Intensive Care Med (2008) 34:833–839
DOI 10.1007/s00134-008-1000-4

ORIGINAL

Aurélie Lefebvre
Suzanne Kural-Menasché
Michael Darmon
Guillaume Thiéry
Jean-Paul Feugeas
Benoît Schlemmer
Élie Azoulay

Use of N-terminal pro-brain natriuretic peptide to detect cardiac origin in critically ill cancer patients with acute respiratory failure

Received: 13 July 2007
Accepted: 4 December 2007
Published online: 24 January 2008

This article is discussed in the editorial available at: http://dx.doi.org/10.1007/s00134-008-1001-3.

This study was supported by grants from the Assistance Publique Hôpitaux de Paris (AOM 04139), the French Society for Critical Care Medicine, and the Sepsis Academy of Ile de France (SAIF).

A. Lefebvre · S. Kural-Menasché · M. Darmon · G. Thiéry · J. Feugeas · B. Schlemmer · É. Azoulay (✉)
Hôpital Saint-Louis, AP-HP, Service de Réanimation Médicale,
1 avenue Claude Vellefaux, 75010 Paris, France
e-mail: elie.azoulay@sls.aphp.fr

Abstract *Objective:* To assess the accuracy of plasma N-terminal-pro-B-type natriuretic peptide concentrations (NT-proBNP) as a diagnostic tool to recognize acute respiratory failure (ARF) of cardiac origin. *Methods:* Prospective observational study in 100 medical intensive care unit (ICU) patients. NT-proBNP was measured at ICU admission, and diagnosis of cardiac dysfunction was performed using echocardiography. *Results:* Sixteen patients had cardiac ARF, 58 patients had noncardiac ARF, and 26 patients were non-ARF controls. Median (IQR) NT-proBNP was 1,951 (617–9,320) pg/ml and was significantly influenced by the level of renal dysfunction. Patients with noncardiac ARF had higher NT-proBNP [1,912 (704–1,922) pg/ml] than non-ARF patients [1,022 (383–2,613) pg/ml], but lower concentrations than cardiac ARF patients [4,536 (1,568–35,171) pg/ml]. The area under the curve (AUC) was 0.663 ± 0.078 (95% confidence interval 0.510–0.815) and was not significantly influenced by the level of renal dysfunction. In addition, using a stepwise logistic regression model, NT-proBNP failed to predict independently the presence of cardiac dysfunction. However, with specificity and negative predictive value of 100%, a NT-proBNP cutoff value of 500 pg/ml seemed useful to rule out cardiac dysfunction. Indeed, none of the 16 patients with cardiac ARF had a NT-proBNP value below 500 pg/ml, whereas it was the case in 8 (30.8%) non-ARF controls and in 12 (20.7%) noncardiac ARF patients. *Conclusions:* In cancer patients with ARF, plasma NT-proBNP concentration is not a relevant tool to recognize cardiac dysfunction, but is specific enough to rule out the diagnosis in patients with plasma NT-proBNP concentrations below 500 pg/ml.

Keywords N-terminal pro B-type natriuretic peptide · Acute respiratory failure · Cancer patients · Congestive heart failure · Bronchoscopy · BAL

Introduction

Acute respiratory failure (ARF) is one of the major reasons for ICU admission in cancer patients [1–4]. ARF complicates the course of the malignancy in about 10% of the patients [5, 6], and half the patients admitted to the ICU will die, particularly when mechanical ventilation is needed [3, 5, 7, 8]. Pulmonary involvement can be of infectious (opportunistic or bacterial) or noninfectious origin (i.e., infiltration by the malignancy, drug-related pulmonary toxicity, or cardiac pulmonary edema) Making every effort to determine the etiology of the ARF improves survival [5, 9–11]. More specifically, patients with ARF of cardiac origin have a better outcome, possibly related to a higher likelihood of reversibility of the respiratory deterioration after adequate therapy [5]. Therefore, a simple and quick strategy allowing rapid detection of cardiac ARF might be useful in enabling earlier adequate therapy and in implementing

a more adequate diagnostic strategy without bronchoscopy and bronchoalveolar lavage (BAL). Therefore, a simple and noninvasive biomarker of cardiac ARF could obviate such invasive procedures in cardiac patients and indicate urgent BAL in noncardiac ARF.

In clinical practice, differentiating congestive heart failure (CHF) from other causes of ARF is the result of clinical examination, chest radiography (CXR), and echocardiography or other tools to evaluate cardiac function [12]. However, echocardiography is a standard method for detecting left ventricular dysfunction, but it is not routinely available round-the-clock in the ICU, and experienced personnel are needed to perform the examination and evaluate the data. Therefore, there may be a place for a fast, simple, and reproducible method to detect CHF in cancer patients admitted to the ICU.

