

# B-type natriuretic peptide following thoracic surgery: a predictor of postoperative cardiopulmonary complications<sup>†</sup>

Lucio Cagini<sup>a,\*</sup>, Marco Andolfi<sup>a</sup>, Christian Leli<sup>b</sup>, Rossella Potenza<sup>a</sup>, Mark Ragusa<sup>a</sup>, Elisa Scarnecchia<sup>a</sup>,  
Jacopo Vannucci<sup>a</sup>, Reitze Rodseth<sup>c</sup> and Francesco Puma<sup>a</sup>

<sup>a</sup> Department of Surgical Science, Thoracic Surgery Unit, Ospedale S. Maria, University of Perugia, Perugia, Italy

<sup>b</sup> Department of Experimental Medicine and Biochemical Sciences, Microbiology Section, University of Perugia, Perugia, Italy

<sup>c</sup> Perioperative Research Group, Department of Anaesthetics, Grey's Hospital, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal, Pietermaritzburg, South Africa

\* Corresponding author. Department of Surgical Science, Thoracic Surgery Unit, Santa Maria della Misericordia Hospital, Piazzale Menghini 1, University of Perugia, 06134 Perugia, Italy. Tel: +39-075-5783651; fax: +39-075-5782240; e-mail: lucio.cagini@unipg.it (L. Cagini).

Received 7 May 2014; received in revised form 27 July 2014; accepted 1 August 2014

## Abstract

**OBJECTIVES:** B-type natriuretic peptides (BNPs) are secreted by the human heart in response to ventricular wall stretch or myocardial ischaemia, and predict adverse cardiovascular events and death in the general population. Following non-cardiac surgical procedures, there is growing evidence supporting BNP measurement as a powerful independent predictor of death and perioperative complications. However, the clinical implication of elevated BNP measurements after pulmonary resection has not been completely defined. This study aimed to evaluate the role of BNP in predicting adverse cardiopulmonary events after thoracic surgery.

**METHODS:** A prospective, short-term, observational cohort study was conducted in a tertiary care hospital, including consecutive patients undergoing scheduled pulmonary resection between April 2012 and October 2013. Baseline clinical details were obtained; serum BNP levels were measured at baseline and on postoperative days 1 and 4.

**RESULTS:** We enrolled 294 consecutive patients, median age 66 [interquartile range (IQR): 57–73], 67% male. There were 2 perioperative deaths, and 52 patients experienced one or more cardiopulmonary complications. The baseline median BNP value was normal (29.5 pg/ml, IQR: 16–57.2), and showed significant postoperative increase, peaking on day 1. Patients who developed postoperative complications had a significantly greater BNP increase ( $P < 0.0001$ ) when compared with those without complications. A postoperative day 1 BNP measurement of  $\geq 118.5$  [receiver operating characteristic area: 0.654; 95% confidence interval (CI): 0.57–0.74;  $P = 0.001$ ] was associated with a 3-fold risk of developing postoperative cardiopulmonary complications [odds ratio (OR): 2.94; 95% CI: 1.32–6.57;  $P = 0.008$ ]. Logistic regression analysis showed major pulmonary resections (lobectomies or pneumonectomies), BNP  $\geq 118.5$  and age  $\geq 65$  to be the only independent predictive variables. In the subset of patients undergoing lobectomy or pneumonectomy ( $n = 226$ ), BNP was the strongest independent predictor of complications (OR: 3.49; 95% CI: 1.51–8.04).

**CONCLUSIONS:** Our results show that BNP elevation, measured in the first days after thoracic surgery, is independently associated with postoperative adverse events. In patients undergoing major pulmonary resections, a postoperative BNP elevation is the strongest independent predictor of cardiopulmonary complications.

**Keywords:** B-type natriuretic peptide • Cardiovascular complication • Pulmonary complication • Pulmonary resection • Perioperative management • Non-small-cell lung cancer

## INTRODUCTION

Natriuretic peptides are vasodilator hormones involved in the regulation of blood pressure and volume homeostasis [1]. B-type natriuretic peptide (BNP) and its inactive cleavage product, N-terminal fragment BNP (NT-proBNP), are produced and secreted by the human heart in response to ventricular wall stretch, or myocardial ischaemia [2].

Under physiological conditions, the ventricular myocardium produces a limited amount of natriuretic peptides [3], but several cardiac

and pulmonary pathological conditions stimulate BNP production and release from ventricular cardiomyocytes [4]. There is growing evidence supporting BNP measurement as a powerful independent predictor of perioperative and long-term cardiovascular complications following non-cardiac surgical procedures [5, 6]. In thoracic surgery, BNP and NT-proBNP have been reported to reflect postoperative right ventricular dysfunction [1], to be an appropriate predictor of atrial fibrillation [7, 8] and to be a useful predictor of postoperative cardiopulmonary complications in elderly patients following lung resection for lung cancer [9]. However, to date, the potential clinical implication of elevations in BNP secretion following pulmonary resections has not been properly defined. We,

<sup>†</sup>Presented at the 22nd European Conference on General Thoracic Surgery, Copenhagen, Denmark, 15–18 June 2014.

therefore, designed and conducted a prospective observational pathophysiology-driven study to serially assess BNP secretion after thoracic surgery and to clarify the role of BNP as a possible risk marker for postoperative cardiopulmonary complications.

