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SHORT REPORT

N-terminal-pro-brain natriuretic peptide as a haemodynamic marker in idiopathic pulmonary arterial hypertension

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ABSTRACT: Patients with idiopathic pulmonary arterial hypertension usually undergo acute vasodilator tests with nitric oxide (NO) for haemodynamic evaluation and therapeutical planning. The aim of this study was to evaluate the link between the variation of N-terminal (NT)-pro-brain natriuretic peptide (BNP) levels and haemodynamic parameters during the acute vasodilator test.

A total of 22 idiopathic pulmonary arterial hypertension patients who underwent acute vasodilator tests were studied. Blood samples were collected at baseline and after 30 and 60 min of NO inhalation. NT-pro-BNP levels were measured in each sample.

A receiver-operating characteristic curve was used to evaluate the capability of the NT-pro-BNP level variation during NO inhalation in recognising nonresponders. To distinguish responders from nonresponders, the increase of the NT-pro-BNP (0% as cut-off value) determined a 50% specificity and 100% sensitivity (positive predictive value of 38% and a negative predictive value of 100%).

These results suggest that N-terminal-pro-brain natriuretic peptide was able to distinguish nonresponder patients with the acute vasodilator test. N-terminal-pro-brain natriuretic peptide may be an interesting additional biological tool in the evaluation of idiopathic pulmonary arterial hypertension patients.

KEYWORDS: Acute vasodilator test, idiopathic pulmonary arterial hypertension, N-terminal-pro-brain natriuretic peptide, pulmonary hypertension

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Idiopathic pulmonary arterial hypertension (IPAH) is a rare disorder characterised by the progressive raise in pulmonary artery pressure leading to right ventricular dysfunction [1]. Although there was a great improvement in survival with the development of new therapies, IPAH is still a condition with high mortality rates.

A subset of patients with IPAH responds to high doses of calcium channel blockers (CCB) [2]. The institution of CCB as the therapeutical option is based on the results of an acute pulmonary vasodilator test [3]. Based on this test, ~10–15% of the patients receive CCB and half of them have a sustained response [4].

Many biochemical markers have been proposed as prognostic factors in IPAH, including uric acid [5], troponin T [6] and brain natriuretic peptide (BNP) [7]. Specifically for BNP, mortality was related to the increase in the BNP levels during treatment.

Pro-BNP is a pro-hormone, secreted mainly by the ventricles, which is cleaved into N-terminal fragment (NT)-pro-BNP and active BNP. Elevated BNP plasma levels have been found in many clinical situations, such as unstable angina, myocardial infarction and heart failure [8, 9].

In pulmonary hypertension, BNP levels increase in proportion to the degree of right ventricular dysfunction and have also been described as an independent predictor of mortality [7, 10, 11].

NT-pro-BNP is highly stable in plasma and has been described as a marker of pulmonary hypertension in patients with systemic sclerosis [12, 13]. Although those described markers have

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a good correlation with survival and even haemodynamic parameters, none have yet been found to be indicative of acute response to vasodilators.

The aim of the current study was to evaluate the link between the variation of NT-pro-BNP levels and haemodynamic parameters during acute vasodilator test in patients with IPAH.

MATERIALS AND METHODS

Study population

A total of 22 IPAH patients were studied, who were submitted to acute vasodilator testing before any chronic therapy was started, including vasodilators, digoxin or even oral anticoagulants. The diagnosis of IPAH was established according to the criteria of the National Institute of Health registry [1].

Methods

A baseline haemodynamic evaluation was performed in all patients while breathing room air, at supine position. All patients presented an arterial oxygen saturation >90% at the beginning of the measurements. A 7F flow-directed pulmonary artery catheter (Baxter Healthcare Corporation, Irvine, CA, USA) was introduced in all patients. Cardiac output (CO) was measured by the standard thermodilution technique. Cardiac index was calculated as CO divided by body surface area (m^2).

