N-Terminal Pro-Brain Natriuretic Peptide as an Indicator of Right Ventricular Dysfunction

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ABSTRACT

Background: Plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) and brain natriuretic peptide (BNP) are elevated in most patients with acute pulmonary embolism (APE) that results in right ventricular overload. Therefore, APE should be considered in the differential diagnosis of patients with acute dyspnea and abnormal levels of BNPs. Moreover, plasma BNPs have been proved to predict outcome in APE.

Methods and Results: Low NT-proBNP or BNP levels characterize an uneventful hospital course, and NT-proBNP levels of <500 pg/mL identify patients who could potentially be candidates for care on a complete outpatient basis. Moreover, plasma NT-proBNP and BNP reflect the degree of right ventricular overload in APE. Plasma BNPs can also be elevated in chronic precapillary pulmonary hypertension and are strongly related to total pulmonary resistance. Elevated plasma levels of BNP/NT-proBNP and especially their further increase during follow-up are a potent predictor of poor survival.

Conclusion: Because levels of brain natriuretic peptides are elevated significantly not only in pathologic conditions that affect the left ventricle but also in clinical conditions that lead to isolated acute or chronic right ventricular overload, it could be proposed that these peptides should not be regarded as biomarkers of congestive heart failure, but as indicators of cardiovascular dyspnea.

Key Words: Acute pulmonary embolism, pulmonary arterial hypertension, N-terminal pro-brain natriuretic peptide.

It is generally accepted that brain natriuretic peptides (BNP) are released from ventricular myocytes on stretch. Experimental studies have shown that increased right ventricular (RV) wall stress, caused, for example, by the banding of the pulmonary trunk, leads to a significant increase in the expression of BNP-coding messenger RNA in the RV myocardium.[1] Therefore, it can be expected that the levels of BNPs can be elevated not only in clinical conditions that lead to left ventricular (LV) dysfunction (such as congestive heart failure or systemic hypertension) but also in pathologic conditions that cause isolated RV strain.

Acute RV Overload

RV dysfunction can be detected by echocardiography in approximately 50% of patients with acute pulmonary embolism (APE). Moreover, RV overload is a potent independent predictor of fatal outcome, even in normotensive patients.[2–6] The significant RV distension and elevated RV systolic and end-diastolic pressures that are observed in APE lead to increased stretching of the RV wall[7] and may therefore result in the release of BNPs.[8] When age- and sex-specific criteria were applied, serum NT-proBNP was found to be elevated in 83% of 79 consecutive patients with APE.[9] Interestingly, serum NT-proBNP was increased in almost all patients with APE that is accompanied by RV overload, but in only 50% of patients without echocardiographic signs of RV dysfunction. Moreover, NT-proBNP levels in massive APE were significantly higher than in submassive or nonmassive APE: massive, 9865 pg/mL (range, 414.5–31,168 pg/mL); submassive, 4650.5 pg/mL (range, 61–60,958 pg/mL); nonmassive, 363.6 pg/mL (range, 16.3–16,329 pg/mL; Kruskal-Wallis analysis of variance, $P < .0002$; Fig.1).[9] Interestingly, significant relationships were found between echocardiographic indices of RV overload and serum NT-proBNP concentration. Right-to-left ventricular end-diastolic diameter ratio (RV/LV) and tricuspid valve peak systolic gradient correlated significantly with serum NT-proBNP levels ($r = 0.53$; $P < .001$, and $r = 0.4$; $P < .03$, respectively).[9] In receiver operating analysis, an NT-proBNP concentration of ≥200 pg/mL demonstrated 98% sensitivity

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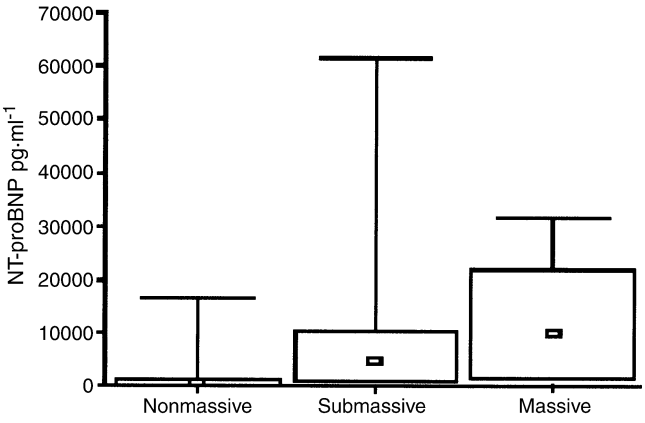

Fig. 1. Serum NT-proBNP levels in 78 patients with APE, classified as nonmassive (n = 18), submassive (n = 51), or massive (n = 9). Data are presented as median, 25% to 75%, and minimum-maximum (P = .0002). Reproduced with permission from reference 9.

and 55% specificity for the identification of RV overload, which was defined by a RV/LV end-diastolic diameter ratio >0.6 with hypokinesis of the free wall of the RV and/or coexistence of a tricuspid valve peak systolic gradient >30 mm Hg with a pulmonary ejection acceleration time of <80 msec. The area under the curve was 0.84 (Fig. 2).[10]