## MATERIALS AND METHODS

### Study design

We designed and conducted a prospective, single-centre short-term observational study in a tertiary care hospital. We planned to enrol consecutive consenting patients among those scheduled to undergo elective pulmonary resection over the period April 2012 to October 2013. The primary aim of this study was to evaluate the role of BNP as a possible marker of short-term postoperative cardiopulmonary complications. All eligible patients had to give their informed consent prior to inclusion. The study protocol was approved by the local regional ethics committee (reference no. 28609/11).

### Study population

Patients were eligible for inclusion in the study if they were  $\geq 18$  years of age, had American Society of Anesthesiologists (ASA) score  $\leq 3$ , New York Heart Association (NYHA) classification  $\leq 2$  and were scheduled for elective pulmonary surgical resections. This included patients undergoing pneumonectomies, lobectomies, anatomical segmentectomies or wedge resections. Patients were excluded based on the following criteria: unwilling to participate, urgent or emergency surgical procedure, cardiac rhythm other than sinus, paroxysmal, persistent or chronic atrial fibrillation, anti-arrhythmic drug use, recent ( $< 3$  months) angina pectoris, myocardial infarction or pneumonia, symptomatic coronary artery disease or congestive heart failure, NYHA classification  $> 2$ , need for mechanical ventilation after the surgical procedure and moderate or severe renal disease (serum creatinine  $> 200 \mu\text{mol/l}$ ). The preoperative evaluation included detailed history, accurate physical examination and thorough cardiopulmonary assessment including blood gas analysis, 12-lead electrocardiogram, spirometry, diffusing capacity of the lung for carbon monoxide (DLCO) and echocardiographic examinations to exclude the presence of right ventricular overload or left ventricular diastolic dysfunction.

The diagnostic evaluation was planned according to the scheduled procedure and, in case of malignancy, it included total body computed tomography (CT), videobronchoscopy and 18-fluorodeoxyglucose-positron emission tomography (PET).

Because of the observational nature of this study, no set guidelines for intraoperative and postoperative management were imposed, and all patients were treated in accordance with local established practice. All patients were scheduled for extubation in the surgical theatre at the end of the operation and were managed in our thoracic unit ward unless complications required their admission to the intensive care unit. Thereafter, intraoperative fluid and drug administration was controlled by the anaesthesiologist and by the surgical team, depending on the clinical course of the patient. From the first postoperative day all patients received daily physiotherapy, which included deep breathing exercises, incentive spirometry, supported coughing and mobilization.

### Surgical procedures

All patients underwent standard posterolateral thoracotomy or video-assisted thoracic surgery (VATS) under general anaesthesia with selective one-lung ventilation and insertion of radial arterial catheters for constant blood pressure monitoring.

In VATS, three access ports were created through 1–4 cm skin incisions. Patients undergoing VATS then converted to open thoracotomy were classified as open thoracotomy patients. In lung cancer patients, pulmonary resection was performed with curative intent and was associated with systematic lymph node dissection. All patients were extubated at the end of operation and thereafter none required reintubation. Postoperative pain control was provided for 3 days by paravertebral analgesia (0.5% levobupivacaine bolus of 15–20 ml via a catheter), in addition to continuous intravenous infusion of morphine by a silicone elastomeric pump and paracetamol. If needed, non-steroidal anti-inflammatory drugs were introduced from the third postoperative day.

### Postoperative complications

All patients during the postoperative period were monitored daily and complications detected using clinical, biochemical and instrumental methods were recorded (Table 1). Postoperative pulmonary complications, defined according to the Melbourne Group Scale Version-2 (MGS-2) score [11] (previously validated within the thoracic surgery population [12]), were diagnosed when four or more of the following dichotomous criteria were present: radiological evidence of atelectasis/consolidation, temperature  $> 38^\circ\text{C}$ , oxygen saturation  $< 90\%$  on room air, abnormal sputum production, sputum culture indicating infection, raised white cell count ( $> 11.2 \times 10^9/\text{l}$ ), abnormal auscultation findings, physician's diagnosis of pulmonary complication, or administration of respiratory antibiotics postoperatively (in addition to prophylactic antibiotics). Postoperative cardiovascular complications included: arrhythmias (atrial fibrillation, paroxysmal supraventricular tachycardia and ventricular tachycardia), angina pectoris, myocardial infarction, congestive heart failure, thromboembolic events, deep vein thrombosis (DVT), acute renal failure (ARF) and transient ischaemic attack (TIA).

