International Journal of Cardiology 178 (2015) 34–36

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Letter to the Editor

Combined BNP and Echocardiographic assessment in interstitial lung disease for pulmonary hypertension detection ☆

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ARTICLE INFO

Article history:
Received 11 September 2014
Accepted 21 October 2014
Available online 22 October 2014

Keywords:
Pulmonary hypertension
Interstitial lung disease
BNP
Echocardiography

Natriuretic peptides (B-type natriuretic peptide [BNP] and NT pro-BNP) are proposed biomarkers to differentiate between cardiac and pulmonary causes of acute dyspnea [1]. Some emerging data proposed the use in respiratory disease and particularly in patients with acute pulmonary embolism and pulmonary hypertension (PH) [2].

Prevalence of pulmonary hypertension (PH) in interstitial lung diseases (ILD) is higher in patients with severe fibrosis but it may develop at any stage of the disease [3,4]. Early recognition is frequently delayed from symptoms onset and diagnosis. For all these reasons the detection of pulmonary arterial pressure (PAP) in patients affected to ILD is critical for diagnosis and clinical assessment [5]. The current gold standard for PH assessment is invasive right heart catheterization, however this procedure is prone to increased risk of complications and it should be carried out in patients with evidence of PH previously identified by non-invasive investigation [6]. Currently, the optimal tool to measure PH remains unclear. The most appropriate, recognized method to detect PAP noninvasively is trans-thoracic echocardiography, which demonstrated a good correlation with invasive measurement [7]. We hypothesized that the combination of echocardiography and BNP measurement may provide a better detection of PH in patients with ILD. Thus the aims of this study were: 1—to determine the accuracy of echo measurement and BNP assay in the detecting PH through building an algorithm model and 2—to compare BNP and echo values with invasive measurement to establish the exact correlation with PAP.

Study design: Patients were eligible if they were admitted with a clinical and radiological diagnosis of interstitial lung disease. All patients underwent to: echocardiography and BNP. We included in this study 120 consecutive patients affected by interstitial lung disease. Patients revealing PAPs > 40 mm Hg (43 patients) were then submitted to RC invasive measurement to calculate PAPs, PAP mean and pulmonary vascular resistance (PVR). Written consent was provided by each patient. Patients were recruited from ARTEMIS-HP trial (www.clinicaltrials.gov: ID number NCT00879229).

Laboratory analysis: Within 24 h from enrolment we measured, in all patients, BNP levels. Plasma BNP was measured with Triage BNP Test (Biosite Inc., San Diego, CA, USA); this test is an immunoassay in a single-use plastic cartridge fluorescently labeled monoclonal antibody against BNP labeled with a fluorescent dye and BNP. The level of BNP in 12 healthy subjects was not higher than 80 pg/mL.

Echocardiography: Right ventricular (RV) dimension and pulmonary pressure (PAPs and PAP mean) were estimated following the American Society of Echocardiography criteria [8].

Invasive measurement: For a subgroup of patients with echocardiographic evidence of PH, hemodynamic results of right heart catheterization were obtained, measuring pulmonary artery pressures, pulmonary artery WEDGE pressures and vascular resistance [9].

Endpoints: 1 — To establish correlations among BNP and echocardiographic measurements in the detecting PH, 2 — to calculate the sensibility and accuracy power of the echocardiographic and BNP assessments in recognizing pulmonary hypertension, and 3 — to compare BNP and echo values with invasive measurement to establish the exact correlation with PH, defined as PAP mean > 25 mm Hg.

Patients' characteristics: 109 patients (age 62 + 11; 46 males) fulfilled the inclusion criteria. ILD diagnoses included: idiopathic pulmonary fibrosis (IPF; n = 72), sarcoidosis (n = 15), systemic sclerosis (n = 4), extrinsic allergic alveolitis (EAA; n = 2), smoking-related interstitial lung disease or drug-related interstitial fibrosis (n = 15) and Langerhans' cell histiocytosis (n = 1). Among these patients there were 43 subjects with PAPs ≥ 40 mm Hg. All patients with PAPs > 40 mm Hg underwent RC to measure invasive parameters PAPs, PAP mean, WEDGE pressure and PVR. Of 43 catheterized patients, 34 showed PH, defined as PAP mean > 25 mm Hg. BNP mean in all population was of 63 pg/mL [CI: 32–96] (Table 1).

☆ Conflict of interests: None declared.

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http://dx.doi.org/10.1016/j.ijcard.2014.10.120
0167-5273/

Table 1
Baseline characteristics of all patients with ILD included in our study. Abbreviations: BNP: B-type natriuretic peptide; FE: Ejection fraction; ILD: Interstitial lung disease; PAPd: End-diastolic pulmonary arterial pressure; PAPs: Pulmonary systolic arterial pressure; PAPm: Pulmonary arterial pressure mean; PVR: Pulmonary vascular resistance; TAPSE: Tricuspid annular plane systolic excursion.

