



Original article

Prognostic value of increased B type natriuretic peptide in cases with acute pancreatitis

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ARTICLE INFO

Article history:

Received 13 January 2012

Received in revised form 11 February 2012

Accepted 22 February 2012

Available online 15 March 2012

Keywords:

BNP

Acute pancreatitis

Prognosis

ABSTRACT

Background: Acute pancreatitis (AP) is a systemic disease with a rising incidence. Cardiac dysfunction may occur as an early complication of AP. B type natriuretic factor (BNP) is a diagnostic and prognostic indicator of cardiac disorders. Therefore, in this study we aimed to assess the relationship between serum BNP concentrations and severity of AP.

Methods: Patients with AP who were admitted to gastroenterology clinic of our center, were included in this study. BNP measurements were performed twice, once on admission to the hospital and another after clinical and laboratory remission of the disease. All patients underwent echocardiography, abdominal ultrasonography and/or computed tomography chest X-ray and routine biochemical assays. Disease severity was determined by Ranson, Balthazar and Glasgow scoring systems.

Results: A total of 55 patients with AP (33 male, 60%) were enrolled in the study. Causes of AP were biliary in 32 patients (58%), alcoholic in 10 (18%), idiopathic in 8 (15%), hyperlipidemic in 4 (7%) and ERCP related in one patient (2%), respectively. Serum BNP levels in first 2 days of admission and after the clinical and laboratory remission of disease were 444 ± 295.9 and 124 ± 109.5 pg/ml, respectively ($p < 0.001$). Increased serum BNP levels were positively correlated with severity of the disease ($p < 0.001$). We could not find a difference between serum BNP levels of edematous and necrotizing patients ($P = 0.683$).

Conclusion: Increased serum BNP levels might be a plausible indicator of severity of AP during the course of the disease.

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1. Introduction

Acute pancreatitis (AP) is a common inflammatory disorder of the pancreas with a significant morbidity and mortality and a rising incidence around the globe [1]. Systemic complications and multiorgan failure are two main causes of morbidity and mortality in patients with AP. Cardiac dysfunction may occur as an early complication of AP. However, Ranson, Balthazar, Glasgow and APACHEII prognostic scoring systems could not determine cardiac functions directly. Most of biochemical assays and clinical findings including heart rate and blood pressure (APACHE II), urea (Ranson and Glasgow), creatinine (APACHE II) and partial oxygen pressure (Ranson, Glasgow and APACHE II), only demonstrate cardiac involvement indirectly, during the course of disease. Therefore, all of them are unreliable diagnostic tools for evaluating cardiac dysfunction [2–4].

B type natriuretic peptide (BNP) is a hormone that predominantly produced by cardiac ventricular myocytes. It is now generally accepted that its release into the peripheral blood is increased by factors

that increase intracardiac pressure and volume load [5,6]. Studies suggested an increase in pulmonary capillary wedge pressure (PCWP) and a decrease in cardiac output, during the course of AP [7,8]. Therefore, an increase in serum BNP concentration could be anticipated and could also be a plausible indicator for demonstration of cardiac dysfunction during the course of disease.

The data in regard with prognostic value of BNP in patients with AP are scant. Although Feng et al. reported in their study an increase in serum concentrations of BNP in patients with AP, there were no sufficient data about the prognostic value of BNP and they also did not assess serum BNP levels during and after the remission of disease [9]. Therefore, in this study we aimed to investigate the relationship between serum BNP concentrations and prognostic scores in patients with edematous and necrotizing AP.

2. Methods

2.1. Patients

Patients with AP who were admitted to the Gastroenterohepatology clinic of our center, were enrolled in the study. Diagnosis of AP was based on the typical clinical findings (upper abdominal pain

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and/or guarding and/or rebound tenderness), increased serum enzyme concentrations (≥ 3 fold increase in amylase and/or lipase), abdominal ultrasonography (performed during the first 24 h of admission or after 24 h for the second time) and/or contrast enhanced computed tomography (CT) of the abdomen (performed after 48–72 h of symptom onset). Healthy control subjects were included for comparison of BNP levels and echocardiographic findings.