Postoperative surgical complications were considered due to surgical factors and were not included in the analysis.

### B-type natriuretic peptide measurements

All of the analytical measurements were performed at the Central Laboratory of the Perugia Teaching Hospital. Fasting haematological, biochemical profile and the levels of BNP were collected and measured before surgery and on the morning of the first (BNP + 24 h) and fourth (BNP + 96 h) postoperative days. Venous blood (4 ml) was obtained from each patient and transferred to tubes containing ethylenediamine tetra-acetic acid, then stored at  $-20^\circ\text{C}$  until determination. BNP plasma concentrations were measured using a chemiluminescent enzyme immunoassay kit (TRIAGE BNP; Biosite Incorporated, San Diego, CA, USA). The minimum quantity of human BNP detectable with this system is 1.0 pg/ml. The intra-assay and interassay coefficients of variation (CVs) of the test were 3.1 and 4.5%, respectively. BNP determination cost was €20 per sample.

**Table 1:** Distribution and definition of the postoperative cardiopulmonary complications

Complications	Definition	Number (n = 294)	%
All complications		52	18
Cardiovascular complications		43	15
Atrial fibrillation	Functional electrical disorder characterized by the absence of P waves and an irregular ventricular rate	31	10
Acute renal failure	Increase in serum creatinine $\geq 0.3$ mg/dl within 48 h; increase in serum creatinine $\geq 1.5$ times of the baseline measure within the preceding 7 days; urine volume $<0.5$ ml/kg/h for 6 h	4	1
Ventricular tachycardia	Any rhythm faster than 100 (or 120) beats/min, with 3 or more irregular beats in a row, arising distal to the bundle of His	1	1
Acute myocardial infarction	According to the universal definition of myocardial infarction by Thygesen et al. [10].	3	1
Transient ischaemic attack	Presence of focal neurological symptoms or signs lasting $<24$ h	2	1
Deep vein thrombosis	Acute, confirmed by venous ultrasound	2	1
Respiratory complications	According to the MGS-2 [11]	32	11
Pneumonia	Fever $>38^{\circ}\text{C}$ , purulent sputum, abnormal findings on chest X-ray, oxygen saturation $<90\%$ on air, physician's diagnosis of pneumonia/chest infection	25	8
Postoperative acute lung injury	Partial pressure of oxygen in arterial blood/fraction of inspired oxygen $<300$ mmHg, bilateral diffuse chest X-ray infiltrates, oxygen saturation $<90\%$ on air	5	2
Acute respiratory distress syndrome	Partial pressure of oxygen in arterial blood/fraction of inspired oxygen $<200$ mmHg, bilateral diffuse chest X-ray infiltrates, oxygen saturation $<90\%$ on air	2	1

## Statistical analysis

Categorical data are presented as absolute values and percentage. Continuous data are presented as median with interquartile range. Independent categorical data were compared using the  $\chi^2$  test. Continuous data were compared using the Mann-Whitney *U*-test. Median postoperative BNP values according to complications were compared for statistical significance using the Wilcoxon signed-rank test.

To establish a BNP cut-off value with appropriate sensitivity and specificity, receiver operating characteristic (ROC) curves were plotted and the area under the curve (AUC) was estimated. The optimal BNP cut-off value was determined as the value that maximized the Youden index, calculated as (sensitivity + specificity) - 1.

Only variables found to be significant in univariate analysis were entered into multivariate analysis. Logistic regression was used to test the predictive value of the BNP cut-off and other selected parameters. A *P*-value of  $<0.05$  was considered statistically significant. SPSS 13.0 (SPSS, Inc., Chicago, IL, USA) was used for the statistical analysis.

## RESULTS

### Patients, procedures and complications

During the study period, 298 eligible patients were enrolled and consented to the study. Four patients were excluded: one for severe long-lasting intraoperative arrhythmia and hypotension, and three who required postoperative mechanical ventilation. Therefore, 294 patients were available for data analysis; the clinical characteristics of the population along with their association with complications at univariate analysis are given in Table 2. Because of the patient selection process, nearly 85% of the study population was NYHA grade 1 (cardiac disease, but no symptoms and no limitation in ordinary physical activity) with the remainder being scored as NYHA grade 2 (mild symptoms, mild shortness of breath and/or angina and slight limitation during ordinary activity).