B-type natriuretic peptide (BNP) is a predominantly ventricular-derived cardiac neurohormone that is secreted in response to ventricular overdistension [13]. Maisel et al. showed that BNP measurement offers a high degree of accuracy in identifying patients with heart failure who present with acute dyspnea [14]. Furthermore, it has been reported that BNP is a sensitive and specific test for the diagnosis of CHF in the urgent-care setting [15], and that BNP measurement was superior to two-dimensional echographic determination of ejection fraction (EF) in identifying CHF, regardless of the threshold value [12]. However, BNP concentrations are frequently elevated in critically ill patients, and several preexisting disorders influences BNP concentration [16–18]. Nevertheless, even though BNP has been used as a marker of cardiac involvement [19], or toxicity in cancer patients receiving chemotherapy [20, 21], BNP or NT-proBNP have never been evaluated in cancer patients admitted to the ICU. In addition, serious doubts have been raised regarding the accuracy of BNP in cancer patients outside the ICU [18, 22–24].

We sought to determine the performance of NT-proBNP to detect cardiac dysfunction in critically ill cancer patients. To do so, we performed a 10-month prospective study in which NT-proBNP plasma concentrations were measured in 100 cancer patients on the day of ICU admission, including patients with cardiac ARF, patients with noncardiac ARF and non-ARF control patients without cardiac dysfunction.

Patients and methods

This prospective observational study included 100 consecutive cancer patients admitted to the medical ICU of

Table 1 Patients' characteristics

	All patients, $n = 100$	Non-ARF controls $n = 26$	Cardiac ARF $n = 16$	Noncardiac ARF $n = 58$	p value
Age, years	53 (37–64)	56 (42–65)	41.5 (18–62)	53 (41–65)	0.17
Male gender	59 (59%)	59 (59%)	37 (63.8%)	16 (61.5%)	0.15
SAPS II score at admission	45 (33–62)	39 (24–52)	54.5 (33–72)	46 (36–63)	**0.09**
LOD score at admission	5 (2–8)	4 (1–6)	6.5 (4–10.5)	6 (3–8)	**0.04**
Risk of cardiovascular disease	32 (32%)	8 (30.8)	6 (37.5)	18 (31)	0.86
Time (days) from respiratory symptoms onset	5 (1–10)	/	2 (1–4)	5 (2–15)	**0.04**
Leukemia or lymphoma	57 (57%)	19 (73)	8 (50)	31 (53.5)	0.31
Time (days) from diagnosis of the malignancy	60 (3–673)	30 (1–365)	82 (13–1229)	90 (10–626)	0.36
Temperature (°C)	38 (37–39.2)	38.3 (37–39.4)	38 (36.7–38.8)	38 (37–39.2)	0.86
$PaCO_2$ at admission	35 (30–40.5)	35 (30–40)	37.5 (29.5–44.5)	35 (30–40)	0.75
Diffuse crackles at lung auscultation	47 (47%)	2 (7.7)	12 (75)	33 (56.9)	**< 0.0001**
Neutropenia	30 (30%)	8 (30.8)	5 (31.2)	17 (29.3)	0.98
Creatinine concentration, μmol/l	80 (60–141)	75.5 (60–119)	89 (67–144)	80 (58–140)	0.89
PaO_2 / FiO_2	216 (122–378)	417 (315–476)	229 (113–361)	145 (100–258)	**< 0.0001**
Chest X-ray findings					
Focal or unilateral alveolar infiltrates	16 (16%)	1 (3.8)	0 (0)	15 (25.9)	**0.006**
Bilateral alveolar infiltrates	7 (7%)	1 (3.8)	1 (6.2)	5 (8.6)	0.70
Interstitial infiltrates	14 (14%)	1 (3.8)	3 (18.7)	10 (17.2)	0.21
Alveolar interstitial	28 (28%)	1 (3.8)	10 (62.5)	17 (29.3)	**< 0.0001**
Cardiothoracic ratio	0.40 (0.40–0.50)	0.40 (0.40–0.40)	0.60 (0.45–0.65)	0.40 (0.40–0.40)	**< 0.0001**
Noninvasive mechanical ventilation	16 (16%)	1 (3.8)	3 (18.7)	12 (20.7)	**0.08**
Mechanical ventilation	44 (44%)	4 (15.4)	9 (56.2)	31 (53.5)	**0.001**
Vasopressors or dobutamine	36 (36%)	4 (15.4)	7 (43.7)	25 (43.1)	**0.02**
Renal replacement therapy	23 (23%)	4 (15.4)	2 (12.5)	17 (29.5)	0.19
Furosemide trial	24 (24%)	0	11 (68.8%)	13 (22.4%)	**< 0.0001**
ICU length of stay (days)	5.5 (3–10)	5.5 (4–8)	4 (2–8)	6 (3–11)	0.27
NT-proBNP concentrations, pg/ml	1951 (617–9320)	1022 (383–2613)	4536 (1568–35171)	1912 (704–1922)	0.01
ICU mortality	32 (32%)	5 (19.2)	5 (21.2)	22 (37.9)	0.21

the Saint-Louis Hospital between 1 November 2004 and 1 September 2005. The Saint-Louis Hospital, a 630-bed university and tertiary hospital in Paris, France, comprises 230 hematology or oncology beds. The medical ICU is a closed unit that admits 650 patients per year, including 150–200 cancer patients. The institutional review board approved the protocol, and informed consent was obtained from the patients or their next of kin.

