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## B-type natriuretic peptide and weaning from mechanical ventilation

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**Abstract** *Objective:* Cardiac function and volume status could play a critical role in the setting of weaning failure. B-type natriuretic peptide (BNP) is a powerful marker of cardiac dysfunction. We assessed the value of BNP during the weaning process. *Design, setting and patients:* One hundred and two consecutive patients considered ready to undergo a 1-h weaning trial (T-piece or low-pressure support level) were prospectively included in a medical intensive care unit of a university hospital. Weaning was considered successful if the patient passed the trial and sustained spontaneous breathing for more than

48 h after extubation. *Interventions:* Plasma BNP was measured just before the trial in all patients, and at the end of the trial in the first 60 patients. *Results:* Overall, 42 patients (41.2%) failed the weaning process (37 patients failed the trial and 5 failed extubation). Logistic regression analysis identified high BNP level before the trial and the product of airway pressure and breathing frequency during ventilation as independent risk factors for weaning failure. BNP values were not different at the end of the trial. In nine of the patients in whom the weaning process failed, it succeeded on a later occasion after diuretic therapy. Their BNP level before weaning decreased between the two attempts (517 vs 226 pg/ml,  $p = 0.01$ ). In survivors, BNP level was significantly correlated to weaning duration ( $\rho = 0.52$ ,  $p < 0.01$ ). *Conclusions:* Baseline plasma BNP level before the first weaning attempt is higher in patients with subsequent weaning failure and correlates to weaning duration.

**Keywords** Cardiac insufficiency · B-type natriuretic peptide · Artificial respiration · Spontaneous breathing trial · Extubation

## Introduction

Complications of invasive mechanical ventilation increase with the duration of ventilator dependence [1, 2]. Patients should therefore be weaned from mechanical ventilation as quickly as possible. However, both delayed and premature weaning may be harmful [3, 4]. The need for accurate prediction of weaning outcome is therefore important. So far, no reliable predictor of weaning failure has been identified while the patient is still under mechanical ventilation [5]. The pathophysiology underlying weaning failure is complex and the relative weight of the different factors involved not completely understood. Cardiac function and, more importantly, volume status may play a key role in this setting [6, 7]. B-type natriuretic peptide (BNP) is a 32-amino acid protein that is released from the cardiac ventricles in response to myocyte stretch [8]. BNP is the most powerful hormonal predictor of left-ventricular dysfunction, and its plasma level has been correlated to left-ventricular filling pressures [9, 10]. The present study aimed at prospectively assessing the possible association of BNP level with weaning outcomes. We hypothesized that patients with unsuccessful weaning might frequently have increased plasma BNP levels as compared to successful weaning patients.

## Condensed methods

See electronic supplementary material for additional details.

### Study population

The study was approved by the institutional ethics committee of the "Société de Réanimation de Langue Française". We prospectively included 102 consecutive patients who had been under mechanical ventilation for more than 24 h and were considered ready to undergo a weaning trial. According to the ICU policy and to guidelines [11], a daily screening test was performed and considered positive when the following criteria were present: clear improvement or resolution of the reason for starting mechanical ventilation, body temperature  $< 39^{\circ}\text{C}$ , hemoglobin  $> 7\text{ g/dl}$ , no further need for continuous sedative agents, adequate gas exchange ( $\text{PaO}_2 > 60\text{ mmHg}$  with  $\text{FiO}_2 \leq 40\%$  and  $\text{PEEP} \leq 5\text{ cmH}_2\text{O}$ ), and no need for high doses of vasoactive agents. Exclusion criteria included tracheostomy and preexisting neuromuscular disease (stroke, myasthenia gravis and Guillain-Barré syndrome), in which weaning is managed differently, as well as renal failure (serum creatinine  $> 180\text{ }\mu\text{mol/l}$ ), which strongly influences the BNP levels.