All surgical procedures were performed with selective one-lung ventilation and all patients were extubated by the end of operation and thereafter none required reintubation. The most frequent procedure was lobectomy ( $n = 176$ , 60%), followed by wedge or segmentectomy ( $n = 68$ , 23%), pneumonectomy ( $n = 22$ , 7%), bilobectomy ( $n = 13$ , 4%), sleeve lobectomies ( $n = 11$ , 4%) and two right sleeve pneumonectomies and two extrapleural pneumonectomies. Two hundred thirty-two (79%) patients had primary lung cancer, 50 (17%) secondary metastatic cancer, 10 (3%) low malignant tumours and two mesothelioma. Fifty-two (18%) patients experienced one or more cardiovascular morbid events or clinical evidence of postoperative pulmonary complications according to the MGS-2 scale and 70% of these arose in the third postoperative day.

As given in Table 1, the most frequent cardiovascular complication was atrial fibrillation in 31 patients, followed by ARF in 4, acute myocardial infarction in 3, TIA in 2, DVT in 2 and ventricular tachycardia in 1, and 32 patients (11%) had clinical evidence of pulmonary complications. The most frequent findings in the MGS-2 scale were a chest X-ray with signs of atelectasis/infiltration, physician diagnosis of pneumonia, oxygen saturation  $<90\%$  on air, white cell count  $>11.2$  units and purulent sputum. There were 3 perioperative deaths, 1 due to myocardial infarction and 2

**Table 2:** Characteristics of the population and their association with postoperative cardiopulmonary complications as evaluated by univariate analysis

Characteristic	Total (n = 294)	Complications (n = 52)	No complications (n = 242)	P-value
Age (years)	66 (57–63)	70 (62–74)	64 (56–72)	0.02
BNP admission (pg/ml)	29.5 (16–57)	38.5 (22–71)	26.5 (15–56)	0.01
C-Reactive Protein (CRP) admission (mg/dl)	0.3 (0.1–1)	0.8 (0.3–1.4)	0.3 (0.2–1.1)	0.91
PaO <sub>2</sub> /FiO <sub>2</sub>	3.3 (2.5–3.9)	3 (2.2–3.8)	3.3 (2.5–4)	0.13
Body Mass Index (BMI) (kg/m <sup>2</sup> )	26 (24–28)	26.1 (24.7–28.3)	26.1 (23.7–28)	0.13
Duration of anaesthesia (min)	210 (180–240)	240 (180–270)	210 (170–240)	0.12
FEV1	91 (75–108)	98 (86–108)	90.5 (74.7–108)	0.38
DLCO	88 (69.7–102.2)	81 (73.5–100)	89 (68.5–102)	0.67
Major surgery (%)	226 (76.8)	48 (92.3)	178 (73.5)	0.001
Males (%)	197 (67)	39 (75)	158 (65.3)	0.17
Diabetes (%)	21 (7.1)	3 (5.8)	18 (7.4)	0.67
Hypertension (%)	98 (33.3)	19 (36.5)	79 (32.6)	0.58

Data are expressed as median (interquartile range)/count (percentage of each column).

BNP: B-type natriuretic peptides; FEV1%: forced expiratory volume in 1 second; DLCO: diffusing capacity of the lung for carbon monoxide.

caused by a pneumonia evolving into acute respiratory distress syndrome. Surgery was complicated by prolonged air leak (4), bronchopleural fistula (2) and chylothorax (3). One patient required rethoracotomy due to haemorrhage a few hours following extubation.

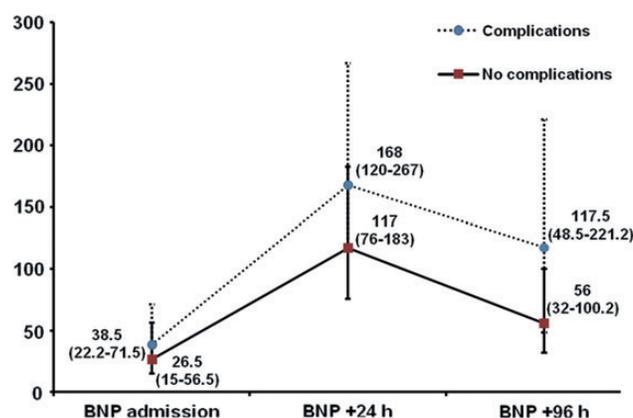
## Primary outcome measures

As given in Table 2, at admission, the only variables associated with adverse events were age, preoperative BNP measurement and major surgery. In the whole study population, the median BNP value was normal (29.5 pg/ml, IQR: 16–57.2) at admission; however, patients who developed postoperative cardiopulmonary complications had, at baseline, significantly greater BNP values when compared with those without complications [38.5 (22.2–71.5) vs 26.5 (15–56.2)  $P < 0.0001$ ].

As shown in Fig. 1, the time course of BNP secretion was characterized by a significant postoperative increase, peaking on the first postoperative day. Patients with postoperative adverse events showed significantly greater BNP increases, compared with those without adverse events ( $P < 0.0001$ ). BNP measurements gradually decreased over the study period, but remained well above baseline. In contrast, BNP measurements in patients without events returned to baseline within 2 days after surgery (Table 3 and Fig. 1).