ARF was defined as respiratory rate > 30 or respiratory distress symptoms, or PaO_2 on room air < 60 mmHg, or need for ventilatory support [1]. In our center, cancer patients are routinely managed by a multidisciplinary team that includes the referring oncologist or hematologist. All cancer patients were included in this study, regardless of their reason for ICU admission. For each study patient, the data reported in Table 1 were collected. Acute renal failure was defined as mild (creatinine > 140 μmol/l) or severe (creatinine > 250 μmol/l), according to the creatinine level at the time of NT-proBNP measurement. The Simplified Acute Physiology Score (SAPS)-II and the Logistic Organ Dysfunction (LOD) score were determined at ICU admission [25, 26]. Vital status at ICU and hospital discharge and lengths of ICU and hospital stay were recorded for all patients.

Plasma levels of NT-proBNP were measured using the Dade Behring Dimension RxL automated NT-proBNP method (Dade Behring, Glasgow, DE, USA), according to National Committee for Clinical Laboratory Standards guidelines and the International Federation of Clinical Chemistry and Laboratory Medicine quality specifications for B-type natriuretic peptide methods. This diagnostic method has been recently evaluated in our laboratories: the detection limit is 2.0 ng/l, the total imprecision is 2.6–3.6% for concentrations from 231 ng/l to 9,471 ng/l, and the total coefficient of variation is < 4.7%. The matrix was heparin plasma. The turnaround time for obtaining the NT-proBNP result was 18 min, and the cost of a single test was, at the time of the study, €23.40.

All patients underwent a two-dimensional transthoracic echocardiography (HF Sonos 5500, Hewlett Packard) and pulsed Doppler techniques by the same operator (S.K.-M.) within 48 h from ICU admission. Left ventricular (LV) volumes were measured in the apical four-chamber view with the use of the area-length method. The LV ejection fraction was calculated with standard formulas. Systolic LV dysfunction was defined as an EF of < 50%. The thickness of the septal and posterior walls of the left ventricle was measured at the level of the tips of the mitral valve leaflets. The blood-flow velocity through the mitral valve was measured through the pulse-wave Doppler imaging. In patients with an EF ≥ 50%, diastolic dysfunction was defined as the presence of at least one of the following patterns: impaired relaxation, defined as a ratio of peak mitral early diastolic and atrial contraction velocity (E/A) of < 1; pseudonormal, defined as an E/A of 1–2 with an E-wave deceleration time (DT) of ≥ 130 ms; or restrictive filling, defined as an E/A > 2 or 1–2 with a DT < 130 ms. In patients with conserved LV EF, the evidence for diastolic dysfunction was considered as a documented cardiac dysfunction [27].

Diagnoses were based on clinical, radiographic, microbiologic, and cytologic findings. They were validated by the multidisciplinary team based on predefined criteria, and at the time of patient's discharge [5]. Diagnosis of ARF of cardiac origin included the absence of associated infection or noninfectious pulmonary involvement, a documented cardiac dysfunction on echocardiography, and a consensus between two senior doctors in the ICU [5]. All patients with suspected acute respiratory failure from cardiac origin received 20–60 mg of furosemide. This furosemide trial was considered as positive when respiratory status improved after diuresis above 300 ml.

Results are reported as medians and quartiles (25th–75th percentiles) or absolute numbers and percentages. Patient characteristics were compared using the chi-square test or the Fisher exact test, as appropriate, for categorical variables and the nonparametric Wilcoxon test or the Kruskal–Wallis test for continuous variables. A receiver operating characteristic (ROC) curve was drawn, depicting the relationship between the proportion of true positives (Se) and the proportion of false positives (1-Sp) depending on the prediction rule used to classify the patients as having cardiac dysfunction. A 2×2 table was calculated to determine the sensitivity and specificity. Cutoff values, defined as the threshold values maximizing the sum of sensitivity and specificity, were determined for each score with ROC curves. To investigate associations between patient characteristics and diagnosis of cardiac ARF, we first performed bivariate analyses to look for a significant influence of each variable by logistic regression, as measured by the estimated odds ratio (OR) with the 95% confidence interval (95% CI). Variables yielding p values no greater than 0.20 in the bivariate analyses were entered into a multiple logistic regression. We checked that omitting each of the selected variables induced no significant increase in likelihood. Statistical analysis was adjusted according to the level of renal dysfunction. All tests were two-sided, and p values smaller than 0.05 were considered statistically significant. Analyses were done using the SAS 9.1 software package (SAS Institute, Cary, NC, USA).