Acute pancreatitis was considered to be biliary in origin if stones or sludge were detected in the gallbladder and/or common bile duct, and of alcoholic etiology if the patient or his/her relatives reported a consumption of > 60 g pure alcohol /day. Serum triglyceride level more than 750 mg/dL, and exclusion of other etiologies were considered as hyperlipidemic etiology. Patients were classified as having an idiopathic etiology if history and laboratory findings ruled out known etiologic factors, and ultrasonography revealed a normal biliary tract.

Patients with established congestive heart failure, a poor image quality on echocardiographic examination, pulmonary embolism, systemic and pulmonary hypertension, cardiac arrhythmias (atrial fibrillation, paroxysmal supraventricular tachycardia), chronic renal failure, cirrhosis, chronic obstructive pulmonary disease, valvular heart disease, congenital heart disease and hyperthyroidism, were excluded from the study.

Ranson and Glasgow (Imrie) scores of prognosis were calculated using the first 48 h data. As described by Balthazar et al., contrast enhanced abdominal CT were used to score "Computed Tomography severity index" (CTSI), 48–72 h after the initial clinical signs of the disease [1,4]. All CT scans were reviewed by a radiologist dedicated to abdominal imaging, who was blinded to laboratory data and clinical course of the patients.

All patients underwent echocardiographic examination by the same cardiologist within the first 2 days of symptoms onset. Transthoracic echocardiographic images on the parasternal long axis as well as apical four-chambers were obtained using a GE Vivid 3 instrument, equipped with a 2.5–3.5 MHz transducer. Left ventricular ejection fraction was determined by dividing the difference between left ventricular end-systolic and end-diastolic volumes by end-diastolic volume.

2.2. Plasma proBNP analysis and biochemical assays

Peripheral blood samples for plasma BNP determination were obtained on hospital admission by direct venipuncture of an antecubital vein after the patient had been resting in the supine position for > 30 min. Blood samples were centrifuged within 1 hour, and EDTA plasma was aspirated. Plasma samples were stored at -80°C pending analysis. Plasma proBNP was measured using a processing-independent assay recently developed in our laboratory. This type of assay quantifies the total proBNP concentration in plasma utilising a pre-analytical enzymatic step. Briefly, plasma is treated with a protease (trypsin) to cleave all proBNP forms at a monobasic cleavage site. The enzymatic reaction is then terminated and all N-terminal fragments (proBNP 1–21) released are subsequently measured with a specific proBNP radioimmunoassay. The assay sensitivity is 0.2 pmol/l, with an upper reference limit in individuals without cardiac disease of 15 pmol/l (confidence interval: 9–16 pmol/l, where 1 pmol/l proBNP equals 2.17 pg/ml). Assay imprecision within-run is 12% at 13 pmol/l and 5% at 130 pmol/l. Serum BNP concentrations were assessed using electrochemiluminescence method (Roche Cobas, Roche Diagnostics GmbH, Mannheim, Germany) with inter-assay and intraassay coefficient of variation (CV) of 2.4% and 5.7%, respectively. Serum BNP concentrations were assessed twice, first, on admission to the hospital (BNP^{e} : $\text{BNP}^{\text{early}}$) and second after the clinical and laboratory remission (BNP^{r} : $\text{BNP}^{\text{remission}}$).

Blood glucose, complete blood count, aspartate transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), serum albumin, amylase and/or lipase, arterial blood gas, serum calcium, blood urea nitrogen (BUN), gamma-glutamyl transpeptidase

(GGT), thyroid stimulating hormone (TSH), triglyceride, total bilirubin and direct bilirubin were measured in all patients. A written informed consent was obtained from all participants and the study protocol was approved by the local ethics committee.

3. Statistical analysis

Scale variables were expressed as mean \pm standard deviation (mean \pm SD). Categorical variables were compared using chi-square and Fisher's exact tests. Scale variables were compared using Student's *t* and paired *t* test. Numeric data was compared using Kruskal Wallis test when distribution was not normal and post-hoc Mann Whitney U tests were used for pairwise comparisons (significance was set at $P < 0.02$ due to multiple testing). Receiver operating characteristic curve analysis (ROC) was performed to assess the relation between BNP levels and AP prognosis scores. A P -value < 0.05 was considered statistically significant. SPSS (statistical package for social sciences, for Windows, release 12.0.0 standard version) software was used for statistical evaluations.