After a steady-state haemodynamic measurement was obtained, patients inhaled an air–nitric oxide (NO) mixture through a face mask at 40 parts per million. In order to evaluate the behaviour of the NT-pro-BNP levels, NO inhalation was sustained for 60 min. At the end of NO inhalation a second set of haemodynamic measures were performed and the data collected.

Acute vasodilator responders were defined as patients showing >20% reduction in both mean pulmonary arterial pressure (mPAP) and total pulmonary resistance during NO inhalation, with a reduction in mPAP of >10 mmHg, reaching an absolute mPAP <40 mmHg [4, 14, 15].

Assay for N-terminal-pro-brain natriuretic peptide measurements

Blood samples were collect at baseline and after 30 and 60 min of NO inhalation. The samples were centrifuged within 60 min of collection. The resulting serum samples were stored at -70℃. The NT-pro-BNP measurements were performed on an Elecsys 2010 instrument (Roche Diagnostics, Basel, Switzerland) by a sandwich immunoassay.

For the determination of the stability of NT-pro-BNP, two blood samples were collected from 12 different IPAH patients (control group) at a 60-min interval, while breathing room air at rest. From those samples, the variation of NT-pro-BNP levels was determined.

Statistical analysis

All results are expressed as mean±SD. The Pearson correlation coefficient was used to evaluate the correlation between the NT-pro-BNP and the other continuous variables. The variables that presented significant correlation ($p<0.05$) were analysed in a multiple regression model.

To compare the clinical and haemodynamic parameters between the responders and nonresponders groups a Mann-Whitney U-test was used, with a p-value of <0.05 regarded as significant. A receiver-operating characteristic curve, generated by plotting sensitivity against 1–specificity for all possible cut-off values, was used in order to evaluate the capability of the NT-pro-BNP level variation during NO inhalation in recognising nonresponders.

RESULTS

The baseline haemodynamic pattern and the clinical characteristics of the 22 patients enrolled in the study are listed in table 1. After the challenge with NO inhalation, five patients (22.7%) were identified as acute responders. This percentage of responders is higher than previously described for this response criteria [4].

The clinical and haemodynamic characteristics of both groups (responders and nonresponders) are described in table 2. The haemodynamic variation during NO inhalation is summarised in table 3.

TABLE 1 Baseline clinical and haemodynamic data

Age yrs	37±10
Sex male/female	6/16
Functional class I–II/III–IV	12/10
Right atrial pressure mmHg	11±6
Mean pulmonary artery pressure mmHg	67±20
Pulmonary artery occlusion pressure mmHg	9±3
Cardiac index $L \cdot min^{-1} \cdot m^{-2}$	2.7±1.4
Indexed pulmonary vascular resistance $dyn \cdot cm^{-5} \cdot m^{-2}$	2058±1595

Data are presented as n and mean±SD.

TABLE 2 Clinical and haemodynamic data according to vasodilator response

	Responders	Nonresponders
Subjects n	5	17
Age yrs	35±9	38±10
Sex male/female	2/3	4/13
Functional class I–II/III–IV	4/1	8/9
Right atrial pressure mmHg	8±2	12±6
Mean pulmonary artery pressure mmHg	51±11	67±20*
Pulmonary artery occlusion pressure mmHg	8±2	11±4
Cardiac index $L \cdot min^{-1} \cdot m^{-2}$	3.5±2.2	2.4±1.1
Indexed pulmonary vascular resistance $dyn \cdot cm^{-5} \cdot m^{-2}$	1083±597	2345±1693*

Data are presented as n and mean±SD. *: p<0.05 for comparison between the two groups.