Number of the patients	109
Age (year)	63 ± 11
Weight (Kg)	77 ± 14
Height (cm)	168 ± 11
Gender (n)	
Male	57
Female	52
Risk factors and comorbidity (%)	
Hypertension	26%
Diabetes	49%
Dyslipidemia	32%
Osteoporosis	76%
Interstitial lung disease (n)	
Pulmonary idiopathic fibrosis	72
Sarcoidosis	15
Extrinsic allergic alveolitis	4
Systemic sclerosis	2
Langherans cell hystiocytosis	1
Other	15
Lung diseases' treatment (%)	
Corticosteroids therapy	94
Immunosuppressive therapy	17
Echocardiographic parameters	
FE (%)	55 ± 3
End-diastolic ventricular diameter (mm)	36 ± 7
Right atrium area (cm^2)	20 ± 3
Caliber inferior cave vein (mm)	17 ± 5
PAPs (mm Hg)	37 ± 12
PAPs ≥ 40 mm Hg (n)	43
PAP mean (mm Hg)	18 ± 7
PAP mean ≥ 20 mm Hg (n)	29
TAPSE (mm)	22 ± 3
TAPSE ≤ 20 mm (n)	31
Invasive Measurements (43 patients)	
PAPs (mm Hg)	45 ± 14
PAP m (mm Hg)	25 ± 10
WEDGE pressure (mm Hg)	12 ± 5
PVR (hru)	3,21 ± 2.20
Pulmonary hypertension defined as invasive PAP mean ≥ 25 mm Hg (n)	34
BNP (pg/mL)	63 [32–96]

In patients with PAPs > 40 mm Hg BNP levels were significantly increased compared to patients without pulmonary hypertension (162 ± 96 vs 18 ± 7 pg/ml p = 0,004), PAPd > 20 mm Hg (205 ± 118 vs 38 ± 19 pg/mL p = 0,001) and PAP mean < 25 mm Hg (128 ± 84 vs 33 ± 12 pg/ml p < 0.001). BNP was also significantly increased in patients with right ventricular dysfunction (TAPSE < 16 mm) (153 ± 104 vs 21 ± 13 pg/ml p < 0.001) and dilatation of RV (end-diastolic diameter ≥ 38 mm) (179 ± 115 vs 36 ± 24 pg/ml p < 0.001).

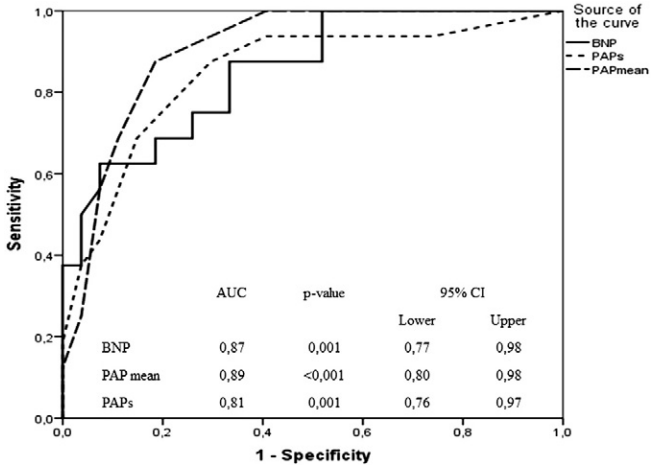

Fig. 1. Receiver operating characteristic (Roc) curve analysis in predicting patients with PH. Logistic regression analysis evaluating ability of echocardiographic parameters (PAPs and PAP mean) and BNP to detect PH. Abbreviations: AUC: Area under the curve; BNP: B-type natriuretic peptide; CI: Confidence interval; PAPs: Pulmonary systolic arterial pressure; PAPm: Pulmonary arterial pressure mean; PH: Pulmonary hypertension; TAPSE: Tricuspid annular plane systolic excursion.

In patients with invasive PAPs > 40 mm Hg and with invasive PAP mean >25 mm Hg, (n. 34) BNP levels were significantly increased respect patients with invasive PAPs < 40 mm Hg (169 ± 110 vs 39 ± 17 pg/ml p < 0,02) and with invasive PAP mean < 25 mm Hg (206 ± 127 vs 25 ± 18 pg/ml p < 0.005). In patients with WEDGE pressure ≥ 14 mm Hg, BNP levels were significantly higher than patients with WEDGE pressure < 14 mm Hg (207 ± 151 vs 43 ± 31 pg/mL; p = 0.01) (Table 2).

Diagnostic prediction for PH: The Roc curve analysis showed that BNP (AUC 0.87; [CI: 0.77–0.98]; p = 0.001), PAP mean (AUC 0.89; [CI: 0.80–0.98]; p = 0.001) and PAPs (AUC 0.81; [CI: 0.76–0.98]; p = 0.001) were all able to detect PH. A cut-off BNP value ≥ 50 pg/ml, recognized patients with PH, with good sensitivity (77%) and good specificity (81%) (Fig. 1). Regression analysis of the above parameters confirmed that echocardiographic measurements (PAPs, PAP mean and TAPSE) and BNP values were significantly related (Table 3).

