

# Accuracy of B-natriuretic peptide for the diagnosis of decompensated heart failure in muscular dystrophies patients with chronic respiratory failure

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## Abstract

Heart failure and restrictive respiratory insufficiency are complications in muscular dystrophies. We aimed to assess the accuracy of the B-natriuretic peptide (BNP) for the diagnosis of decompensated heart failure in muscular dystrophy. We included patients with muscular dystrophy and chronic respiratory insufficiency admitted in the Intensive Care Unit of the Raymond Poincaré hospital (Garches, France) for suspected decompensated heart failure. Thirty-seven patients were included, among them, 23 Duchenne muscular dystrophy (DMD) (62%), 10 myotonic dystrophy type 1 (DM1) (27%). Median age was 35 years [27.5; 48.5]. 86.5% of patients were on home mechanical ventilation (HMV). Median left ventricular ejection fraction (LVEF) was 47% [35.0; 59.5]. Median BNP blood level was 104 pg/mL [50; 399]. The BNP level was significantly inversely associated with LVEF ( $r = -0.37$ ,  $p = 0.03$ ) and positively associated with the LVEDD (left ventricular end diastolic diameter) ( $r = 0.59$ ,  $P < 0.001$ ). The discriminative value of the BNP level for the diagnosis of decompensated heart failure was high with an AUROC = 0.94 ( $P < 0.001$ ). The best discrim-

inating BNP threshold was 307 pg/mL (Youden index 0.85).

The BNP level measurement may add a supplemental key for the final diagnosis of decompensated heart failure.

## Introduction

Heart failure is a classical complication in patients with muscular dystrophy, particularly in Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD). In parallel with heart impairment, respiratory muscles are often involved, providing a restrictive pulmonary insufficiency requiring HMV before adult age in patients with DMD. The concomitant presence of skeletal muscle involvement leading to limited mobility, together with chronic respiratory failure, may make it challenging to diagnose acute decompensated heart failure. Cardiac symptoms are subtle and non-specific<sup>1</sup> and the presence of mechanical ventilation may provide respiratory clinical picture modifications.<sup>2</sup> In this difficult clinical context, biomarkers could represent an interesting tool to help bedside decision making. Brain natriuretic peptide (BNP) is a 32-amino acid protein produced and released by the heart ventricles.<sup>3</sup> BNP is used as a biomarker for the diagnosis and prognostic evaluation of heart failure.<sup>4</sup> Little is known about the diagnostic value of BNP in patients with muscular dystrophies and mechanical ventilation.

We aimed to assess the accuracy of the BNP level for the diagnosis of decompensated heart failure in patients with muscular dystrophies and chronic respiratory insufficiency and the association between BNP level and cardiac function.

## Materials and Methods

### Study design

For this retrospective study, we included patients with muscular dystrophy (DMD, BMD, sarcoglycanopathy, myotonic dystrophy type 1 (DM1), Facio scapulo humeral disease type 1 (FSHD1) admitted in the Intensive Care Unit (ICU) department of the Raymond Poincaré Hospital (Garches, France) and who had a BNP level dosage and an echocardiography at admission. Our institution is specialized for the follow up of patients with neuromuscular disorders and chronic respiratory insufficiency due to respiratory muscles failure.

We excluded patients admitted for the following causes: septic shock, traumatism, post-operative surgery, and acute cerebral

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disorders. We recorded the following parameters at hospital admission: peripheral skeletal muscular impairment (wheelchair or not), systolic blood pressure (SBP), diastolic blood pressure (DBP), previous cardiac drugs before admission, previous forced vital capacity (VC) before admission, respiratory settings for patients with HMV, co-morbidities, biological results (BNP, blood creatinine) as well as electrocardiogram and echocardiography. Diagnosis of decompensated heart failure was established by an experimented cardiologist (AF) after checking the global record of the patients blindly to BNP level, taking into account clinic, Chest X ray and echocardiography, according to European Society of Cardiology (ESC) guidelines.<sup>5</sup> The study was performed in compliance with the ethical principles formulated in the declaration of Helsinki and was approved by the French regulatory Board (*commission nationale de l'informatique et des libertés, CNIL*).

### Plasma BNP level measurement

Venous blood sample was obtained and collected on an EDTA tube at admission in our hospital. The BNP level was then measured by a sandwich-type immunoassay using direct chemiluminescence measurement technology with two monoclonal antibodies (ADVIA Centaur BNP).