The ROC curve, in assessing the utility of BNP on postoperative day 1 as a predictor of postoperative cardiopulmonary adverse events (Fig. 2), yielded a cut-off value of 118.5 pg/ml, with a sensitivity of 78.4% and a specificity of 51% [AUC: 0.654 (95% confidence interval (CI) 0.571–0.738);  $P = 0.001$ ]; a positive predictive value (PPV) of 25.6% and a negative predictive value (NPV) of 91.7%, a positive likelihood ratio of 1.60 and a negative likelihood ratio of 0.42. As a matter of fact 78.8% of patients who developed postoperative cardiopulmonary adverse events had BNP levels  $> 118.5$  pg/ml ( $P < 0.0001$ ) on postoperative day 1 (Fig. 3).

The logistic regression analysis (Table 4) showed major surgery, BNP + 24 h  $\geq 118.5$  pg/ml and age  $\geq 65$  years as the only independent variables predictive of complications. Patients showing a postoperative BNP value of  $\geq 118.5$  pg/ml had a nearly 3-fold



**Figure 1:** Comparison of postoperative BNP measurements between patients with postoperative complications and those without complications ( $P < 0.0001$ ).

increase in the risk of developing postoperative complications [odds ratio (OR): 2.94; 95% CI: 1.32–6.57;  $P = 0.008$ ].

The ROC analysis, using preoperative BNP measurements, gave worse results (AUC: 0.613; 95% CI: 0.535–0.692;  $P = 0.01$ ); and the BNP level on admission, included in the logistic regression analysis in place of BNP on postoperative day 1, failed to enter the final model (OR: 1.03; 95% CI: 0.997–1.09;  $P = 0.33$ ).

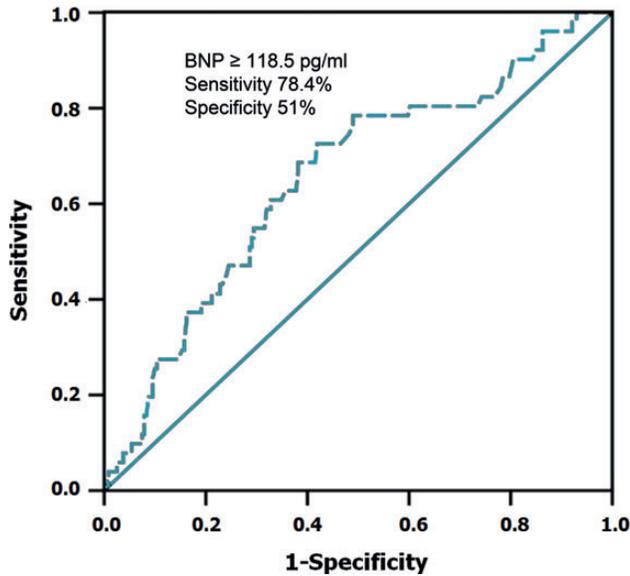
When restricted to patients undergoing major pulmonary resections (i.e. lobectomies and pneumonectomies;  $n = 226$ ), the risk of developing postoperative complications with BNP + 24 h values  $\geq 118$  pg/ml was even greater (OR: 3.49; 95% CI: 1.51–8.04;  $P = 0.005$ ); however, in this group of patients (with a complication prevalence rate of 21.1%), a *post hoc* ROC analysis yielded an optimal cut-off value of 137.5 pg/ml (Youden index 0.310) with a sensitivity of 72%, a specificity of 58% (AUC: 0.666, 95% CI: 0.579–0.753;  $P = 0.001$ ), a PPV of 32.1%, NPV of 88.8%, a positive likelihood ratio of 1.71 and negative likelihood ratio of 0.47.

We found no correlation between postoperative BNP level and length of anaesthesia and found no significant differences of BNP measurements according to the surgical approach: thoracotomy vs VATS lobectomy.

**Table 3:** B-type natriuretic peptide secretion serial measurements according to complications

Variable	Total (n = 294)	Complications (n = 52)	No complications (n = 242)	P-value
BNP admission (pg/ml)	29.5 (16–57)	38.5 (22–71)	26.5 (15–56)	0.01
BNP + 24 h (pg/ml)	123 (79–193)	168 (120–267)	117 (76–183)	<0.0001
BNP + 48 h (pg/ml)	73.0 (51–152)	167.0 (91–251)	69.5 (46–126)	0.03
BNP + 96 h (pg/ml)	61.0 (34–116)	117.5 (48–221)	56.0 (32–100)	<0.0001
BNP + 168 h (pg/ml)	85.0 (32–127)	183.0 (66–310)	64.0 (31–102)	0.08

Data are expressed as median (interquartile range).

