

## B-type natriuretic peptide: Usefulness in the management of critically-ill neonates

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### ABSTRACT

B-type natriuretic peptide (BNP) is responsible for changes in the heart organogenesis and is associated with transition to extrauterine life. In the first week of life, BNP levels are high and return to normal with the physiological loss in weight. High BNP levels are associated with different conditions.

**Objective.** To establish the relationship between BNP levels and criticality and the short-term clinical course among patients hospitalized in the neonatal intensive care unit.

**Method.** Observational and analytical study conducted in a prospective cohort. Criticality was defined as a requirement for assisted mechanical ventilation with a fraction of inspired oxygen of more than 50% and/or inotropes. Two blood samples were collected 72 hours apart.

**Results.** Seventy-three patients were included in the study. Depending on their clinical course on day 7, they were divided into 2 groups: patients with a good clinical course or a persistent, severe clinical course. The median baseline BNP level was similar in both groups ( $p: 0.15$ ). The median BNP level at 72 hours was higher among patients with a persistent, severe clinical course ( $p: 0.005$ ). The difference between both BNP values was calculated ( $\Delta$ BNP: BNP level at 72 hours – BNP level at 0 hours). The  $\Delta$ BNP was positive among patients with a persistent, severe clinical course ( $X = 1260$  pg/mL; range: 426-2094) and negative in the group with a good clinical course ( $X = -967$  pg/mL; range: -1656/-278) ( $p: 0.0002$ ); sensitivity: 87%; specificity: 86%; positive predictive value: 74%; and negative predictive value: 93%.

**Conclusion.** In this group of patients, the delta-BNP value reflected the short-term clinical course.

**Key words:** B-type natriuretic peptide, neonates.

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### INTRODUCTION

B-type natriuretic peptide (BNP) is a cardiac peptide released by the heart ventricles in response to changes in the ventricular pressure and/or volume.<sup>1,2</sup>

BNP is a peptide made up of 32 amino acids with a ring structure; its mechanism of action is mediated by the increase in cyclic guanosine monophosphate (cGMP). It has a diuretic and pulmonary vasodilatory effect. BNP plays a major role in the organogenesis of the fetal heart and during the transition of newborn infants (NBIs) to extrauterine life.<sup>3,4</sup>

In the first week of life, BNP levels are normally high, up to 12 times higher than maternal levels, since it does not cross the placental barrier. Such high value observed among healthy NBIs in the first days of life tends to return to normal with physiological loss in weight reaching a level similar to that observed in adults.<sup>5-7</sup>

In the neonatal population, BNP measurements vary widely. Several studies have reported BNP levels ranging from 200 to 6000 pg/mL. Following the first week, BNP levels tend to normalize and can even be lower than 300 pg/mL.<sup>8</sup>

In the adult population, there is evidence that an increase in BNP and its N-terminal fraction (NT-proBNP) is associated with heart failure<sup>9,10</sup> and an increase in mortality due to severe sepsis and septic shock.<sup>11</sup>

In the pediatric population, a dramatic rise in BNP and NT-proBNP levels has been associated with hemodynamic compromise, congenital heart malformations, and a poor clinical course.<sup>12-14</sup>

For patients with pulmonary hypertension (PHT), BNP has demonstrated to be a useful prognostic marker. Changes in BNP levels during the longitudinal follow-up of a patient appear to be more important than an isolated measurement, even if it was high.<sup>15</sup>

Among preterm NBIs, elevated BNP and NT-proBNP levels have been associated with the presence of patent ductus arteriosus (PDA)<sup>16,17</sup> and the severity of hemodynamic compromise.<sup>18,19</sup> Such high levels correlate with the size of the PDA and the increase in pulmonary blood flow.<sup>20,21</sup>

To date, no reports have been published on the assessment of this marker as a predictor of clinical course among sick neonates or on whether there is an association between BNP levels and/or an increase in BNP levels and the lack of stabilization among critically-ill NBIs.

The hypothesis posed by this study was that BNP levels were higher among critically-ill NBIs and that a decrease in BNP levels was related to a good clinical course (GCC) and treatment response. BNP measurement may help to make decisions regarding the timely transfer of patients in this subgroup to tertiary care (level III) hospitals, in advance of their need for more complex therapeutic support.

The objective of this study was to establish whether there is a relationship between BNP levels and/or variations and criticality and the short-term clinical course among patients with cardiorespiratory instability hospitalized in the neonatal intensive care unit (NICU).