### Classification of weaning outcomes

The ability of patients to sustain spontaneous breathing was evaluated via a weaning trial (WT). The WT lasted 1 h and consisted in 93 patients of a T-piece trial and in 9 patients of a low-pressure support trial with zero end-expiratory positive pressure, previously shown to offer results similar to a T-piece trial in terms of extubation outcome [3]. A priori criteria for WT failure [12] were: (1) respiratory frequency  $> 35$  breaths/min and increased accessory muscle activity, (2) arterial oxygen saturation  $< 90\%$  on pulse oximetry, (3) heart rate  $> 140$  beats/min, (4) systolic blood pressure  $> 200$  or  $< 80\text{ mmHg}$ , and (5) diaphoresis and clinical signs of distress. Patients free of these features at the end of the WT succeeded the trial and were extubated. Extubation was considered a failure if the patient required reintubation within 48 h. Weaning duration was defined as the time elapsed between the first WT and successful extubation.

### Data collection and BNP measurement

During assisted mechanical ventilation, the patient's respiratory frequency monitored by the ventilator (only triggered breaths were taken into account, ineffective efforts being not recorded,  $f_{\text{MV}}$ ), tidal volume ( $V_{\text{T}}$ ), minute ventilation ( $V_{\text{E}}$ ), level of pressure support (PS), and positive end-expiratory pressure (PEEP) were recorded just before performing the WT. Dynamic compliance ( $C_{\text{dyn}}$ ) of the respiratory system was calculated as  $V_{\text{T}}$  divided by the PS level. We tried to estimate patient's tolerance to assisted breathing by calculating the product of airway pressure and breathing frequency (pressure-frequency product, PFP) as  $f_{\text{MV}} \times \text{PS}$  level.

A sample of arterial blood was collected within the 2 h preceding the WT for blood gas analysis and plasma BNP measurement using a rapid fluorescence immunoassay (Triage, Biosite Diagnostics). In addition, BNP measurement was repeated at the end of the WT in the first 60 patients. Physicians were blinded for BNP result. In 66 patients, an echocardiography was ordered on clinical grounds by the attending physician to evaluate left-ventricular ejection fraction [13], a median of 6 days before weaning.

### Statistical analysis

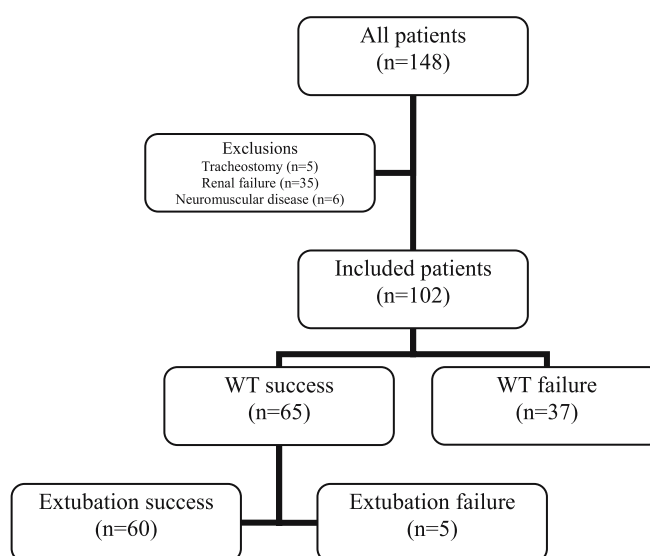
Statistical analysis was performed using SPSS Base 11.5 statistical software (SPSS, Chicago, IL). Continuous variables were expressed as median (25th–75th percentile) and were compared using the Wilcoxon paired test (for related