Results

One hundred cancer patients were prospectively included. As reported in Table 1, patients were aged 53 (37–64) years and 59 (59%) of them were men. The most frequent malignancies were acute leukemia and non-Hodgkin lymphoma [57 (57%) patients]. Twenty (20%) patients benefited from hematopoietic stem cell transplantation (HSCT) (11 autologous and 9 allogeneic). Time from diagnosis of the malig-

nancy was 60 (3–673) days, 45 (45%) patients had a newly diagnosed malignancy at ICU admission, and 25 (25%) were in complete or partial remission. Eighteen (18%) patients were neutropenic at ICU admission, and 30 (30%) were neutropenic throughout the ICU stay. Additional comorbidities consisted in arterial hypertension in 30 (30%) patients and diabetes in 2 (2%) patients. Fifty-one patients had received at least one course of cancer chemotherapy including anthracyclines before ICU admission. However, only 11 patients had received more than one course of anthracyclines.

At clinical examination, temperature was 38°C (37–39.1). Sixty-three (63%) patients presented with crackles at lung auscultation (16 localized and 47 bilateral). CXR disclosed focal or unilateral alveolar infiltrates ($n = 19$), bilateral alveolar infiltrates ($n = 6$), or diffuse interstitial or alveolo-interstitial infiltrates ($n = 46$). Pleural effusion was found in 5 (5%) patients. The cardiothoracic ratio (CTR) was 0.40 (0.4–0.48). Among 17 patients with cardiomegaly (CTR > 0.5), 10 (59%) had a final diagnosis of CHF. PaO_2 was 93 (74–118) mmHg on 9 (5–10) l/min oxygen and $PaCO_2$ was 35 (30–40.5) mmHg.

At ICU admission, 60 patients had normal renal function, 15 had a creatinine level between 100 μmol/l and 140 μmol/l, 14 had a creatinine level between 141 μmol/l and 250 μmol/l, and 11 had a creatinine level above 250 μmol/l.

Sixteen (16%) patients had cardiac pulmonary edema, 58 had noncardiac ARF, and the 26 control patients had neither ARF nor cardiac dysfunction. Echocardiography identified cardiac dysfunction in all the 16 patients with ARF of cardiac origin, and in none of the remaining 84 patients. A furosemide trial had been performed in 24 (24%) patients, including 7 patients in whom furosemide resulted in a respiratory improvement, 6 of whom had

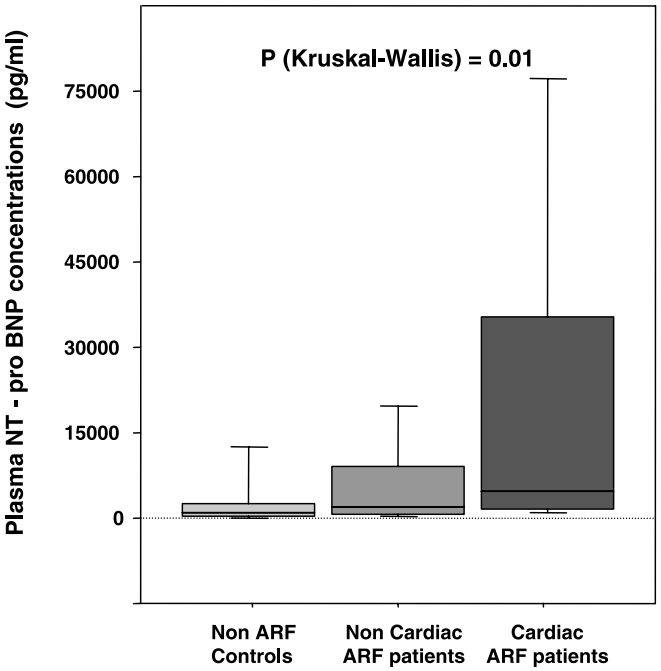

Fig. 1 NT-proBNP and ICU admission diagnosis. NT-proBNP concentrations were 1,022 (383–2,613) pg/ml, 1,912 (704–9,182) pg/ml, and 4,536 (1,568–35,171) pg/ml in patients without acute respiratory failure (*ARF*), with noncardiac ARF, and with cardiac pulmonary edema, respectively