4. Results

Fifty five patients with AP (33 males, 60%) and 47 age-matched healthy controls (25 males, 58%) were enrolled in this study. Causes of AP were biliary in 32 patients (58%), alcoholic in 10 (18%), idiopathic in 8 (15%), hyperlipidemic in 4 (7%) and ERCP related in one patient (2%), respectively. The demographic and laboratory features as well as prognostic scores of the patients are summarized in Table 1.

Serum BNP levels in all patients with AP were assessed on admission and after clinical and laboratory remission. The mean serum BNP levels on admission (BNP^{e}) were 444 ± 295.9 pg/ml. However, serum BNP levels decreased to 124 ± 109.5 pg/ml, after clinical and laboratory remission of disease, ($p < 0.001$). The mean BNP^{e} level showed a gradual increase with increasing Ranson's prognostic ranges (0–3: good, 3–6: poor, > 6 very poor) ($p < 0.001$). The serum BNP^{e} levels were 196 ± 136 pg/ml in patients with a Ranson score range of 0–3, 528 ± 245 pg/ml in patients with a Ranson score range of 3–6 and 812 ± 301 pg/ml in those with a Ranson score range of > 6 , respectively. Serum BNP^{e} concentrations were significantly correlated with Ranson's prognostic ranges (Fig. 1).

Between prognostic indices of AP, serum BNP^{e} concentrations were significantly correlated with Ranson ($r = 0.818$ and $p < 0.001$) and Glasgow ($r = 0.712$, $p < 0.001$) scales (Fig. 2). However, we found a weak adequacy correlation between serum BNP^{e} and BNP^{r} concentrations with Balthazar scoring ($r = 0.229$, $p = 0.260$ and $r = 0.048$, $p = 0.810$, respectively).

The best cutoff value for C4 to determine a Ranson's score > 4 was 257 pg/ml in receiver operating characteristic curve analysis with 100% sensitivity and 42% specificity (area under curve :0.699; 95% confidence interval, 0.519–0.819)(Fig. 3).

Among patients, 10 (19%) were diagnosed as necrotizing pancreatitis in whom six cases were alcoholic and 4 were biliary origin. Serum BNP^{e} and BNP^{r} concentrations of these patients were 509 ± 87.56 pg/ml (range: 387–620 pg/ml) and 82 ± 27.7 pg/ml (range: 49–110 pg/ml),

Table 1

The demographic, laboratory and clinical features of the patients with acute pancreatitis.

Patient characteristics maximum	Variables	Ranges (min–max)
Age (year)	57.72 ± 15.23	15–82
BMI (kg/m^2)	26.09 ± 4.19	19–37
Ranson score	3.65 ± 1.98	1–7
Glasgow score	2.54 ± 1.31	0–5
CTSI	2.71 ± 2.97	0–12

Abbreviations. BMI: Body Mass Index and CTSI: Computed tomography severity index.

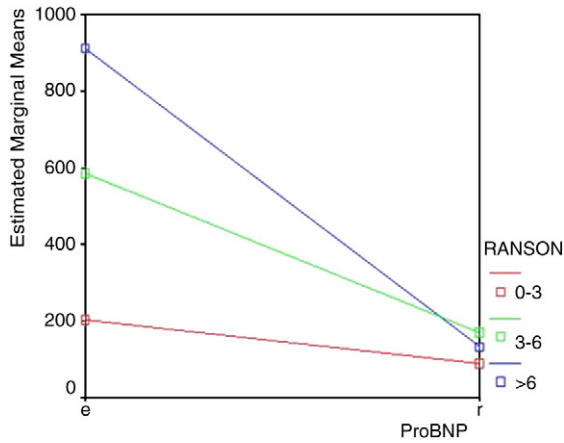


Fig. 1. General linear model repeated measures and Pillai's Trace for serum BNP^e and BNP^f concentrations. The reduction in patients with a Ranson score in the range of 3–6 and >6 were significantly larger than those with a Ranson score range of 0–3.

respectively. We could not find a difference between serum BNP^e levels of edematous and necrotizing patients ($P = 0,683$).

Patients divided into two groups in terms of co-existence of organ failure. Eight patients (14%) had multiorgan failure like pulmonary insufficiency and prerenal failure. BNP^e levels of patients with/without organ failure were 420 ± 208 and 398 ± 77 pg/ml respectively ($p = 0,579$).