Early detection of PH in patients with ILD is determinative to better establish prognostic impact of lung disease and to begin a specific treatment. The current European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines recommend annual echocardiographic screening in symptomatic patients [10]. Our study

Table 2
T-test evaluating BNP value changes relation to echocardiographic and invasive parameters. Abbreviations: BNP: B-type natriuretic peptide; PAPd: End-diastolic pulmonary arterial pressure; PAPs: Pulmonary systolic arterial pressure; PAPm: Pulmonary arterial pressure mean; TAPSE: Tricuspid annular plane systolic excursion.

All patients (109)				
Echocardiographic parameters	BNP mean (pg/mL)	Echocardiographic parameters	BNP mean (pg/mL)	p-Values
PAPs < 40 mm Hg	18 ± 7	PAPs ≥ 40 mm Hg	162 ± 96	0.004
PAPd < 20 mm Hg	39 ± 19	PAPd ≥ 20 mm Hg	205 ± 118	0.001
PAP mean < 25 mm Hg	33 ± 12	PAP mean ≥ 25 mm Hg	128 ± 84	0.001
End diastolic diameter < 38 mm	36 ± 24	End diastolic diameter ≥ 38 mm	179 ± 115	0.001
TAPSE > 16 mm	21 ± 13	TAPSE ≤ 16 mm	153 ± 104	0.001
Catheterized patients (43)				
Invasive measurement	BNP mean (pg/mL)	Invasive measurement	BNP mean (pg/mL)	p-Values
PAPs < 40 mm Hg	39 ± 17	PAP ≥ 40 mm Hg	169 ± 110	0.02
PAP mean <25 mm Hg	25 ± 18	PAP mean ≥ 25 mm Hg	206 ± 127	0.005
WEDGE pressure < 14 mm Hg	43 ± 31	WEDGE pressure ≥ 14 mm Hg	207 ± 151	0.01

Table 3
Logistic regression analysis evaluating ability of echocardiographic parameters (PAPs, PAPm and TAPSE) and BNP to detect PH. Abbreviations: BNP: B-type natriuretic peptide; CI: Confidence interval; OR: Odds ratio; PAPs: Pulmonary systolic arterial pressure; PAPm: Pulmonary arterial pressure mean; PH: Pulmonary hypertension; TAPSE: Tricuspid annular plane systolic excursion.

	OR [CI]	p-Value
BNP > 50 pg/mL	11.53 [3.61–24.87]	0.001
PAPs ≥ 40 mm Hg	22.13 [4.47–42.17]	0.003
PAP mean ≥ 25 mm Hg	10.07 [1.17–28.24]	0.04
TAPSE ≤ 16 mm	6.71 [1.72–18.15]	0.006

is the first attempt to evaluate the diagnostic role of echocardiography and BNP levels in patients with ILD and associated PH. Our findings showed that BNP is significantly correlated to echo-Doppler measurement, particularly those patients with signs of PH or RV dysfunction evidenced higher BNP values when compared with patients who experienced normal pressure and RV function. The logistic regression analysis demonstrated that a cutoff of 50 pg/ml for BNP had a good sensibility and specificity to recognize subjects with PH. The current non-invasive data have been validated in the subgroup submitted to right heart catheterization (n = 43) after echocardiographic screening. In these patients we demonstrated a good correlation between non-invasive and invasive pressure assessments confirming the role of BNP in the detection of moderate PAP increase. All together our findings summarized previous reports showing that BNP is a good diagnostic indicator for PH in ILD. Echocardiography when used in patients with a good acoustic window is a reliable tool to measure PAP and early recognize PH.

Recently a good correlation between hemodynamic and echocardiographic measurements has been evidenced in the current setting [11] confirming our results. Therefore an algorithm considering laboratory and echo measurement could help in the identification of those patients with ILD affected with moderate PH.

BNP has also demonstrated a prognostic impact in patients with ILD in more recent studies: in an oriental population Song et al. [12] showed that a combination of BNP level and PAPs measured by echocardiography may provide a better prediction of mortality than either parameter alone. In another study Corte et al. [13] demonstrated the prognostic value of BNP and echocardiography over the ILD population as a whole, independently of the underlying disease severity. Elevated BNP concentration and pulmonary vascular resistance levels were linked to increased mortality across ILD patients.

Our data suggest that BNP levels and echocardiography are clinically useful and easily repeatable tools for mild PH detection in patients with ILD. If our preliminary results will be confirmed in a larger population, an algorithm including echocardiographic measurements associated with a BNP cutoff > 50 pg/ml should be applied in clinical practice as a preliminary screening for invasive hemodynamic study selection.

Acknowledgment

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

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