samples) or the Kolmogorov–Smirnov test (for independent samples). Categorical variables, expressed as percentages, were analyzed with a chi-square test or a Fisher’s exact test. A two-tailed  $p$  value of less than 0.05 was taken to indicate statistical significance. Correlations were tested using Spearman’s method. Receiver operating characteristic (ROC) curve analysis was performed to assess plasma BNP’s ability to discriminate between patients who succeeded weaning and those who failed. A true-positive (TP) result was defined as when the test predicted successful weaning and weaning actually occurred; a false-positive (FP) result was when the test predicted successful weaning but weaning failed; a false-negative (FN) result was when the test predicted weaning failure but it was indeed successful; a true-negative (TN) result as when the test predicted weaning failure and the patient really failed weaning. To evaluate independent risk factors for weaning failure, significant univariate risk factors were examined using backward stepwise logistic regression analysis. To avoid overfitting of the model, we considered that we could enter a total a number of four variables in the model, in view of the 42 events observed [14, 15]. Among the two related respiratory variables ( $f_{MV}$  and PFP), only the most clinically relevant (PFP) was entered into the regression model in order to minimize the effect of colinearity. Thus, the four variables entered into the model (as continuous variables) were: age,  $C_{dyn}$ , PFP, and BNP.

## Results

### Patient characteristics and weaning outcome

Patient clinical characteristics are reported in Table 1. Figure 1 displays weaning outcomes in the study population. Overall, 42 patients (41.2%) failed the weaning process (37 patients failed the WT and 5 patients failed extubation). Reasons for extubation failure included one case of



**Fig. 1** Flow chart of weaning outcomes in the study population. WT, weaning trial

stridor, one case of pulmonary edema, one case of septic shock, and two cases of delayed cardiac arrest. Table 2 displays clinical and biological parameters before weaning in the weaning success and weaning failure groups. As compared to the success group, patients who failed weaning were older, with lower values of  $C_{dyn}$  and higher levels of  $f_{MV}$ , PFP, and plasma BNP (Table 2). Logistic regression analysis identified plasma BNP level and PFP as independent risk factors for weaning failure (Table 3). In 66 patients, left-ventricular ejection fraction was estimated by echocardiography before weaning, revealing systolic cardiac dysfunction (ejection fraction < 45%) in 21 cases. Among these 66 patients explored with echocardiography, there was no difference between the weaning success and the weaning failure patients concerning prevalence of systolic cardiac dysfunction [12 (37.5%) vs 9 (26.5%),  $p = 0.43$ ].

**Table 1** Clinical characteristics of patients ( $n = 102$ )

	Success of weaning ( $n = 60$ )	Failure of weaning ( $n = 42$ )	$p$
Age, years	57 (46–71)	73 (60–80)	0.001
Male sex	36 (60)	29 (69)	0.41
SAPS II at admission	53 (37–65)	48 (36–65)	0.99
Cause of mechanical ventilation			0.10
Respiratory failure	21 (35)	24 (57)	
Coma	25 (41)	8 (19)	
Surgery	5 (8)	2 (5)	
Cardiac arrest	6 (10)	4 (10)	
Septic shock	3 (5)	4 (10)	
COPD	12 (20)	14 (33)	0.17
Congestive heart failure	12 (20)	12 (29)	0.35

Data are number (% of patients) or median (25th–75th percentile) SAPS, Simplified Acute Physiologic Score; COPD, chronic obstructive pulmonary disease

**Table 2** Clinical and biological parameters before weaning

	Success of weaning (n = 60)	Failure of weaning (n = 42)	p
Mean blood pressure, mmHg	87 (77–100)	83 (75–93)	0.30
Heart rate, beats/min	93 (80–108)	95 (81–103)	0.96
MV duration prior to weaning, days	5 (2–10)	5 (3–10)	0.98
Mode of ventilation			0.20
Pressure-support	57 (95.0%)	37 (88.1%)	
Assist-control	3 (5.0%)	5 (11.9%)	
f <sub>MV</sub> , breaths/min	21 (17–26)	25 (23–28)	0.001
V <sub>E</sub> , L/min	10.8 (7.6–11.8)	10.4 (9.8–13.8)	0.18
PS, cmH <sub>2</sub> O	12.0 (12.0–16.0)	15.5 (12.8–18.5)	0.09
PEEP, cmH <sub>2</sub> O	5.0 (3.0–5.0)	5.0 (4.0–6.0)	0.40
C <sub>dyn</sub> , ml/cmH <sub>2</sub> O	39 (29–51)	32 (22–38)	0.02
PFP, cmH <sub>2</sub> O.breaths/min	264 (206–342)	390 (277–503)	0.001
Arterial pH	7.46 (7.42–7.50)	7.45 (7.39–7.49)	0.92
PaO <sub>2</sub> /FiO <sub>2</sub> ratio, mmHg	278 (218–333)	239 (173–313)	0.11
PaCO <sub>2</sub> , mmHg	39 (34–45)	41 (38–52)	0.15
Plasma creatinine, μM	78 (65–95)	83 (59–120)	0.08
Hemoglobin, g/dl	11.0 (9.1–12.1)	9.5 (8.2–11.8)	0.18
BNP, pg/ml	104 (42–242)	516 (345–776)	<0.001