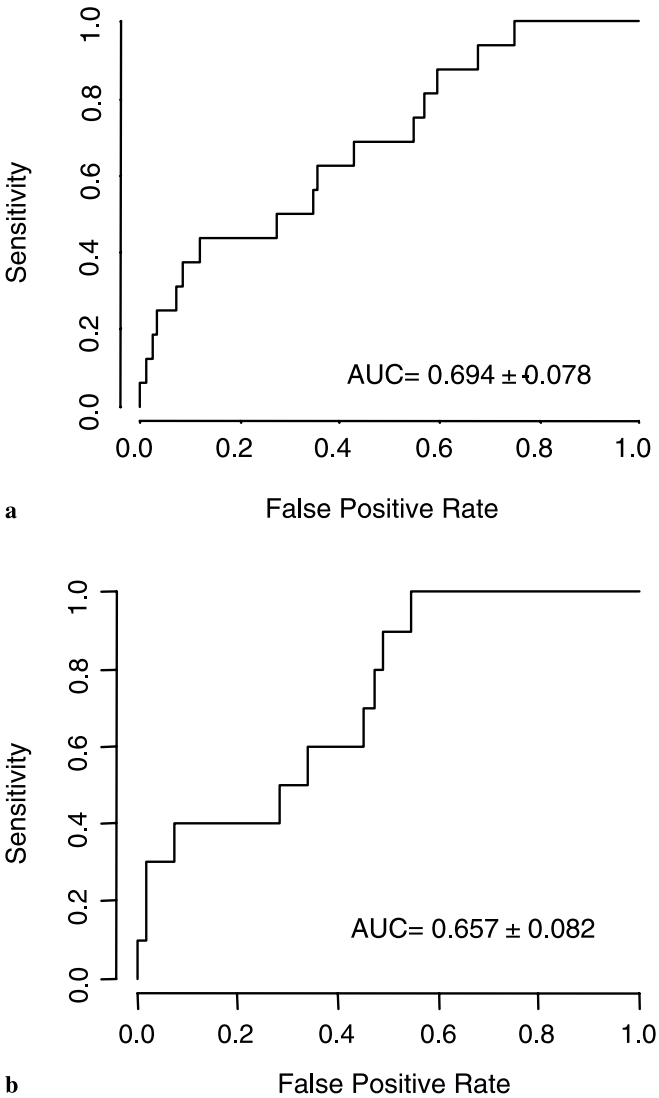

Fig. 2 Accuracy of NT-proBNP in patients with acute respiratory failure. A receiver operating characteristic (ROC) curve was drawn, depicting the relationship between the proportion of true positives (Se) and the proportion of false positives (1-Sp) depending on the prediction rule used to classify the patients as having cardiac dysfunction. **a** The ROC curve including the entire patient population (including non-ARF controls). **b** The ROC curve including only patients with ARF. The areas under the curve (*AUC*) were not significantly influenced by the level of renal dysfunction: 0.694 ± 0.078, 0.664 ± 0.103, and 0.613 ± 0.152 in patients with normal renal function, mild renal dysfunction, and severe renal dysfunction ($p = 0.19$)

Table 2 Factors associated with the diagnosis of cardiac pulmonary edema among the 74 patients with acute respiratory failure

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% Confidence interval	*p* value	Odds ratio	95% Confidence interval	*p* value
Female gender	0.34	0.11–1.07	0.06	/		
Cardiovascular risk factors	1.33	0.42–4.23	0.62	/		
Time from respiratory symptoms onset	0.84	0.70–1.01	0.06	/		
Cardiothoracic ratio > 0.5	12.82	3.46–47.43	0.0001	13.02	3.05–55.59	0.0005
Long-term steroid therapy	0.09	0.01–0.76	0.02	/		
NT-proBNP	1.00	1.00–1.00	0.07	/		
Diffuse crackles at lung auscultation	2.27	0.65–7.89	0.19	/		
Alveolar interstitial pattern at CXR	4.02	1.26–12.81	0.02	8.68	1.13–66.48	0.03

cardiac ARF. Noninvasive mechanical ventilation was needed in 16 (16%) patients and invasive mechanical ventilation in 44 (44%). Vasopressors or dobutamine were needed in 36 (36%) patients and renal replacement therapy in 23 (23%). ICU length of stay was 5.5 (3–10) days, and ICU mortality was 32%. NT-proBNP levels were not significantly different in survivors and nonsurvivors [1,698 (462–8,931) in survivors and 2396 (1,108–11,040) in nonsurvivors, $p = 0.08$].

Figure 1 shows the plasma NT-proBNP concentrations in the three groups of patients. Patients with noncardiac ARF had higher plasma NT-proBNP concentrations than non-ARF patients, but lower concentrations than cardiac ARF patients. Overall, the NT-proBNP concentration was 1,951 (617–9,320) pg/ml. NT-proBNP concentrations were significantly correlated with the level of renal dysfunction. Namely, median (25th–75th percentile) concentrations of NT-proBNP were 1,671 (524–3,488), 5,319 (1,683–20,812), and 11,874 (1,980–21,879) in patients with a creatinine level less than 140 μmol/l, between 140 and 250 μmol/l, and more than 250 μmol/l, respectively ($p = 0.007$).

The accuracy of NT-proBNP in detection of cardiac ARF patients was measured using ROC curves (Fig. 2) and stepwise logistic regression where cardiac ARF was the variable of interest (Table 2). The area under the curve (AUC) was 0.663 ± 0.078 (95% CI 0.510–0.815). The AUC values were not significantly influenced by the level of renal dysfunction. Namely, AUC was 0.694 ± 0.078, 0.664 ± 0.103, and 0.613 ± 0.152 in patients with normal renal function, mild renal dysfunction, and severe renal dysfunction, respectively ($p = 0.19$). In addition, as shown in Table 2, only radiographic criteria were predictors of ARF of cardiac origin, whereas NT-proBNP was not. Last, the use of anthracyclines was not associated with the diagnosis of cardiac ARF.