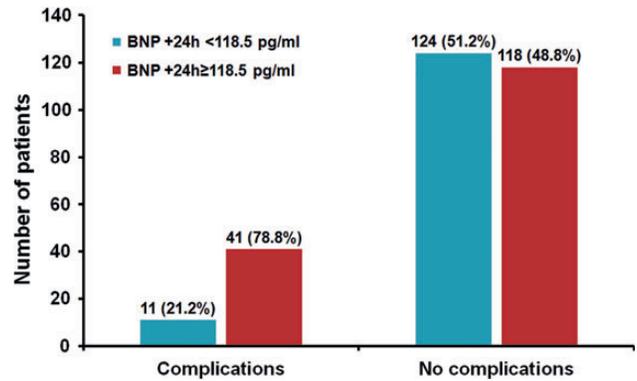


**Figure 2:** ROC curve for development of complications according to different cut-off values of BNP + 24 h. Area under the curve: 0.654 (95% CI: 0.571–0.738); P = 0.001.

**DISCUSSION**

This study shows that BNP measured 24 h after pulmonary resection is an independent predictor of postoperative complications and that patients with elevated BNP levels are at increased risk for adverse cardiopulmonary events. Using the ROC curve, the postoperative BNP measurement of 118 pg/ml was identified as being the optimal cut-off point for the prediction of complications and was present in almost 80% of patients undergoing adverse events. At admission patients who develop postoperative cardiopulmonary complications have, at baseline, significantly greater BNP level when compared with those without complications. Preoperative BNP levels were also found to be significantly associated with postoperative complications on univariate analysis, but were excluded by the subsequent multivariate analysis. Furthermore, in the subset of patients undergoing mayor pulmonary resection (lobectomy and pneumonectomy), a BNP value of  $\geq 118.5$  pg/ml at 24 h after surgery was associated with a 3.5-fold increase in the risk of cardiopulmonary complications.

BNPs are secreted from the myocardium in response to multiple stimuli such as ischaemia, myocardial stretch, inflammation and other neuroendocrine stimuli [13–15]. International guidelines recommend NP measurement for the diagnosis, risk



**Figure 3:** On postoperative day 1, 78.8% of patients who developed postoperative cardiopulmonary adverse events had BNP measurements  $>118.5$  pg/ml ( $P < 0.0001$ ).

**Table 4:** Multiple logistic regression analysis for predictors of postoperative complications

Factor	Odds ratio (95% CI)	P-value
Major surgery	9.77 (1.29–73.9)	0.027
BNP + 24 h ( $\geq 118.5$ pg/ml)	2.94 (1.32–6.57)	0.008
Age ( $\geq 65$ years)	2.15 (1.02–4.53)	0.043

stratification and follow-up of patients with chronic or acute heart failure [16] and acute coronary syndrome [17]. Moreover, elevated NP levels are associated with several pulmonary pathological conditions related to right ventricular overload. This suggests that certain chronic pulmonary diseases and cardiac dysfunction could be closely related [1].

Growing evidence confirms the role for NP in the risk assessment of surgical patients; the European Society of Cardiology and European Society of Anesthesiology guidelines for preoperative cardiac risk assessment have recommended NP measurement in high-risk non-cardiac surgery patients [18]. Further, in vascular surgical patients preoperative NP risk stratification has been shown to outperform traditional clinical risk stratification [19]. Two recent systematic reviews that have included various types of non-cardiac surgery (in both elective and emergency patients) have shown that preoperative NP measurements are powerful predictors of postoperative mortality and myocardial infarction, and that elevated postoperative NP measurements are independently associated with adverse cardiac events at 30 and  $\geq 180$  days [5, 6].

In thoracic surgery preoperative NP measurement has been reported to be an independent risk factor for postoperative atrial fibrillation [7, 8, 20]. Recently, Nojiri *et al.* [9] reported, in a limited series of older patients, of mean age 78 years and undergoing pulmonary resection for lung cancer, that preoperative NP was a useful predictor not only of cardiovascular but also of respiratory complications. After thoracic surgery, early NP elevations have been correlated with postoperative fluid retention [21]. NP elevations have also been correlated with the extent of pulmonary resection, possibly due to the increase in pulmonary artery pressure and total pulmonary vascular resistance requiring right ventricular compensation [1].

The incidence of pulmonary complications after thoracic surgery ranges from 15 to 37%, and several independent risk factors have been identified [22, 23]. However, as reported by Agostini *et al.* [12], the results of existing studies are difficult to compare because outcome definitions vary widely between studies; many of the identified risk factors are interrelated; small sample size preclude multivariate logistic regression; and finally many studies are retrospective in design and so there are valid concerns as to the sensitivity and specificity of data scoring.