Data are number (% of patients) or median (25th–75th percentile) MV, mechanical ventilation; f<sub>MV</sub>, respiratory frequency under mechanical ventilation; V<sub>E</sub>, minute ventilation; PS, level of pressure support; PEEP, positive end-expiratory pressure; C<sub>dyn</sub>, dynamic compliance (tidal volume/level of pressure support); PFP, pressure frequency product (respiratory frequency × level of pressure support); BNP, plasma B-type natriuretic peptide concentration

**Table 3** Multivariate analysis of risk factors for weaning failure

Variable	Logistic regression O.R. (95% CI)	Wald chi-square	p
Age, years	1.02 (0.97–1.08)	0.77	0.38
C <sub>dyn</sub> , ml/cmH <sub>2</sub> O	0.99 (0.93–1.05)	0.15	0.70
PFP, per 10 cmH <sub>2</sub> O.breaths/min	1.09 (1.03–1.15)	10.0	0.002
BNP, per 100 pg/ml	1.90 (1.40–2.62)	16.4	<0.0001

C<sub>dyn</sub>, dynamic compliance (tidal volume/level of pressure support); PFP, pressure frequency product (respiratory frequency × level of pressure support); BNP, plasma B-type natriuretic peptide concentration; OR, odds ratio; CI, confidence interval

The Hosmer and Lemeshow goodness of fit test showed a good calibration of the model:  
 $\chi^2$  (7 df) = 9.830, p = 0.19

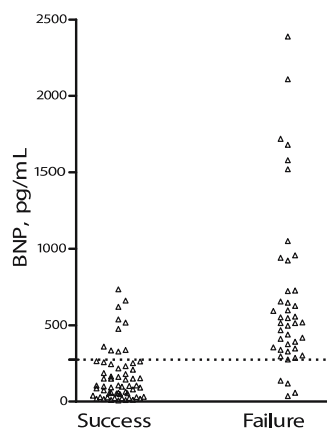
### Predictive capacity of BNP

Plasma BNP level before first weaning attempt in patients with success or failure of weaning is displayed in Fig. 2. The area under the ROC curve for plasma BNP to predict weaning failure was  $0.89 \pm 0.04$  and a cutoff value of 275 pg/ml was associated with the highest diagnostic accuracy (86%; Fig. 3). The predictive value of BNP for the outcome of the sole WT was similarly high, with a ROC curve displaying an area of  $0.90 \pm 0.03$  and a diagnostic accuracy of 85% for a cutoff value of 275 pg/ml. In the group of patients with a successful WT, BNP did not significantly differ between those succeeding extubation and those failing extubation: 105 (39–245) vs 355 (78–524) pg/ml, p = 0.26.

