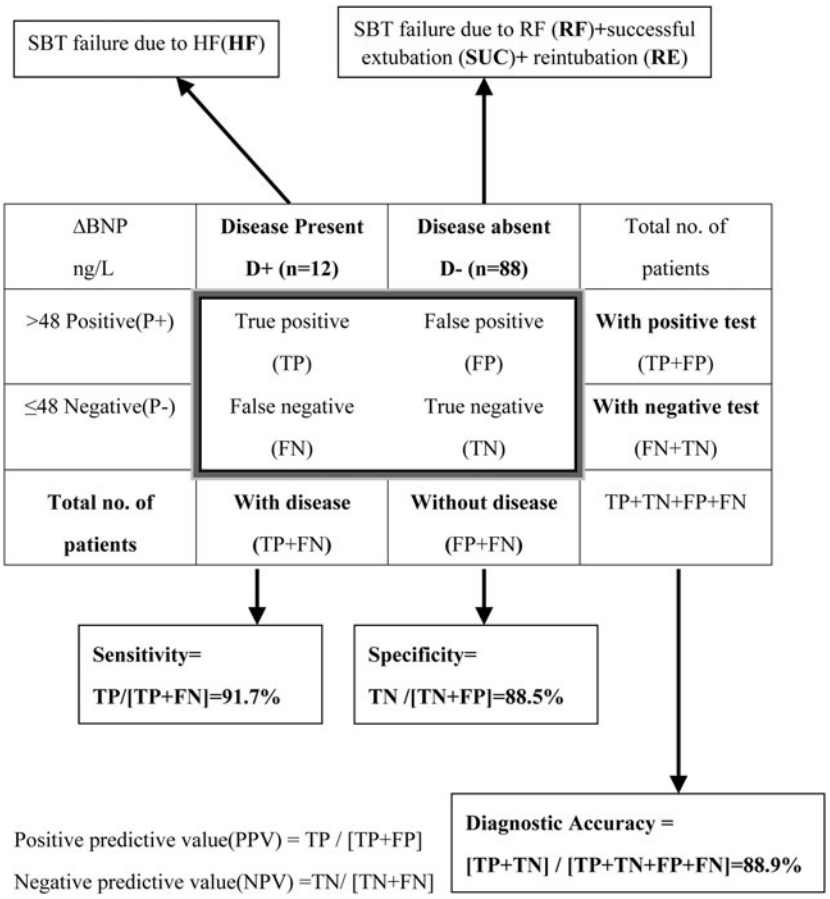

Fig. 1 Diagnostic test (ΔBNP) summarized as a 2 × 2 table. Readings of ΔBNP >48 ng/l are classified as positive test results (P+) and readings ≤48 ng/l are classified as negative test results (P−). The relationship of these binary results with disease status (D+ or D−) forms a decision matrix that has four possible combinations (TP, TN, FP and FN). PPV (52.1%) can be calculated from the sensitivity, specificity, diagnostic accuracy and the prevalence of the disease in this population (12 out of 100, 12%), using the formulas given in the figure. *RF* respiratory failure, *SBT* spontaneous breathing trial, *HF* heart failure, *BNP* B-type natriuretic peptide

groups including those failing the SBT due to respiratory failure, those succeeding extubation and those failing extubation even after a successful SBT (Fig. 1). Given the nature of BNP as a promising biomarker for HF, the low ability of BNP to discriminate between the two defined groups (D+ and D−) could partly be explained by the fact that both the D+ and D− groups would include patients developing HF during the weaning process. Indeed, six of the seven reintubated patients failing extubation due to HF had a baseline BNP >263 ng/l and were actually classified into the D− group. This defect in the definition of disease status could further be illustrated by the low positive predictive value of a ΔBNP >48 ng/l (52.1%) in predicting SBT failure due to HF, despite the presence of a relatively high sensitivity (91.7%) and specificity (88.5%).

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Conflict of interest None.

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Increases in B-type natriuretic peptide for detecting weaning-induced heart failure: reply to Liu et al.

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Dear Editor,
We thank Liu et al. [1] for their comments on our study published in your journal [2] and would like to clarify the points raised.

First, it is important to keep in mind that our study aimed to predict and diagnose the onset of heart failure (HF) during a spontaneous breathing trial (SBT). HF was *predicted* by determining *BNP before* the SBT (baseline BNP >263 ng/l, accuracy 68%), while HF was *diagnosed* during the SBT based on the *changes in BNP* (ΔBNP >48 ng/l, accuracy 88.9%).

Second, the use of non-invasive ventilation (NIV) certainly reduces the need for reintubation by 16% [3], but only in a selected group of patients at risk of postextubation respiratory failure. In our study ten patients were reintubated, but only five could be considered "at risk" [3]. This means that less than one patient would have benefited from the prophylactic use of NIV. We do not therefore consider that this bias alters the interpretation of our results.

Third, we agree that our SBT failure rate (32%), albeit within the range described in other studies [4], may seem high, especially compared with that of Segal et al. [5] (19%). This discrepancy, however, could be due to differences in populations. In our study the mean days of mechanical ventilation (MV) prior to SBT in patients who failed was 10 days, whereas in Segal's study it was 6 days. This suggests that a greater proportion of patients in our study had weaning defined as difficult according to the international consensus conference [6].

In reply to the next point, we did not study mortality in our study. However, we observed that patients who failed their first SBT due to HF had a longer duration of MV and ICU stay. Predicting (*baseline BNP*) the onset of HF caused by the SBT allows for prompt treatment, possibly reducing the days of MV. A ΔBNP >48 ng/l during SBT is a non-invasive *diagnostic* indicator of HF, available 24 h a day.

To answer Liu et al.'s question, we would like to point out that we did not analyze the following SBTs, so we do not possess any data that allow us to elucidate to what extent the patients may have benefited from diuretic and vasodilator treatment.

Lastly, regarding their suggestion to combine analysis of HF at the end of the SBT with that appearing in the next 48 h after extubation, we consider such an approach would be erroneous for the following reasons. First, the two groups were not homogenous as the timing between blood tests was shorter in the patients failing the SBT than in the patients requiring reintubation within 48 h. Second, after succeeding in the SBT trial and until reintubation was necessary, patients requiring reintubation were on therapies that could alter natriuretic peptide concentrations. Third, the disease under study is HF during SBT. Therefore, even extubated patients that were reintubated because of HF should be considered "disease absent" (D−). Analysis of these patients would require a specific study design.

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