A comparison were also performed between serum BNP^e concentrations and echocardiographic findings. The ratio of early and late filling pressure of the left atrium (E/A ratio) were found to be ≥ 1.1 in 82% and < 1.1 in 18% of patients with AP. The E/A ratio and serum BNP concentrations were significantly correlated with each other ($p < 0,001$). On the other hand, we did not find a relationship between serum BNP^e concentrations and other echocardiographic findings (Table 2).

5. Discussion

In this study, serum BNP^e concentrations were found to be significantly higher in patient with acute pancreatitis as compared with serum BNP^f concentrations. A transient increase in left ventricular diameter and PCWP which is equal to the left ventricular end diastolic pressure, have previously been demonstrated in the early stage of disease [10–13]. Therefore, the increase in serum BNP levels during the early stage of AP may be related to the changes in left ventricular volume load and pressure.

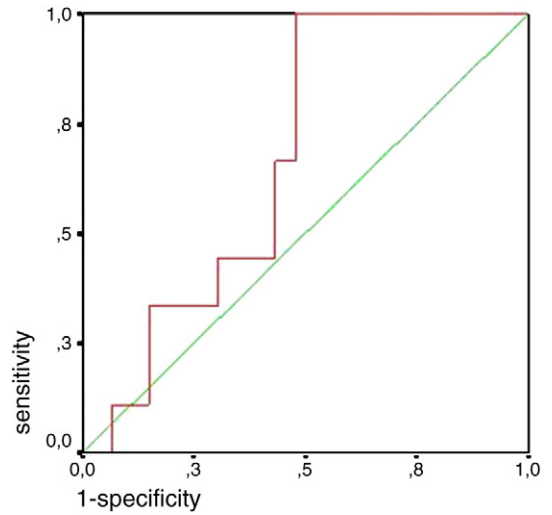


Fig. 3. Receiver operating characteristic curve analysis for prediction of BNP cutoff value.

In the current study, we found a significant relationship between increased serum BNP^e concentrations and the severity of disease as determined by the Ranson and Glasgow scoring systems, independent from the etiology of disease. The increase in serum BNP concentrations could be explained by the release of inflammatory cytokines, particularly cardio-depressant factors such as quinines and myocardial depressant factor [14].

The positive correlation that we found between serum concentrations of BNP and disease severity in the context of normal ejection fraction on echocardiographic examination, may leads us to a inconsistency. However, this could be explained by the low sensitivity of echocardiography to determine mild changes in pressure and volume load in the left ventricle [15]. Another issue that must be explained is that how serum concentrations of BNP, which is an indicator of cardiac overload, could be increased in patients with AP, who often require flude replacement [16]. Nevertheless, the absences of a hypovolemia during the early stage of AP [17] and the presence of a decrease in cardiac output and an increase in PCWP, which have already been documented in patients with AP, may be the possible explanations [7,8]. On the other hand, in this study, E/A ratio and serum BNP^e concentrations were significantly correlated with each other and E/A ratio was also predominantly higher in patients with AP as compared with controls. It has been reported that E/A ratio was positively correlated