### Echocardiography

Echocardiography was performed at admission, according to the current international Guidelines. We recorded the echocar-

diographic data available from the patient's records: left ventricular end diastolic diameter (LVEDD), left ventricular ejection fraction (LVEF) and systolic pulmonary arterial pressure (SPAP).

### Statistical analysis

Continuous data are presented as median [interquartile range], categorical data are presented as number (percentage). Intergroup comparisons were performed using non-parametric tests because of data distribution. Spearman's correlations were performed to evaluate association between variables. Linear regression was performed to fit association lines on the corresponding figures. Discriminative value of BNP was evaluated using receiver-operator characteristic (ROC) curve. Optimal threshold of BNP was found using Youden's index. All analyses and figures were performed using GraphPad Prism (GraphPad Software, Inc., State of California, USA).

## Results

### Study population

37 patients were included in our study with the following repartition: 23 DM2 (62%), 10 DM1 (27%), 2 *gamma*-sarcoglycanopathies (5%), 1 BMD and 1 FSHD type 1. The median age was 35 years [27.5; 48.5]. All patients were wheelchair bound. Diabetes mellitus was present in 5% of patients, exclusively in DM1. Mean forced VC was 13.5% [5.0; 29.75] of predicted value and 86.5% of patients were on HMV. 51% of patients were invasively ventilated. Previous cardiac drugs prescribed for patients were divided as follow: Angiotensin receptors blockers (ARB) in 59%, beta-blockers in 43% and diuretics in 27%. All patients were in sinus rhythm and median LVEF was 47% [35.0; 59.5]. Median BNP blood level was 104 pg/mL.

The reason for admission was dyspnea in 18 patients (48%), pulmonary congestion in 10 patients (27%), lipothymia in 3 patients (8%), anasarca in 3 patients (8%) and abdominal discomfort in 3 patients (8%). Nine patients (24%) disclosed the final diagnosis of decompensated heart failure. The causes of decompensated heart failure were: sepsis (3 patients), influenza like illness (1 patient), bronchial stasis (3 patients).

The differential final diagnoses were:

- Exacerbation of chronic respiratory insufficiency caused by pulmonary sepsis (14 patients), bronchial stasis (2 patients), undetermined.<sup>3</sup>
- Pulmonary atelectasis (3 patients)

- Pulmonary sepsis (3 patients)
- Pulmonary thrombo-embolism (1 patient),
- Bowel occlusion (1 patient),
- Dehydration (1 patient).

The Table 1 summarizes clinical, biological and echocardiographic findings of patients at admission.

### Relationship between BNP, echocardiographic finding and LVEDD/SBP ratio

The BNP level was significantly inversely associated with the left ventricular systolic function ( $r = -0.37$ ,  $P = 0.03$ ) (Figure 1). The BNP level was significantly associated with the LVEDD ( $r = 0.59$ ,  $P < 0.001$ ) (Figure 2).

### Discriminative value of BNP for the diagnosis of decompensate heart failure

The discriminative value of the BNP level for the diagnosis of decompensated heart failure was high with an

AUROC=0.94,  $P < 0.001$ ) (Figure 3). The best discriminating BNP threshold was 307 pg/mL (Youden index 0.85), corresponding to a sensitivity of 100% and specificity of 85%, with a positive predictive value of 69% and a negative predictive value of 100%.

## Discussion

Our results suggest that BNP may be a helpful biomarker for the cardiological assessment of patients with muscular dystrophy. In fact, we found a significant inverse association between BNP and the left ventricular systolic function and an association between BNP level and the left ventricle dilation. Plasma BNP level is classically increased in patients with heart failure,<sup>6</sup> in parallel with NYHA functional class deterioration and in relation with cardiac failure severity. From a physiological point of view, BNP belongs to the regulatory response to ventricular overload. BNP