### Changes in hemodynamics and BNP levels during a WT

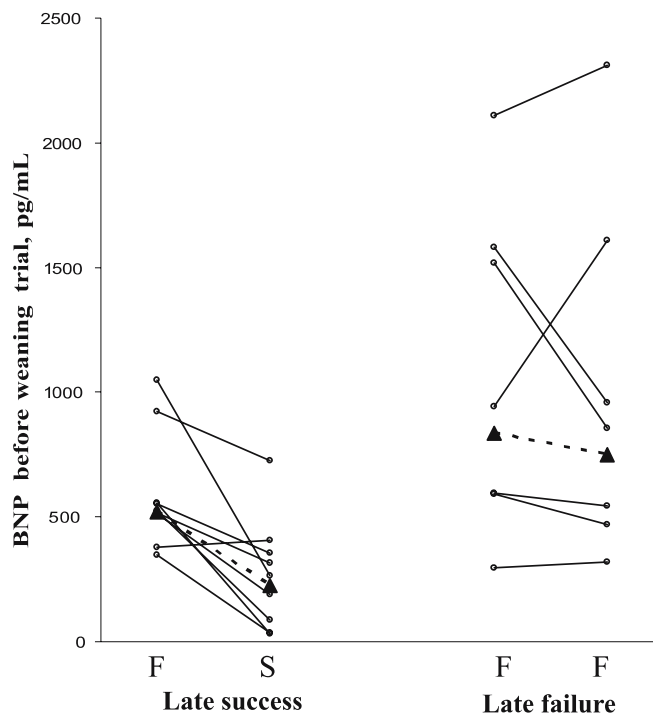
The change in mean arterial pressure between the beginning and the end of the WT was marginally significant: 87 (76–97) vs 90 (81–100) mmHg, p = 0.045. The change in heart rate between beginning and end of WT was not significant: 93 (80–104) vs 97 (84–110) bpm, p = 0.08. In the first 60 patients, BNP level was measured before and at the end of WT. Among them, 37 patients accomplished the WT successfully, whereas 23 failed the WT. There was no significant difference in BNP levels before and at the end of WT in the two groups of patients (162 (56–338) vs 152 (69–390) pg/ml, p = 0.14, and 518 (419–958) vs 675 (419–1200) pg/ml, p = 0.22, respectively; see Figure E1 in the electronic supplementary material).

**Fig. 2** Individual BNP levels before WT's in patients with success or failure of weaning



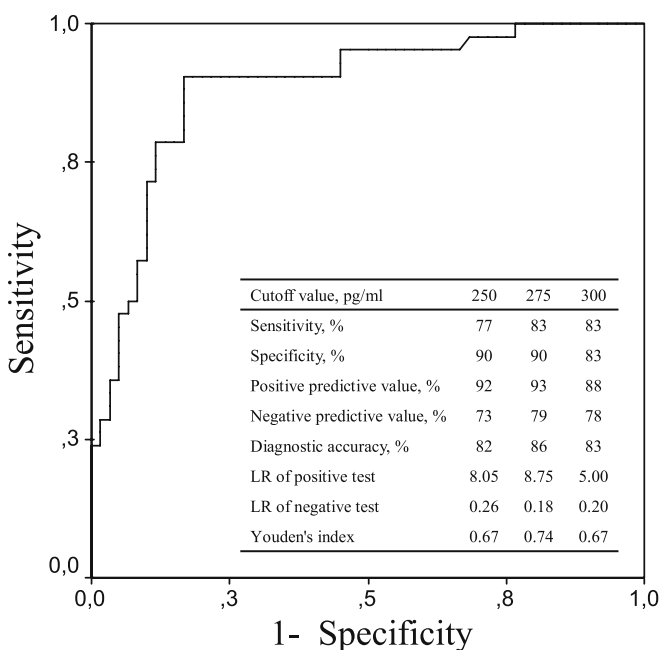
#### Changes in BNP levels between consecutive WT attempts

In 18 patients who had failed their first WT, BNP was measured again during a second WT (this second value is not included in the above analysis of BNP predictive capacity at first attempt), after a median of 3 (1–8) days. During the second attempt, 10 of these patients succeeded the WT (late success) whereas the 8 others failed again (late failure). Between the two trials, 8 (80%) patients in the late success group and 4 (50%) patients in the late failure group received diuretics ( $p = 0.32$ ). BNP level significantly decreased in late-success patients (517 (370–648) vs 226 (61–368) pg/ml,  $p < 0.01$ ), whereas no significant change



**Fig. 4** Changes in plasma BNP levels observed between two consecutive WT attempts in patients experiencing success (*Late success*) or failure (*Late failure*) at the second WT attempt ( $n = 18$ ). Broken lines represent median values

occurred in late-failure patients (834 (593–1565) vs 748 (488–1447) pg/ml,  $p = 0.58$ , Fig. 4). Fluid balance during the 3 days preceding the last WT was marginally lower in late-success patients than in late-failure patients: +820 (–2327, +1950) vs +4197 (+2770, +5140) ml,  $p = 0.06$ .