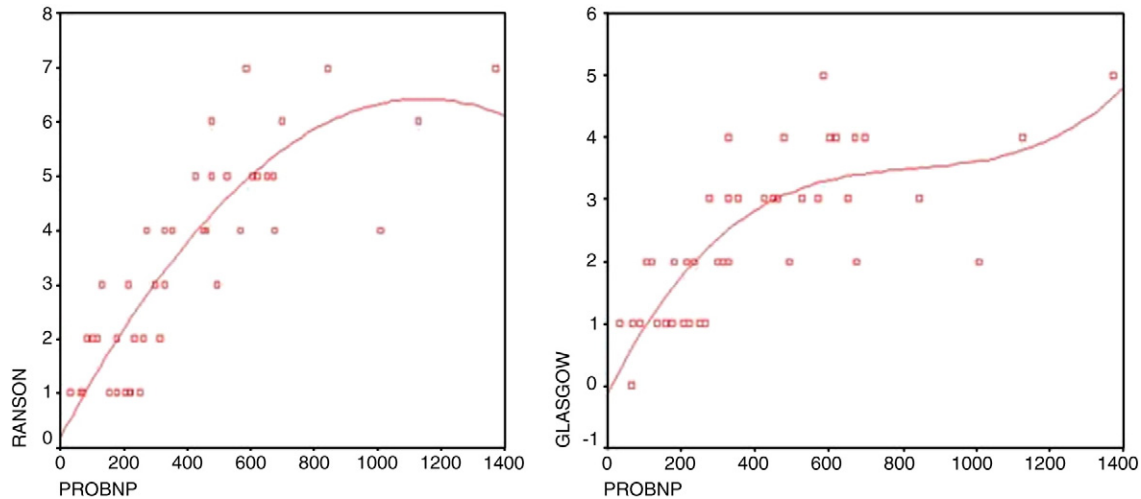


Fig. 2. The correlation between serum BNP^e concentrations with Ranson and Glasgow scores. The curve estimation analysis reveals the highest r squared value with a quadratic curve for Ranson-BNP^e correlation ($r: 0,752, p < 0,001$). Glasgow-BNP^e correlation has also a high r squared value with a cubic curve ($r: 0,588, p < 0,001$).

Table 2
Echocardiography and serum ProBNP level data of AP cases.

Characteristic	Data of AP cases (n: 55)	Control (n: 47)	p value
ProBNP ^e	425.05 ± 299.91	85.75 ± 22.87	0.000
ProBNP ^f	127.98 ± 133.27	85.75 ± 22.87	0.047
LAD	3.55 ± 0.39	3.37 ± 0.38	0.957
ST	0.927 ± 0.1	0.880 ± 0.12	0.684
LVEDD	4.81 ± 0.61	4.83 ± 0.48	0.437
LVPWT	0.88 ± 0.12	0.850 ± 0.10	0.755
LVESD	3.06 ± 0.48	3.01 ± 0.38	0.775
EF	64.10 ± 6.31	69 ± 4.72	0.065
E/A			0.001
	≥ 1.1	45(81.8%)	12(25.5%)
	< 1.1	10(18.2%)	35(74.5%)

ProBNP^e: Pro B-type natriuretic peptide early phase of acute pancreatitis; ProBNP^f: Pro B-type natriuretic peptide after clinic and laboratory remission; LAD: Left atrial diameter; SWT: Septal wall thickness LVEDD: Left ventricle end diastolic diameter, LVPWT: Left ventricle posterior wall thickness, LVESD: Left ventricle end systolic diameter, EF: Ejection fraction.

Normal laboratory range: ProBNP: 0–120 pg/ml; LAD: 1.9–4 cm; SWT: 0.6–1.1 cm; LVEDD: 3.5–5.7 cm; LVPWT: 0.6–1.1 cm; LVESD: < 3.5 cm; EF: > 50.

with PCWP which is equal to the left ventricular end-diastolic pressure [18–20]. In our opinion, as a result of the adverse effects of myocardial depressors such as quinine and myocardial depressant factor, a left ventricular overload may occur in spite of volume deficit.

In our study, higher serum BNP concentrations were associated with the severity of disease. Therefore, we think that, unlike the indirect and non-specific parameters of prognostic scores (Ranson, Glasgow and APACHE II) such as urea, creatinine, blood pressure and heart rate, the increase over the normal levels in serum BNP concentrations during the course of AP, could be a more plausible and objective biochemical assay for the prediction of cardiac dysfunction.

In the present study we did not find a relationship between modified radiologic scoring system and serum levels of BNP. Although Balthazar scoring is suggested to be associated with the prognosis of AP in most studies, there is also data in regard with its poor correlation with the severity of disease [8,13].

The limitations of this study were exclusion of patients with systemic disorders such as heart and chronic renal failure which are known to be associated with increased serum BNP concentrations and the limited number of patients. However, statistically significant increase in BNP levels in all of the patients and a significant decrease in BNP levels after the remission led the authors to think that more cases not necessary. Because obtained results are highly significant and incredible.

In conclusion, serum BNP concentrations are correlated with the severity of AP and could be a plausible follow-up marker of cardiac dysfunction in patients with AP.

Learning points

- The most common cause of acute pancreatitis is biliary and alcoholic disorders.
- B type natriuretic peptide (BNP) is increase in acute pancreatitis patients without cardiac disorders at acute attack of the disease.

- Increase in B type natriuretic peptide resolve after the resolution of acute pancreatitis.
- Increase in BNP significantly related with severity of acute pancreatitis.
- Balthazar scoring system poorly associated with severity of acute pancreatitis.

Conflict of interest statement

The authors declare that no conflict of interest exists.

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