## METHOD

This was an observational and analytical study conducted in a prospective cohort. All neonates who met the criteria for hemodynamic instability and admitted to the NICU were included in the study consecutively and only once.

The study was conducted in the Neonatal Intensive Care Unit of Hospital Nacional de Pediatría SAMIC "Prof. Dr. Juan P. Garrahan", a tertiary care (level IIIB) hospital, in the period between July 1<sup>st</sup>, 2013 and June 30<sup>th</sup>, 2014.

Inclusion criteria were as follows: patients with hemodynamic instability, defined as requiring assisted mechanical ventilation (AMV) with a fraction of inspired oxygen (FIO<sub>2</sub>) of more than 50% or as requiring AMV, with any level of FIO<sub>2</sub>, plus inotropes.

Neonates born at less than 35 weeks' gestation, patients with malformations incompatible with life, and those for whom informed consent was not obtained were excluded.

All patients who died before 72 hours of life were removed.

Two blood samples were obtained from all patients: the first one at inclusion in the study and the second one, 72 hours later.

Samples consisted in 1.3 mL of blood collected in ethylenediaminetetraacetic acid (EDTA) tubes, which were centrifuged immediately for plasma BNP measurement. Measurements were made by microparticle enzyme immunoassay (AXSYM system, ABBOTT laboratory) and values were reported as pg/mL.

Additionally, baseline and clinical course data were collected over 7 days after inclusion in the study.

Study outcome measures were age in days, sex, gestational age, birth weight, Apgar score, delivery mode, referral requirement, diagnosis, Score for Neonatal Acute Physiology-Perinatal Extension (SNAPPE) on admission. Criticality and clinical course were established based on AMV requirement, mean airway pressure (MAP), FIO<sub>2</sub>, oxygenation index (OI), inotrope use, vasoactive-inotropic score (VIS)<sup>22</sup> (dose: dopamine + dobutamine + 100 x epinephrine + 10 x milrinone + 10 000 x vasopressin + 100 x norepinephrine), inhaled nitric oxide (iNO) use, extracorporeal membrane oxygenation (ECMO) requirement, impairment of liver and/or kidney function, multiple organ dysfunction syndrome (MODS), and death.

Based on their clinical condition on day 7, patients were divided into 2 groups to establish the primary outcome measure: patients with a good clinical course or patients with a persistent severe clinical course (PSCC), defined as cardiorespiratory instability in spite of treatment (AMV and inotrope requirement that is the same or higher than at study inclusion, ECMO requirement or death).

The  $\Delta$ BNP was measured to analyze the role of marker variations. It was calculated as the difference between the BNP level at 72 hours minus the BNP level at admission, for each patient.

The protocol was assessed and approved by the Review Committee and the Ethics Committee of Hospital Nacional de Pediatría SAMIC "Prof. Dr. Juan P. Garrahan". An informed consent for study participation was obtained from patients families.

## Statistical analysis

All outcome measures were summarized using descriptive statistics of central tendency,

position, and dispersion.

The sample size was estimated to establish a 500 pg difference with a more/less 500 pg variability; considering an 0.05 alpha error and an 0.10 beta error, 22 children were required in each arm (patients with GCC and PSCC).

BNP levels at baseline and at 72 hours were described as median and interquartile range.

To measure marker variations, the  $\Delta$ BNP was defined as the difference between the second BNP value minus the first BNP value for each patient.

Patients' BNP levels,  $\Delta$ BNP, and clinical course (GCC versus PSCC) were compared using a Wilcoxon non-parametric test. A value of  $p < 0.05$  was considered statistically significant. Categorical outcome measures were compared using the  $\chi^2$  test.

A non-parametric receiver operating characteristic (ROC) curve was developed to establish the cut-off point at which the highest sensitivity and specificity were achieved and to assess its discrimination power as diagnostic test, i.e., its capability to differentiate GCC from PSCC. The area under the curve and the 95% confidence interval (CI), as well as sensitivity, specificity,

positive predictive value (PPV), and negative predictive value (NPV), were estimated for said cut-off value, which was selected based on the Youden index.

The statistical analysis was performed with the STATA SE 12.0 software (StataCorp LP, USA).

## RESULTS

Seventy-three critically-ill patients were included in the study (Figure 1).