**Fig. 3** ROC curve and diagnostic accuracy for BNP to predict weaning failure. LR, likelihood ratio. The BNP cut-offs associated with a ~100% positive predictive value and 100% negative predictive value are 35 pg/ml and 750 pg/ml respectively

#### Patient outcome

Patients with a BNP level above 275 pg/ml had a significantly longer duration of weaning than others (72 (24–192) vs 0 (0–24) h,  $p < 0.01$ ). The rate of ICU death was significantly higher in the weaning failure group than in patients successfully weaned (35.7% vs 5.0%,  $p < 0.01$ ). In ICU survivors, BNP level was significantly correlated to weaning duration ( $\rho = 0.52$ ,  $p < 0.01$ ).

#### Discussion

The present study identified BNP, along with PFP, as an independent risk factor for weaning failure by logistic regression analysis. BNP level was significantly correlated to weaning duration in ICU survivors.

The higher plasma BNP level measured in patients with subsequent failure of weaning reflects volume or pressure overload state. At the cellular level, cardiomy-

ocyte stretch is the predominant stimulus controlling the release of BNP from the ventricles. BNP is therefore a powerful marker of ventricular dysfunction. In our study, however, there was no difference between the weaning success and the weaning failure groups concerning prevalence of systolic cardiac dysfunction in the subgroup of patients explored with echocardiography. It is also possible that the previous finding of systolic cardiac dysfunction had already resulted in a specific management of patients by the attending physician prior to the WT, thus favoring successful weaning. However, increased levels of BNP in the failure group may also embody other phenomena on top of cardiac systolic dysfunction, including diastolic dysfunction, pulmonary hypertension (and right ventricular dysfunction), or fluid overload.

BNP is a reliable marker of ventricular diastolic dysfunction [16, 17]. Abnormalities of diastolic function are frequent in critically ill patients [18] and may play a role in patients failing weaning from mechanical ventilation. Withdrawal of mechanical ventilation has several physiological consequences that may challenge the cardiovascular system during weaning and unmask subclinical diastolic dysfunction and/or fluid overload. The reduction in intrathoracic pressures raises venous return and central blood volume [6, 19], and increases left ventricular transmural ejection pressure and afterload [20]. Catecholamine secretion results in tachycardia and increases right and left ventricular afterloads [7, 21]. Also, baseline pulmonary artery pressure has been previously shown to be higher in weaning failure patients than in the success group [7, 22]. BNP has a diagnostic role in pulmonary hypertension and right ventricular overload. Studies in patients with pulmonary hypertension have demonstrated significant correlations between BNP levels and mean pulmonary arterial pressure, as well as pulmonary vascular resistance [23, 24, 25]. Finally, positive fluid balance has been recently shown to be associated with weaning failure in medical critically ill patients [26].

Patients with weaning failure were older than those who succeeded the weaning, a factor which influences BNP level [27]. However, we checked in bivariate (data not shown) and multivariate analysis that BNP remained significantly associated with weaning failure after adjustment for age. In addition, the age-predicted change in BNP in our patients would be much smaller than the difference observed between the weaning failure and weaning success groups [28].

Identification of cardiovascular dysfunction as a cause of weaning failure is clinically difficult, but, more importantly, such dysfunction is not predictable before weaning is attempted. Several studies have demonstrated the occurrence of cardiac dysfunction [29] with increase in filling pressures during withdrawal of mechanical ventilation in some patients failing WT [6, 7, 30], as well as subclinical ischemic manifestations during weaning of patients with coronary artery disease [31]. Lemaire et al. [6] documented