BNPs are proposed as a marker to differentiate between cardiac and pulmonary causes of acute dyspnea in an emergency department setting. The results obtained by Morrison et al[11] support this concept. Patients with congestive heart failure had BNP levels significantly higher than patients with

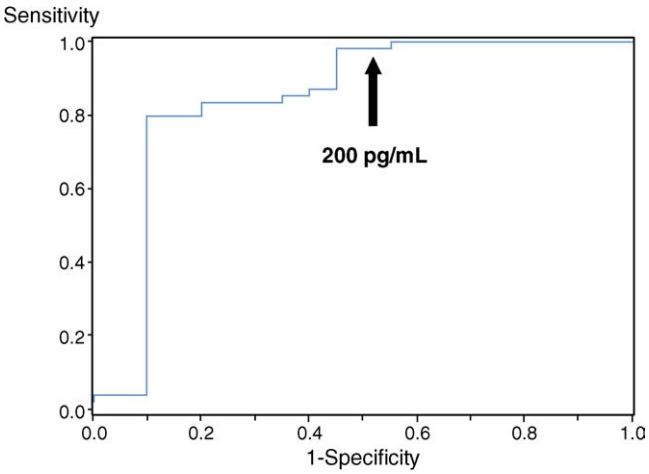

Fig. 2. Receiver operating characteristic curve of serum NT-proBNP in the detection of RV overload, defined by echocardiography in the following manner: right-to-LV end-diastolic diameter ratio >0.6 with hypokinesis of the free wall of the RV and/or coexistence of a tricuspid valve peak systolic gradient >30 mm Hg, with a pulmonary ejection acceleration time <80 msec. Area under the curve 0.84. NT-proBNP >200 pg/mL demonstrated sensitivity 98%, specificity 55% in the detection of RV overload. Reproduced with permission from reference 10.

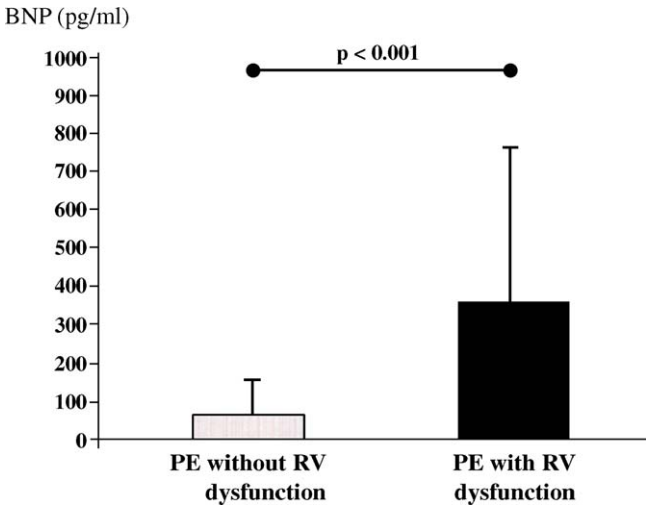

Fig. 3. Plasma BNP in 50 patients with APE (*PE*), grouped according to the presence of RV overload, defined by the presence of any of following: dilation of the RV or an RV/LV end-diastolic diameter ratio ≥1 in the 4-chamber view; RV hypokinesis, abnormal motion of the interventricular septum; or tricuspid valve regurgitation with a jet velocity of at least 2.5 m/sec. Reproduced with permission from reference 14.

a final diagnosis of pulmonary disease ([n = 134 patients] 758.5 ± 798 pg/mL vs [n = 85 patients] 61 ± 10 pg/mL). However, BNP was also elevated in 3 patients with APE (207 ± 272 pg/mL). Indeed, according to data published by Kucher et al,[12] plasma BNP levels frequently can be elevated in patients with APE, and were found to exceed 90 pg/mL in almost one half of them. Similarly to NT-proBNP, levels of BNP were higher in APE accompanied by RV overload than in patients with preserved RV function.[13] Kruger et al[14] observed that patients without RV dysfunction (defined by the presence of any of the following: dilation of the RV or an RV/LV end-diastolic diameter ratio ≥1, RV hypokinesis, abnormal motion of the interventricular septum, or tricuspid valve regurgitation with a jet velocity of at least 2.5 m/sec) had significantly lower plasma BNP levels than patients with RV dysfunction (55 ± 69 pg/mL vs 340 ± 362 pg/mL; $P < .001$; Fig. 3). There was a significant correlation between RV end-diastolic diameter and plasma BNP level ($r = 0.43$; $P < .05$). Moreover, plasma BNP was found to discriminate patients according to presence or lack of RV dysfunction (area under the ROC curve, 0.78; 95% CI, 0.64–0.92), and BNP >90 pg/mL was associated with a risk ratio of 28.4 (95% CI, 3.22–251.12) for the diagnosis of RV dysfunction. These data confirm that APE should be included in the differential diagnosis of acute dyspnea in patients with elevated levels of BNPs.[15]

Prognostic Value of BNPs in APE

Kucher et al[16] assessed the prognostic value of NT-proBNP in patients with APE. They measured biomarker