TABLE 3 Haemodynamic variation during nitric oxide (NO) inhalation

	Responders#		Nonresponders¶	
	Baseline	Post-NO	Baseline	Post-NO
Right atrial pressure mmHg	8±2	5±2	12±6	9±6
Mean pulmonary artery pressure mmHg	51±11	28±8	67±20	62±18
Pulmonary artery occlusion pressure mmHg	8±2	10±2	11±4	12±4
Cardiac index $L \cdot min^{-1} \cdot m^{-2}$	3.5±2.2	3.7±1.4	2.4±1.1	2.6±1.0
Indexed pulmonary vascular resistance $dyn \cdot cm^{-5} \cdot m^{-2}$	1083±597	506±179	2345±1693	1802±991

Results are presented as mean±SD. #: n=5; ¶: n=17.

The comparison between the two groups showed a significant difference for the mPAP and the indexed pulmonary vascular resistance, indicative of a more preserved haemodynamic status in the responders group, as previously suggested [4].

N-terminal-pro-brain natriuretic peptide

Linear regression analysis disclosed a significant association between plasma NT-pro-BNP concentrations and right atrial pressure (r=0.66, p=0.001), mPAP (r=0.64, p=0.001), cardiac index (r=-0.716, p<0.001) and indexed pulmonary vascular resistance (r=0.716; p<0.001; fig. 1).

Multivariate analysis computing all significant variables resulted in a significant correlation of NT-pro-BNP with cardiac index (p=0.007) and right atrial pressure (p=0.04), with an excellent correlation factor (r^2=0.791).

Acute response analysis

Receiver-operating characteristic curves were generated to determine the sensitivity and specificity of NT-pro-BNP level variation during the acute vasodilator test for detecting nonresponder patients.

One of the patients did not stay under NO inhalation for 60 min and so the analysis of NT-pro-BNP variation could not be performed. For the variation of the NT-pro-BNP levels during the 60 min of NO inhalation of the other 21 patients, an area under the curve of 0.83 (95% confidence interval (CI) 0.60–1.00) was obtained. The increase of the NT-pro-BNP (0% as cut-off value) determined a 50% specificity (95% CI 31–74%) and 100% sensitivity (95% CI 51–100%) with a positive predictive value of 38% (95% CI 21–62%) and a negative predictive value of 100% (95% CI 77–100%) in distinguishing responders from nonresponders. The variation of the NT-pro-BNP levels in the control group reinforces its stability in plasma (fig. 2). The variation of PVR during NO inhalation also correlated with NT-pro-BNP levels' variation (r=0.42, p=0.04).

DISCUSSION

The results from the current study show that NT-pro-BNP has a reliable correlation with the haemodynamic pattern of patients with IPAH, and an acceptable ability to differentiate responders and nonresponder patients during a 60-min NO challenge.

Although only a small number of patients were studied, the clinical and, mainly, the haemodynamic data from the population were closely related to the previously described data from patients with IPAH [1].

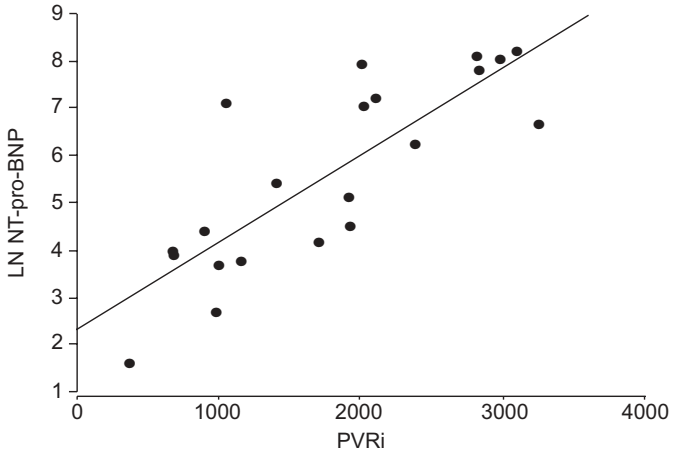

FIGURE 1. Correlation between N-terminal-pro-brain natriuretic peptide (NT-pro-BNP) and indexed pulmonary vascular resistance (PVRi; $dyn \cdot cm^{-5} \cdot m^{-2}$; r=0.716; p<0.001). LN: natural log.