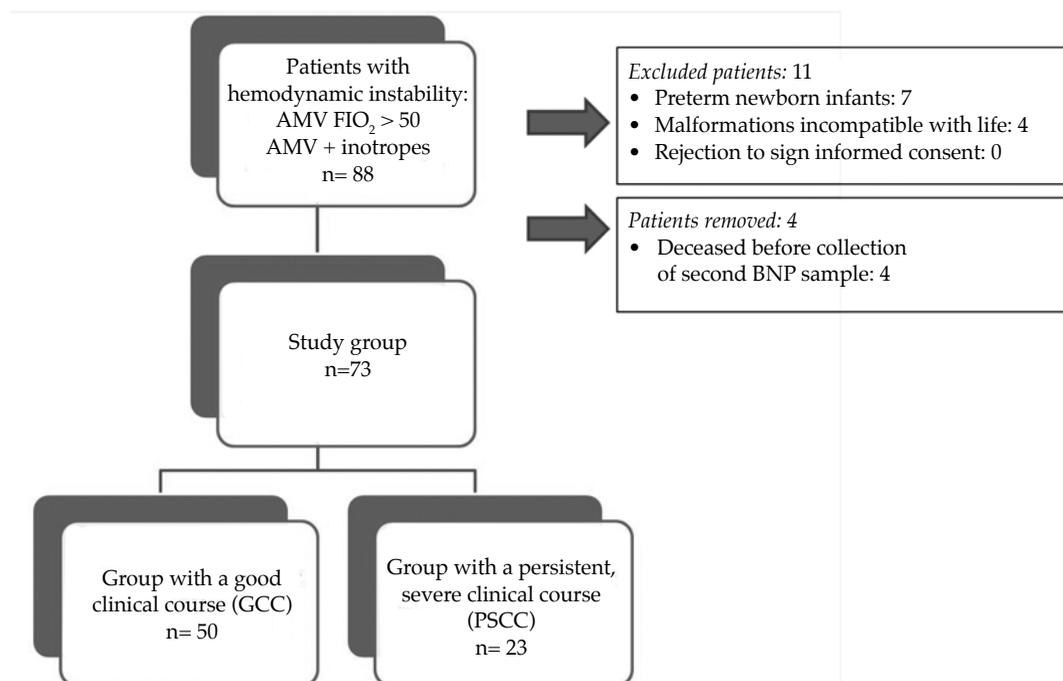
The general characteristics of patients are summarized in Table 1.

As shown in Table 2, no statistically significant differences were observed in clinical and demographic outcome measures between both groups (GCC and PSCC) upon study inclusion.

On day 7 after inclusion in the study, 23 out of 73 patients (31%) had a GCC. Of these, 73% required AMV and had a  $FIO_2 > 50\%$ , and a mean OI of 13 (standard deviation [SD]:  $\pm 13$ ); 83% required inotropes and had a mean VIS of 24 (SD:  $24 \pm 38$ ); 11% required ECMO, and 86% met the criteria for MODS.

The overall mortality was 7% (5/73). After 72 hours of study inclusion, 5 patients in the group

FIGURE 1. Flowchart of the study



AMV: assisted mechanical ventilation;  $FIO_2$ : fraction of inspired oxygen; BNP: B-type natriuretic peptide.

with a PSCC had died. Four died within the 72 hours of protocol initiation and were removed.

TABLE 1. Characteristics of patients included in the study

	N= 73
Age in days*	3 (1-14)
Gestational age in weeks*	37 (35-38)
Male sex	64%
Birth weight*	2880 g (2120-3500)
C-section	63%
Apgar score at 5 min	9 (7-9)
Referred from other healthcare facilities	73%
Diagnoses	Respiratory condition (65%) Heart condition (8%) Sepsis (19%) Other (8%)

\* Values expressed as median with its corresponding interquartile range.

The median baseline BNP level was similar among patients from both groups (GCC and PSCC) ( $p$ : 0.15). However, the median BNP level at 72 hours was higher among patients with a PSCC compared to those with a GCC ( $p$ : 0.005) (Table 3).

Among all patients in the group with PSCC, the  $\Delta$ BNP was positive, i.e., the BNP level at 72 hours was higher than at baseline. On the contrary, NBIs with a GCC showed a negative  $\Delta$ BNP. Such differences were statistically significant ( $p$ : 0.0002) (Tables 3 and 4).

The best cut-off point for  $\Delta$ BNP was +11 with a sensitivity of 0.87 and a specificity of 0.86 (PPV: 0.74; NPV: 0.93) (Table 5).

Figure 2 shows the ROC curve for  $\Delta$ BNP relative to patients' clinical course on day 7; the area under the curve was 0.86 (0.76-0.97).