However, with sensitivity and a negative predictive value of 100%, a cutoff value of 500 pg/ml of NT-proBNP seemed useful to rule out the diagnosis of ARF of cardiac origin. Figure 3 shows the negative and positive predictive values of a cutoff value of 500 pg/ml of NT-proBNP according to the prevalence of the disease. Indeed, none of the 16 patients with cardiac ARF had a NT-proBNP below 500 pg/ml, whereas this was the case in 8 (30.8%) of the non-ARF controls and in 12 (20.7%) of the noncardiac ARF patients. The specificity of a cutoff value of 500 pg/ml of NT-proBNP was therefore only 20.7%.

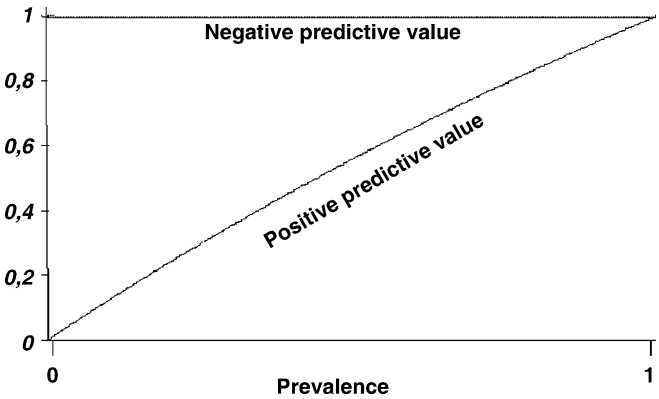

Fig. 3 Negative and positive predictive values of a NT-proBNP value of 500 pg/ml according to the prevalence of cardiac ARF. In our patient population, with a prevalence of ARF from cardiac origin of 16%, the positive predictive value was 25.8% and the negative predictive value was 100%

Discussion

Cardiac dysfunction is frequent in cancer patients. Indeed, it is being encountered increasingly often with advanced patient age, comorbidities, and prolonged survival after intensive and potentially cardiotoxic chemotherapy regimens [28]. Because of the rapidly reversible respiratory failure in patients with cardiac pulmonary edema, early recognition of this condition might obviate unnecessary ICU admission and potentially harmful diagnostic investigations such as bronchoscopy and BAL [5]. NT-proBNP concentrations were of only limited value in this cohort of critically ill cancer patients where the prevalence of cardiac pulmonary edema was 16%. Even though the sensitivity and the negative predictive value of NT-proBNP

were 100%, the marker had very poor specificity and an AUC of 0.66, indicating that it could serve to rule out the diagnostic of cardiac dysfunction but it could not form the basis of the decision whether to admit a patient to the ICU.

Previous studies have reported that NT-proBNP concentrations were to be interpreted in the context of age, gender, race, hemoglobin level, and renal function [14–16, 18]. In cancer patients, all these conditions were likely to impact on our patients' NT-proBNP concentrations. Along these lines, the significant influence of renal dysfunction on NT-proBNP concentrations has been demonstrated in our patients. In addition, NT-proBNP is frequently elevated in critically ill patients with sepsis, shock, trauma or surgery [29, 30]. McLean et al. have already suggested that raising the upper limit of BNP might be needed in ICU patients [16]. This was confirmed by Jefic et al., who found that a NT-proBNP concentration of 1,550 pg/ml had good accuracy for detecting impaired cardiac contractility, that is, two times the upper limit of normal for NT-proBNP even after accounting for variations in age and gender [31]. In cancer patients, it has been reported that BNP concentrations increase early in anthracycline-induced cardiac toxicity [32–34]. However, Daugaard et al. stressed that neither baseline BNP concentrations nor serial measurements could safely replace EF monitoring in the detection of cardiac toxicity anthracycline therapy [32]. In keeping with our results, NT-proBNP concentration at admission is not a relevant tool to diagnose ARF of cardiac origin in critically ill cancer patients. However, a striking finding of this study is that using a cutoff value of 500 pg/ml, NT-proBNP ruled out the diagnosis of cardiac dysfunction.

Our study has several limitations. First, the timing of echocardiography differed from that of NT-proBNP measurements. Nevertheless, transient systolic dysfunction is rare and EF appears stable even after acute pulmonary edema [12]. Second, we performed a single measurement of NT-proBNP; repeated measures might have increased the accuracy of the marker. However, we know that the half-life of NT-proBNP (90–120 min) is longer than that of BNP with a more stable plasmatic concentration. Moreover, the expected benefit of NT-proBNP would be avoidance of ICU admission or useless diagnostic investigations, thus indicating very early use of the marker. Third, apart from the significant impact of renal failure on NT-proBNP concentrations, this study does not identify the probably multiple factors leading to the low performance of NT-proBNP in critically ill cancer patients. Fourth, the relatively low performance of NT-proBNP in our patient population may be ascribable to septic myocardial depression in noncardiac ARF patients with septic shock. However, because only three patients in this group had cardiac dysfunction, we cannot draw any conclusion from this study. Fifth, the use of anthracyclines, with major cardiotoxicity, was not associated with the diagnosis of cardiac ARF. However, only few patients had received more than one course of anthracyclines and none had a total cumulative dose of anthracyclines in the toxic range. Sixth, in this study the diagnosis of cardiac ARF was not associated with a better outcome than noncardiac ARF. However, it should be noted that the mortality among cardiac ARF patients was 19.2%, compared with 38% in noncardiac ARF patients. However, this difference was not significant because of a lack of power (this was not our study objective). Last, the identification of cardiac dysfunction using cardiac sonography as the gold standard could be viewed as different from identifying heart failure as the cause of respiratory failure. Indeed, in this study we assumed that all patients with some degree of cardiac dysfunction on sonography did have cardiac pulmonary edema. However, all the diagnoses were validated by the clinicians, and the reversibility of the respiratory failure using adequate therapy indicates per se that there was a causative relationship between cardiac dysfunction and ARF. Nevertheless, the fact that half the cardiac ARF patients were receiving mechanical ventilation suggests that not admitting these patients may be deleterious.