**Table 1. Clinical, biological and echocardiographic findings of patients at admission.**

Overall cohort (n=37)		
Clinical characteristics		
Male, n (%)	30	(81)
Age (years)	35	[27.5; 48.5]
Hypertension, n (%)	0	(0)
Diabete mellitus, n (%)	2	(5.4)
Pacemaker, n (%)	5	(13.5)
ICD, n (%)	1	(2.7)
Weight (kg)	53.5	[34.25; 80.0]
Height (cm)	163	[160.0; 166.5]
BMI	19.0	[12.0; 27.0]
SBP (mm Hg)	104	[96; 130]
DBP (mm Hg)	60	[54; 76]
HR (bpm)	104	[87; 119]
Cardiac drugs		
ARB, n (%)	22	(59.5)
Betablockers, n (%)	16	(43.2)
Diuretics, n (%)	10	(27.0)
Respiratory setting		
VC (% of predicted)	13.5	[5; 30]
HMV at inclusion, n (%)	32	(86.5)
Invasive ventilation at inclusion, n (%)	19	(51.4)
HMV 24/24 h, n (%)	19	(51.4)
ECG and echocardiography		
Sinus rythm, n (%)	36	(97)
LBBB, n (%)	8	(22)
RBBB, n (%)	9	(25)
LVEF (%)	47	[35; 59.5]
LVEDD (mm)	42	[40; 56.5]
SPAP (mmHg)	35.5	[30; 40.23]
Laboratory tests		
BNP (pg/L)	104	[50; 399]
Creatininemia (µmol/L)	21	[20; 36.8]

Data are presented as median [interquartile range] or number (percentage). ARB, angiotensin receptor blocker; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; LBBB, left bundle branch block; RBBB, right bundle branch block; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; ICD, implantable cardioverter defibrillator; ECG, electrocardiogram; HR, heart rate; HMV, home mechanical ventilation; SPAP, systolic pulmonary arterial pressure.

production induces vasodilation, diuresis, natriuresis, inhibition of aldosterone, renine and inhibition of fibrosis. BNP is removed from the circulation by a receptor-mediated mechanism and degraded by neutral endopeptidases, *i.e.*, neprilysin.<sup>7</sup>

In patients with muscular dystrophies, data about BNP level are scarce. In a study that included patients with dystrophinopathies and respiration failure, the authors reported a curvilinear relationship between BNP and LVEF without a significant increased BNP level.<sup>8</sup> In the neuromuscular field, older studies suggested BNP to be a less sensitive biomarker for the early detection of chronic cardiac failure with a curvilinear relationship between LV shortening fraction and BNP level in DMD patients with significant left ventricular dysfunction.<sup>9</sup> The ACCF (American College of Cardiology Foundation) and the AHA (American Heart Association) heart failure guidelines have given BNP a class I recommendation for diagnosis and prognosis of patients with heart failure (level of evidence: A).<sup>10</sup> The current ESC guidelines recommend measuring levels of BNP, Nt-proBNP or MR-proANP to exclude non-cardiac causes of acute dyspnea in patients with suspected acute heart failure.<sup>5</sup> In our population, BNP showed a good accuracy for the diagnosis of decompensated heart failure, with an AUC ROC of 0.94 and a 100% sensitivity using a cut off of 307 pg/mL. The cut off BNP for the diagnosis of heart failure in our study was higher than the classical value reported in guidelines (100 pg/mL).<sup>10</sup> Our finding may be explained by the presence of mechanical ventilation that alleviates cardiac symptoms of decompensated heart failure by unloading the ventricle and reducing respiratory workload. Also, in our study, 59% of patients were treated with ARB; diuretics were prescribed in 27% of patients. Cardiac drugs may influence BNP levels since diuretic may reduce plasma BNP levels as well as ACE inhibitors, angiotensin receptor blockers and aldosterone antagonists.<sup>11</sup> Finally, our study was performed in patients admitted to ICU, in acute situations that are different from those of patients consulting for routine cardiac follow-up evaluation. Indeed, in ICU, because of co morbidities, the best BNP cut off level for the diagnosis of heart failure was reported to be 150 pg/mL rather than standard cut off (100 pg/mL).<sup>12</sup>

The AUC found in our study was similar to AUC reported in other populations.<sup>13</sup> In the Multinational study reported by McCullough *et al.*,<sup>14</sup> using a cut off of 100 pg/mL for the plasma BNP level, the sensitivity was reported to be 90% (95% CI: 88-92%) and the specificity 76% (95% CI: 73-