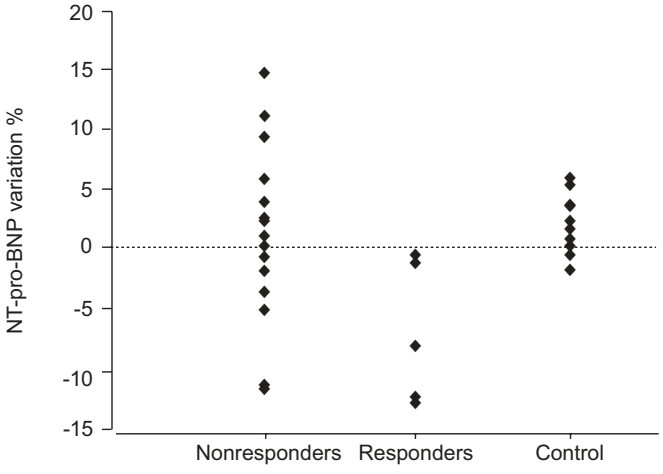

FIGURE 2. Haemodynamic response *versus* N-terminal-pro-brain natriuretic peptide (NT-pro-BNP) variation during NO inhalation or room air (control group).

The physiological rationale for the use of natriuretic peptides as markers of heart disease is based on the hypothesis that these peptides are involved in the activation of the cyclic guanylate cyclase system as a counterregulatory mechanism in heart failure, probably with increased cardiac wall stress as the trigger mechanism [16].

Natriuretic peptides have been correlated with haemodynamic parameters and the prognosis in patients with heart failure [17, 18]. In pulmonary hypertension, BNP, but not NT-pro-BNP, has been correlated with treatment response and prognosis [7].

The NT-pro-BNP has been shown to correlate with haemodynamics in patients with sclerosis-related pulmonary hypertension [13]. The findings from the current study showed that the same behaviour is found in IPAH. Furthermore, NT-pro-BNP demonstrated an ability to identify nonresponders in an acute vasodilator test. The close correlation with the haemodynamic data and the acute variation during vasodilator therapy suggest that NT-pro-BNP may also be a prognostic and treatment marker.

The available treatment options for patients with IPAH include prostanoids, endothelin antagonists, phosphodiesterase inhibitors and CCBs. The initial therapy is based mainly on the baseline functional class and on the identification of patients that respond in an acute vasodilator test [19].

The high negative predictive value of NT-pro-BNP in distinguishing responders from nonresponders sets a perspective for the use of a noninvasive marker to evaluate the vasoconstriction component of IPAH. This would be clinically useful not only for ruling out the use of CCBs in nonresponders, but also to evaluate the behaviour of the cardiovascular system with the use of the other available therapies.

Even though this is a nice perspective, one of the limitations of the current study relies on the cut-off value chosen for the NT-pro-BNP variation. This value was derived from the current authors' data once it was determined that there are no other studies that used NT-pro-BNP as a marker in IPAH. Nevertheless, the current authors found a significant difference between the groups that states the potential of this test in this population.

The high stability of NT-pro-BNP in plasma at room temperature, together with the fact that this test can be performed under normal laboratory conditions, appoints it as a feasible test in the clinical setting [13]. The use of a marker with shorter half-life than NT-pro-BNP, such as BNP, might improve test performance, but it is also possible that the results would be noisier and, thus, reduce the sensitivity of the test to distinguish between responders and nonresponders.

In the current study, NT-pro-BNP variation would decrease the number of NO testing needed at right cardiac catheterisation from 22 to 13 and, therefore, increase the rate of responders.

In conclusion, N-terminal-pro-brain natriuretic peptide significantly correlated with the haemodynamic parameters in idiopathic pulmonary arterial hypertension patients and was able to distinguish nonresponder patients in an acute vasodilator test. These characteristics suggest that N-terminal-pro-brain natriuretic peptide may be an interesting additional biological tool in the evaluation of idiopathic pulmonary arterial hypertension patients.

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