In conclusion, in critically ill cancer patients, the measurement of NT-proBNP concentrations remains a weak detector of cardiac dysfunction. However, a cutoff value of 500 pg/ml could be used to rule out the diagnosis of cardiac dysfunction.

References

1. Azoulay E, Schlemmer B (2006) Diagnostic strategy in cancer patients with acute respiratory failure. Intensive Care Med 32:808–822
2. Kress JP, Christenson J, Pohlman AS, Linkin DR, Hall JB (1999) Outcomes of critically ill cancer patients in a university hospital setting. Am J Respir Crit Care Med 160:1957–1961
3. Soares M, Salluh JI, Spector N, Rocco JR (2005) Characteristics and outcomes of cancer patients requiring mechanical ventilatory support for > 24 hrs. Crit Care Med 33:520–526
4. Staudinger T, Stoiser B, Mullner M, Locker GJ, Laczika K, Knapp S, Burgmann H, Wilfing A, Kofler J, Thalhammer F, Frass M (2000) Outcome and prognostic factors in critically ill cancer patients admitted to the intensive care unit. Crit Care Med 28:1322–1328
5. Azoulay E, Thiery G, Chevret S, Moreau D, Darmon M, Bergeron A, Yang K, Meignin V, Ciroldi M, Le Gall JR, Tazi A, Schlemmer B (2004) The prognosis of acute respiratory failure in critically ill cancer patients. Medicine (Baltimore) 83:360–370
6. Chaoui D, Legrand O, Roche N, Cornet M, Lefebvre A, Peffault de Latour R, Sanhes L, Huchon G, Marie JP, Rabbat A (2004) Incidence and prognostic value of respiratory events in acute leukemia. Leukemia 18:670–675