huge increases in pulmonary artery occlusion pressure during unsuccessful weaning attempts in 15 patients with severe chronic obstructive pulmonary disease and cardiovascular disease. However, baseline filling pressures (right atrial and occlusion pulmonary artery pressure) have been reported as unreliable predictors of weaning failure [6, 7]. Jubran et al. [7] reported a progressive fall in mixed venous oxygen saturation on discontinuation of the ventilator in eight patients who failed a WT, as a result of increased oxygen extraction by tissues and relative decrease in convective oxygen transport. However, mixed venous oxygen saturation was not different between the success and the failure group before the WT and the value under mechanical ventilation could not be used to predict weaning outcome. In a recent study, Zakyntinos et al. [32] demonstrated that in patients who failed WT having increased oxygen consumption, this increase was met mainly by an increase in oxygen extraction, with a decrease of SvO<sub>2</sub>. Arterial lactate significantly increased in only three patients who failed WT with increased oxygen consumption and exhibited heart failure and the highest decreases in SvO<sub>2</sub>.

In our study, BNP level did not significantly change between the beginning and the end of the WT. Thus, measuring BNP at the end of the WT did not add any significant information. One possible explanation is that the rise in filling pressures in patients failing weaning appears small in the absence of heart disease [33, 34]. Another explanation is the particular secretion profile of BNP. In fact, contrary to preformed ANP, which is released rapidly from secretory granules in atrial myocytes [35], BNP is regulated at the level of gene expression and, therefore, its release is delayed [36]. Patients could thus have increased concentrations of precursors while lacking biologically active peptides. In this setting, Matsumoto et al. reported a nonsignificant increase in BNP despite the raised left-ventricular end-diastolic pressure in an early phase of ventricular overload [37].

In our study, baseline plasma BNP level was significantly correlated to duration of weaning. In patients having failed the first weaning attempt, a decrease in BNP level was associated with success of the second attempt. These results are in accordance with those of Lemaire et al. [6], who demonstrated a reduction in blood volume after diuretic treatment in patients having previously failed weaning with markedly increased pulmonary artery occlusion pressure. BNP seems able to mirror the effectiveness of therapies designed to reduce filling pressures. In patients being treated for acutely decompensated heart failure, BNP concentration has been shown to decrease in parallel with the fall in pulmonary capillary wedge pressure during a period of 24 h [38].

Our study has some limitations. Firstly, the exclusion of patients with tracheostomy, renal failure, and neuromuscular disease precludes generalization of our findings to all intensive care unit populations. In particular, because of its relationship to renal function [39], whether plasma

BNP maintains a high level of accuracy in patients with kidney disease warrants further investigations. Secondly, we could not demonstrate which precise mechanism explains plasma BNP increase in patients failing the weaning process. All patients were not evaluated by echocardiography. Furthermore, besides systolic dysfunction, diastolic abnormalities and pulmonary hypertension, which were not systematically assessed in our study, may play an important role. Moreover, having no systematic recordings of fluid balance, we cannot definitely link the pathophysiology of weaning failure in patients with high BNP value before the WT to fluid overload. Thirdly, the small sample size limited the number of variables included into the regression model. Finally, the single-center nature of the study, with a high proportion of patients with some degree of systolic dysfunction (one third), should make one cautious regarding the external validity of our data, since the results may heavily depend on the type of patients, the ventilator practices, and the general fluid management in the ICU.

The present study has potential clinical implications. BNP could be useful to guide therapy when managing acute left ventricular failure or fluid overload during weaning from mechanical ventilation. In this setting, incorporation of BNP measurement in a formal weaning protocol to optimize the weaning process and reduce weaning duration warrants further research. The evidence that BNP could be used as a diagnostic tool to aid in the prediction of weaning failure before starting a WT is more problematic. Although a cutoff value of 275 pg/ml was associated with a high diagnostic accuracy, this threshold may not be optimal in terms of individual clinical decision analysis whenever the medical consequences of a false-negative or false-positive result are dissimilar. Furthermore, the clinical interest of this prediction may be limited, since the harmfulness of the WT is not clearly demonstrated.

In conclusion, baseline plasma BNP level before the first weaning attempt is higher in patients with subsequent weaning failure and correlates to weaning duration.

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