TABLE 2. Comparison of population upon admission, by clinical course

	Good clinical course N: 50	PSCC at 7 days N: 23	P
Age (days)			
M (IQR)	3 (13)	6 (17)	0.09
Weight (g)			
$\bar{X}$ (SD)	2818 (836)	2487 (1101)	0.16
Gestational age (weeks)			
M (IQR)	37 (2)	38 (1.5)	0.09
Male sex			
n (%)	32 (64%)	15 (65%)	0.92
PHT*			
n (%)	22 (44%)	9 (39%)	0.69
Apgar score at 5 min			
$\bar{X}$ (SD)	8.2 (1.8)	7.6 (0.7)	0.09
SNAPPE			
$\bar{X}$ (SD)	30 (22)	29 (19)	0.99
Lactic acid (mmol/L)			
$\bar{X}$ (SD)	3.5 (3.7)	3.5 (4.1)	0.76
$\text{FIO}_2^{**} > 50\%$			
n (%)	39 (78%)	17 (74%)	0.70
Oxygenation index			
$\bar{X}$ (SD)	12 (9)	12 (11)	0.59
Inotropes			
n (%)	39 (78%)	16 (70%)	0.43
Inotropic index			
$\bar{X}$ (SD)	25 (38)	27 (65)	0.18
Pulmonary vasodilators			
n (%)	17 (34%)	9 (39%)	0.21
Nitric oxide (iNO)			
n (%)	13 (26%)	3 (13%)	0.21
Impairment of renal function			
n (%)	6 (12%)	3 (13%)	0.9
Impairment of liver function			
n (%)	11 (22%)	5 (21%)	0.98
Multiple organ dysfunction syndrome			
n (%)	44 (88%)	18 (78%)	0.28

Values are expressed as average ( $\bar{X}$ ) and standard deviation (SD) or as median (M) and interquartile range (IQR).

\* PHT: pulmonary hypertension. \*\*  $\text{FIO}_2$ : fraction of inspired oxygen. PSCC: persistent, severe clinical course.

SNAPPE: Score for Neonatal Acute Physiology-Perinatal Extension.

## DISCUSSION

BNP modulates biological processes through the activation of natriuretic peptide receptor-A (NPR-A), and is a fast and highly sensitive marker of myocardial dysfunction.<sup>23</sup> The production ratio of BNP and NT-proBNP, its inactive precursor, is 1:1, so they may be equally useful and can be used based on their availability in each facility.<sup>24</sup>

Our study demonstrated the usefulness of measuring BNP in critically-ill NBIs to predict their clinical course in the short term.

Although the baseline BNP level on admission was not associated with the patient's prognosis, sequential determinations showed that a reduced BNP level in the second sample correlated with GCC whereas an increased BNP level was related to an unfavorable clinical course in the short term.

The low discrimination power of BNP measurement on admission, as an isolated value, had also been observed by other authors,<sup>34</sup> who reported that serial determinations of NT-proBNP were better prognostic predictors than an isolated measurement. However, other authors have reported an adequate correlation between the measurement of BNP on the first day of life of NBIs with diaphragmatic hernia and their clinical course.<sup>35</sup>

The wide dispersion of BNP levels observed in the first week of life shows the important role played by BNP during transition to extrauterine life.<sup>7</sup> In our study, the isolated baseline BNP value also exhibited a wide dispersion among patients.

BNP has been extensively studied in patients with congenital heart disease; it has been demonstrated that BNP was higher in this population than in control individuals, including clinically stable patients.<sup>12,13,25</sup>

It is also a useful tool to identify in advance patients who, following a corrective surgery for heart malformations, will develop heart failure, and also as an indicator of the right time for the procedure.<sup>26,27</sup>

BNP measurements in preterm NBIs showed a strong correlation between an increased BNP and the presence of hemodynamically significant ductus arteriosus.<sup>20</sup>

There are reports about the capability of BNP to differentiate respiratory distress syndrome from PHT in NBIs; this means that BNP measurement may tell the difference between patients with a purely respiratory condition and those with hemodynamic or cardiac compromise.<sup>28</sup> A strong correlation has been observed, in NBIs with PHT, among BNP,

TABLE 3. Comparison of B-type natriuretic peptide levels at 0 and 72 hours and delta B-type natriuretic peptide value as per the patients' clinical course

	*TOTAL n= 73	**GCC n= 50	***PSCC n= 23	<i>p</i>
BNP 0 h	459 (185/1555)	498 (196/2297)	378 (92/1238)	0.15
BNP 72 h	360 (91/1165)	271 (68/737)	1386 (136/3760)	0.005
ΔBNP	-265 (DE 2494)	-967 (-1656/-278)	1260 (426/2094)	0.0002

BNP values are expressed as pg/mL. Values are expressed as median (IQR: 25-75).