7. Groeger JS, White P, Jr., Nierman DM, Glassman J, Shi W, Horak D, Price K (1999) Outcome for cancer patients requiring mechanical ventilation. J Clin Oncol 17:991–997
8. Hilbert G, Gruson D, Vargas F, Valentino R, Favier JC, Portel L, Gbikpi-Benissan G, Cardinaud JP (2001) Bronchoscopy with bronchoalveolar lavage via the laryngeal mask airway in high-risk hypoxemic immunosuppressed patients. Crit Care Med 29:249–255
9. Gruson D, Hilbert G, Portel L, Boiron JM, Bebear CM, Vargas F, Bebear C, Reiffers J, Gbikpi-Benissan G, Cardinaud JP (1999) Severe respiratory failure requiring ICU admission in bone marrow transplant recipients. Eur Respir J 13:883–887
10. Shorr AF, Susla GM, O'Grady NP (2004) Pulmonary infiltrates in the non-HIV-infected immunocompromised patient: etiologies, diagnostic strategies, and outcomes. Chest 125:260–271
11. Stover DE, Zaman MB, Hajdu SI, Lange M, Gold J, Armstrong D (1984) Bronchoalveolar lavage in the diagnosis of diffuse pulmonary infiltrates in the immunosuppressed host. Ann Intern Med 101:1–7
12. Steg PG, Joubin L, McCord J, Abraham WT, Hollander JE, Omland T, Mentre F, McCullough PA, Maisel AS (2005) B-type natriuretic peptide and echocardiographic determination of ejection fraction in the diagnosis of congestive heart failure in patients with acute dyspnea. Chest 128:21–29
13. Mukoyama M, Nakao K, Hosoda K, Suga S, Saito Y, Ogawa Y, Shirakami G, Jougasaki M, Obata K, Yasue H, et al. (1991) Brain natriuretic peptide as a novel cardiac hormone in humans. Evidence for an exquisite dual natriuretic peptide system, atrial natriuretic peptide and brain natriuretic peptide. J Clin Invest 87:1402–1412
14. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, Omland T, Storrow AB, Abraham WT, Wu AH, Clopton P, Steg PG, Westheim A, Knudsen CW, Perez A, Kazanegra R, Herrmann HC, McCullough PA (2002) Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 347:161–167
15. Dao Q, Krishnaswamy P, Kazanegra R, Harrison A, Amirnovin R, Lenert L, Clopton P, Alberto J, Hlavin P, Maisel AS (2001) Utility of B-type natriuretic peptide in the diagnosis of congestive heart failure in an urgent-care setting. J Am Coll Cardiol 37:379–385
16. McLean AS, Huang SJ, Nalos M, Tang B, Stewart DE (2003) The confounding effects of age, gender, serum creatinine, and electrolyte concentrations on plasma B-type natriuretic peptide concentrations in critically ill patients. Crit Care Med 31:2611–2618
17. Rana R, Vlahakis NE, Daniels CE, Jaffe AS, Klee GG, Hubmayr RD, Gajic O (2006) B-type natriuretic peptide in the assessment of acute lung injury and cardiogenic pulmonary edema. Crit Care Med 34:1941–1946
18. Rudiger A, Gasser S, Fischler M, Hornemann T, von Eckardstein A, Maggiorini M (2006) Comparable increase of B-type natriuretic peptide and amino-terminal pro-B-type natriuretic peptide levels in patients with severe sepsis, septic shock, and acute heart failure. Crit Care Med 34:2140–2144
19. Bahlis NJ, Lazarus HM (2006) Multiple myeloma-associated AL amyloidosis: is a distinctive therapeutic approach warranted? Bone Marrow Transplant 38:7–15
20. Meinardi MT, van Veldhuisen DJ, Gietema JA, Dolsma WV, Boomsma F, van den Berg MP, Volkers C, Haaksma J, de Vries EG, Sleijfer DT, van der Graaf WT (2001) Prospective evaluation of early cardiac damage induced by epirubicin-containing adjuvant chemotherapy and locoregional radiotherapy in breast cancer patients. J Clin Oncol 19:2746–2753
21. Snowden JA, Hill GR, Hunt P, Carnoutsos S, Spearing RL, Espiner E, Hart DN (2000) Assessment of cardiotoxicity during haemopoietic stem cell transplantation with plasma brain natriuretic peptide. Bone Marrow Transplant 26:309–313
22. Burjonroppa SC, Tong AT, Xiao LC, Johnson MM, Yusuf SW, Lenihan DJ (2007) Cancer patients with markedly elevated B-type natriuretic peptide may not have volume overload. Am J Clin Oncol 30:287–293
23. Forfia PR, Watkins SP, Rame JE, Stewart KJ, Shapiro EP (2005) Relationship between B-type natriuretic peptides and pulmonary capillary wedge pressure in the intensive care unit. J Am Coll Cardiol 45:1667–1671
24. Shor R, Rozenman Y, Bolshinsky A, Harpaz D, Tilis Y, Matas Z, Fux A, Boaz M, Halabe A (2006) BNP in septic patients without systolic myocardial dysfunction. Eur J Intern Med 17:536–540
25. Le Gall JR, Klar J, Lemeshow S, Saulnier F, Alberti C, Artigas A, Teres D (1996) The Logistic Organ Dysfunction system. A new way to assess organ dysfunction in the intensive care unit. ICU Scoring Group. JAMA 276:802–810
26. Le Gall JR, Lemeshow S, Saulnier F (1993) A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 270:2957–2963
27. Gandhi SK, Powers JC, Nomeir AM, Fowle K, Kitzman DW, Rankin KM, Little WC (2001) The pathogenesis of acute pulmonary edema associated with hypertension. N Engl J Med 344:17–22
28. Brenner H (2002) Long-term survival rates of cancer patients achieved by the end of the 20th century: a period analysis. Lancet 360:1131–1135
29. Kia M, Cooley A, Rimmer G, MacDonald T, Barber K, Manion P, Shapiro B, Socey J, Iddings D (2006) The efficacy of B-type natriuretic peptide for early identification of blood loss in traumatic injury. Am J Surg 191:353–357
30. Witthaut R, Busch C, Fraunberger P, Walli A, Seidel D, Pilz G, Stuttmann R, Speichermann N, Verner L, Werdan K (2003) Plasma atrial natriuretic peptide and brain natriuretic peptide are increased in septic shock: impact of interleukin-6 and sepsis-associated left ventricular dysfunction. Intensive Care Med 29:1696–1702
31. Jefic D, Lee JW, Savoy-Moore RT, Rosman HS (2005) Utility of B-type natriuretic peptide and N-terminal pro B-type natriuretic peptide in evaluation of respiratory failure in critically ill patients. Chest 128:288–295
32. Daugaard G, Lassen U, Bie P, Pedersen EB, Jensen KT, Abildgaard U, Hesse B, Kjaer A (2005) Natriuretic peptides in the monitoring of anthracycline induced reduction in left ventricular ejection fraction. Eur J Heart Fail 7:87–93
33. Horacek JM, Pudil R, Tichy M, Jebavy L, Strasova A, Praus R, Zak P, Maly J (2005) The use of biochemical markers in cardiotoxicity monitoring in patients treated for leukemia. Neoplasma 52:430–434
34. Okumura H, Iuchi K, Yoshida T, Nakamura S, Takeshima M, Takamatsu H, Ikeno A, Usuda K, Ishikawa T, Ohtake S, Matsuda T (2000) Brain natriuretic peptide is a predictor of anthracycline-induced cardiotoxicity. Acta Haematol 104:158–163