In our series, we experienced a low rate of pulmonary complications (11%), probably related to our patient selection process and to the intense preoperative physiotherapy programme. Twenty-five percent of pulmonary complications occurred in patients who also developed cardiovascular events. This association has previously been reported by Nojiri *et al.* and could be related to the poor cardiopulmonary reserve in patients who develop significant morbidity after thoracic surgery [9].

The patients included in our study underwent surgery after a thorough cardiological and respiratory examination and most of them (77%) underwent major pulmonary resections (lobectomies or pneumonectomies). In our series, at baseline, the median BNP level was far below the threshold value, the median forced expiratory volume in 1 second value was 91% (75–108), the median DLCO was 88 (69.7–102.2) and none of patients showed evidence of RV overload or LV diastolic dysfunction on echocardiographic examination. This study was therefore conducted in a relatively low-risk population, fit to undergo elective major pulmonary resection. Consequently, our results show that the BNP assessment could have a powerful prognostic value to identify patients at major risk of perioperative adverse events. In our series, the incidence of cardiovascular and respiratory complications was significantly higher in patients with elevated postoperative BNP levels; therefore BNP determination could represent a rapid and relatively inexpensive method to enhance the perioperative risk prediction. Since surgery-related complication risk is still the main focus of surgeons, there is a lack of knowledge evaluating patients' specific responses after surgery. In this series, we show the relationship between BNP and the risk of short-term cardiopulmonary impairment; this evidence allows us to generate the hypothesis of a potential translational perspective. It is possible that BNP could identify minor changes in ventricular function caused by transient myocardial ischaemia or fluid overload during surgery [24]; this could be useful in identifying patients at high risk of adverse cardiac and pulmonary events who may benefit from closer postoperative monitoring and more rigorous heart rate and fluid balance assessment [6]. More research is needed to transform this hypothesis into clinical practice, but 'markers of risk' together with 'markers of disease' can be very useful for directing the attention of perioperative physicians to those patients most at risk of an upcoming event.

Our findings have limitations; this is a single-centre pathophysiology-driven clinical study. Little a priori knowledge was available to formally define an ideal sample size, which therefore limits the generalizability of our results and did not permit us to assess the interaction between pre- and postoperative BNP levels. The study time frame was short by design, and the number of observed events was limited, thus it cannot fully elucidate the independent prognostic impact of the findings without incurring the risk of model overfitting.

Finally, the PPV found for the BNP cut-off of 118.5 pg/ml was quite low (25.6%), which is not surprising, since PPV depends on the prevalence of the disease in a given population [25], which is quite low (18%) in the present study. Nevertheless, the same analysis, performed on the group of patients who underwent major surgery (with a higher prevalence of complications, 21.1%), gave substantially the same results.

In our opinion, before postoperative BNP measurement after thoracic surgery is widely adopted, additional prospective multicentre investigations are necessary to completely define the prognostic value of BNP in the prediction of adverse postoperative cardiovascular and pulmonary complications in patients undergoing pulmonary resection. Therefore, the results of this observational non-randomized study should be regarded as hypothesis-generating, deserving further confirmatory studies.

**Conflicts of interest:** none declared.

## References

- [1] Tayama K, Takamori S, Mitsuoka M, Hayashi A, Tamura K, Mifune H *et al.* Natriuretic peptides after pulmonary resection. *Ann Thorac Surg* 2002;73:1582–6.
- [2] Rodseth RN. B type natriuretic peptide—a diagnostic breakthrough in perioperative cardiac risk assessment? *Anaesthesia* 2009;64:165–78.
- [3] Clerico A, Passino C, Emdin M. Surgery casualties: do not leave hearts behind enemy lines. *J Am Coll Cardiol* 2014;63:181–3.
- [4] Ford MK, Beattie WS, Wijeyesundera DN. Systematic review: prediction of perioperative cardiac complications and mortality by the revised cardiac risk index. *Ann Intern Med* 2010;152:26–35.
- [5] Rodseth RN, Biccard BM, Le Manach Y, Sessler DI, Lurati Buse GA, Thabane L *et al.* The prognostic value of pre-operative and post-operative B-type natriuretic peptides in patients undergoing noncardiac surgery: B-type natriuretic peptide and N-terminal fragment of pro-B-type natriuretic peptide: a systematic review and individual patient data meta-analysis. *J Am Coll Cardiol* 2014;63:170–80.
- [6] Rodseth RN, Biccard BM, Chu R, Lurati Buse GA, Thabane L, Bakhai A *et al.* Postoperative B-type natriuretic peptide for prediction of major cardiac events in patients undergoing noncardiac surgery: systematic review and individual patient meta-analysis. *Anesthesiology* 2013;119:270–83.
- [7] Nojiri T, Maeda H, Takeuchi Y, Funakoshi Y, Kimura T, Maekura R *et al.* Predictive value of B-type natriuretic peptide for postoperative atrial fibrillation following pulmonary resection for lung cancer. *Eur J Cardiothorac Surg* 2010;37:787–91.
- [8] Cardinale D, Colombo A, Sandri MT, Lamantia G, Colombo N, Civelli M *et al.* Increased perioperative N-terminal pro-B-type natriuretic peptide levels predict atrial fibrillation after thoracic surgery for lung cancer. *Circulation* 2007;115:1339–44.
- [9] Nojiri T, Inoue M, Yamamoto K, Maeda H, Takeuchi Y, Funakoshi Y *et al.* B-type natriuretic peptide as a predictor of postoperative cardiopulmonary complications in elderly patients undergoing pulmonary resection for lung cancer. *Ann Thorac Surg* 2011;92:1051–5.
- [10] Thygesen K, Alpert JS, White HD, Jaffe AS, Apple FS, Galvani M *et al.* Joint ESC/ACC/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *Circulation* 2007;116:2634–53.
- [11] Scholes RL, Browning L, Sztendur EM, Denehy L. Duration of anaesthesia, type of surgery, respiratory co-morbidity, predicted VO2 max