ΔBNP values are expressed as median (SD). \* Total: all patients included in the study.

\*\* GCC: good clinical course. \*\*\* PSCC: persistent, severe clinical course.

TABLE 4. Result of variations in B-type natriuretic peptide among studied patients and its relationship to their clinical course

	<sup>1</sup> GCC n= 23	<sup>2</sup> PSCC n= 50	Total n= 73
* ΔBNP +	20	7	27
** ΔBNP -	3	43	46

\* Delta-BNP +: patients with an increased BNP level in their second sample compared to the first.

\*\* Delta-BNP -: patients with a reduced BNP level in their second sample compared to the first.

<sup>1</sup> PSCC: persistent, severe clinical course.

<sup>2</sup> GCC: good clinical course.

TABLE 5. Result of variations in B-type natriuretic peptide among patients and its capability to predict their clinical course

	95% CI	
Sensitivity	87.0%	67.9-95.5%
Specificity	86.0%	73.8-93.0%
Positive predictive value	74.1%	55.3-86.8%
Negative predictive value	93.5%	82.5-97.8%
False positive ratio	14.0%	7.0-26.2%
False negative ratio	13.0%	4.5-32.1%
Accuracy	86.3%	76.6-92.4%
Youden index (J)	0.7	

CI: confidence interval.

clinical severity,<sup>29,30</sup> and treatment response.<sup>31</sup>

Baptista et al.<sup>32</sup> studied BNP levels in patients with congenital diaphragmatic hernia (CDH) and observed an association among BNP levels, the severity of PHT, and mortality in this population. Other authors have reported that serial measurements of BNP levels among NBIs with CDH predicted the severity of PHT and ECMO requirement,<sup>33</sup> which was consistent with our findings.

Based on them, it may be stated that an increase in BNP levels obtained from 2 consecutive samples collected 72 hours apart predicts PSCC whereas a reduction predicts GCC in the short term. Likewise, it may be stated that such difference can be useful as a short-term prognostic tool.

An increase in BNP levels measured sequentially in critically-ill patients hospitalized in the NICU may predict hemodynamic changes, prognosis and/or response to treatment.

One of the limitations of our study is that no correlation was established between patients' BNP levels and echocardiograms, as reported in other studies.<sup>34,35</sup> Likewise, it is necessary to study whether these outcomes are reproducible in other facilities.

Further studies are required to support the usefulness of BNP measurements as a predictor of clinical course among critically-ill NBIs.

To conclude, BNP measurements in a population of NBIs with cardiorespiratory instability, as per our results, can predict their clinical course in the short term. It is a sensitive,

readily available test that can be easily performed in many healthcare facilities, and is especially aimed for those sites where there is not a tertiary care neonatal intensive care unit because it makes it possible to know, in advance, whether it is necessary to transfer a patient to a facility with a higher level of care. ■

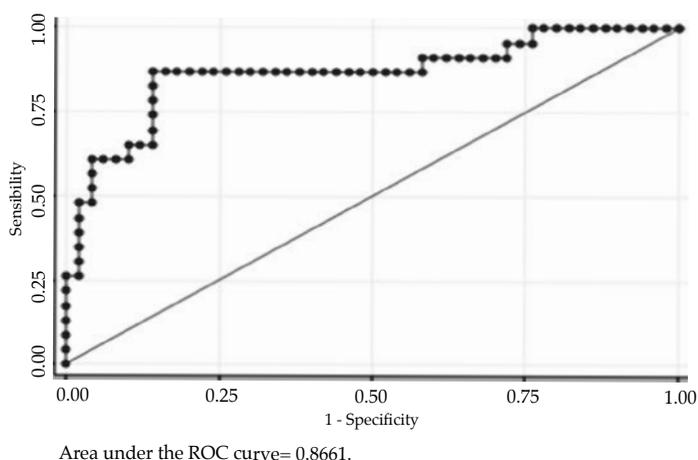
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FIGURE 2. Receiver operating characteristic curve for delta B-type natriuretic peptide



ROC curve: receiver operating characteristic curve.

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