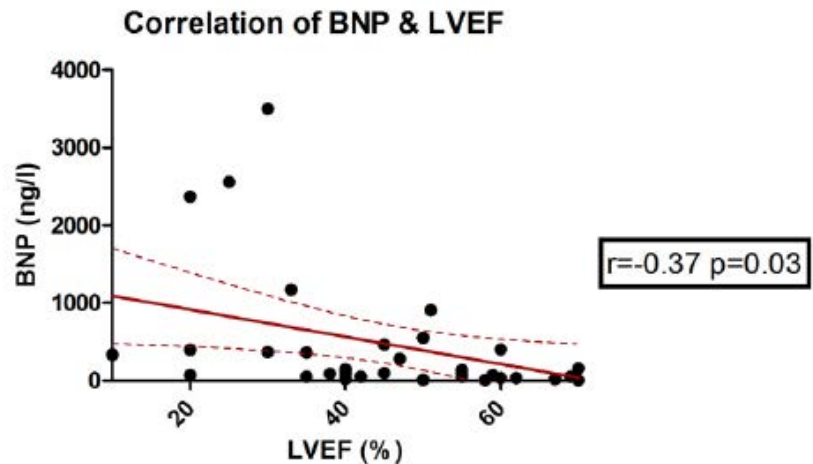


Figure 1. Association between BNP level and LVEF using linear regression (solid line). The dotted lines represent the 95% confidence band of the best-fit line. BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction.

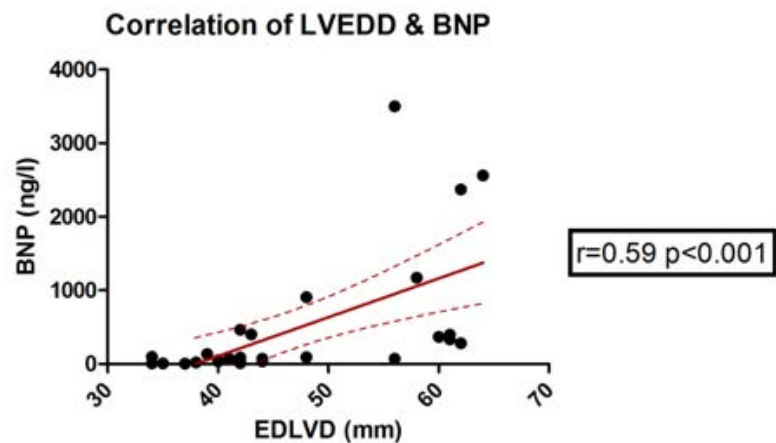


Figure 2. Association between BNP level and EDLVD using linear regression (solid line). The dotted lines represent the 95% confidence band of the best-fit line. BNP, brain natriuretic peptide; EDLVD, end diastolic left ventricular diameter.

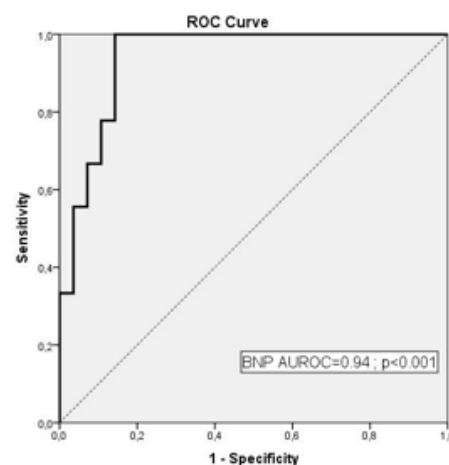


Figure 3. ROC curve for the accuracy of BNP in the diagnosis of decompensated heart failure in patients with muscular dystrophies. ROC, receiver operating characteristic; BNP, brain natriuretic peptide.

79%). In this previous study,<sup>14</sup> the BNP level was found to be more accurate than clinical judgment and classical explorations for the diagnosis of heart failure (81% vs 74%). Finally, The Breathing Not Properly Multinational Study reported a cut off BNP value >100 pg/mL for the diagnosis AHF with a high accuracy (85%).<sup>4</sup>

### Limits of the study

The limits of our study rely on its retrospective design and the relatively small number of patients. Also, we combined patients with dystrophinopathies and patients with myotonic dystrophies. Furthermore, the best BNP cutoff was derived in a single population and should be confirmed in an external multicentric validation population.

Plasma BNP levels has been showed to correlate with age, body mass index (BMI), renal function<sup>15</sup> and BNP level is lower in obese patients.<sup>16</sup> Other non-cardiac factors may increase modestly the BNP level, including chronic obstructive pulmonary disease, pulmonary embolism, pulmonary hypertension, pneumonia, atrial fibrillation, acute coronary syndrome.<sup>17</sup> However, in our study, median BMI was 19 kg/m<sup>2</sup> and gender was mainly male. No patient experienced chronic renal failure.

### Conclusions

The BNP level measurement may add a supplemental key for the final diagnosis of decompensated heart failure, in addition with echocardiography in patients with muscular dystrophy.

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