- and smoking predict postoperative pulmonary complications after upper abdominal surgery: an observational study. *Aust J Physiother* 2009;55: 191–8.
- [12] Agostini P, Cieslik H, Rathinam S, Bishay E, Kalkat MS, Rajesh PB *et al.* Postoperative pulmonary complications following thoracic surgery: are there any modifiable risk factors?. *Thorax* 2010;65:815–8.
- [13] Struthers A, Lang C. The potential to improve primary prevention in the future by using BNP/N-BNP as an indicator of silent ‘pancardiac’ target organ damage: BNP/N-BNP could become for the heart what microalbuminuria is for the kidney. *Eur Heart J* 2007;28:1678–82.
- [14] Clerico A, Giannoni A, Vittorini S, Passino C. Thirty years of the heart as an endocrine organ: physiological role and clinical utility of cardiac natriuretic hormones. *Am J Physiol Heart Circ Physiol* 2011;301:H12–20.
- [15] Mezzasoma L, Cagini L, Antognelli C, Puma F, Pacifico E, Talesa VN. TNF- $\alpha$  regulates natriuretic peptides and aquaporins in human bronchial epithelial cells BEAS-2B. *Mediators Inflamm* 2013;2013:159349.
- [16] Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH *et al.* 2013 ACCF/AHA Guideline for the Management of Heart Failure: a Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;62: 147–239.
- [17] Morrow DA, Cannon CP, Jesse RL, Newby LK, Ravkilde J, Storrow AB *et al.* National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: clinical characteristics and utilization of biochemical markers in acute coronary syndromes. *Clin Chem* 2007;53: 552–74.
- [18] Poldermans D, Bax JJ, Boersma E, De Hert S, Eckhout E, Fowkes G *et al.* Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery. *Eur Heart J* 2009;30: 2769–812.
- [19] Biccari BM, Lurati Buse GA, Burkhart C, Cuthbertson BH, Filipovic M, Gibson SC *et al.* The influence of clinical risk factors on pre-operative B-type natriuretic peptide risk stratification of vascular surgical patients. *Anaesthesia* 2012;67:55–9.
- [20] Amar D, Zhang H, Shi W, Downey RJ, Bains MS, Park BJ *et al.* Brain natriuretic peptide and risk of atrial fibrillation after thoracic surgery. *J Thorac Cardiovasc Surg* 2012;144:1249–53.
- [21] Cagini L, Capozzi R, Tassi V, Savignani C, Quintaliani G, Reboldi G *et al.* Fluid and electrolyte balance after major thoracic surgery by bioimpedance and endocrine evaluation. *Eur J Cardiothorac Surg* 2011;40: 71–6.
- [22] Stephan F, Boucheseiche S, Hollande J, Flahault A, Cheffi A, Bazelly B *et al.* Pulmonary complications following lung resection: a comprehensive analysis of incidence and possible risk factors. *Chest* 2000;118:1263–70.
- [23] Licker MJ, Widikker I, Robert J, Frey JG, Spiliopoulos A, Ellenberger C *et al.* Operative mortality and respiratory complications after lung resection for cancer: impact of chronic obstructive pulmonary disease and time trends. *Ann Thorac Surg* 2006;81:1830–7.
- [24] Vanzetto G, Jacon P, Calizzano A, Neuder Y, Faure P, Fagret D *et al.* N-terminal pro-brain natriuretic peptide predicts myocardial ischemia and is related to postischemic left-ventricular dysfunction in patients with stable coronary artery disease. *J Nucl Cardiol* 2007;14:835–42.
- [25] Mittendorf R, Pryde P, Herschel M, Williams M. Is routine antenatal toxoplasmosis screening justified in the United States? Statistical considerations in the application of medical screening tests. *Clin Obstet Gynecol* 1999;42:163–73.