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Natriuretic peptide B plasma concentration increases in the first 12 h of pulmonary edema recovery

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ABSTRACT

Background: According to guidelines, single determination of B-type Natriuretic peptide (BNP) should be used for distinguishing between cardiac and non-cardiac acute dyspnea at the emergency room. BNP measurement is also recommended before hospital discharge in patients hospitalized for heart failure to assess prognosis and to evaluate treatment efficacy.

In acute cardiogenic pulmonary edema, BNP is measured using a single BNP determination, but the temporal behavior of BNP during pulmonary edema recovery is unknown.

Methods: Fifty chronic low ejection fraction (< 40%) heart failure patients (age 77 ± 9 years, 17 M-33F) admitted for acute pulmonary edema were studied. Patients were grouped according to 50% dyspnea recovery time into 3 groups: ≤30 min (n = 14), 30 to 60 min (n = 19), and > 60 min (n = 17). BNP was measured at arrival and 4, 8, 12 and 24 h afterwards.

Results: At arrival, BNP was elevated in all patients without significant difference among groups. In the entire population, BNP median and interquartile range value were 791 (528–1327) pg/ml, 785(559–1299) pg/ml, 1014(761–1573) pg/ml, 1049(784–1412) pg/ml, 805(497–1271) pg/ml at arrival and 4, 8, 12 and 24 h afterwards, respectively, showing higher values at 8 and 12 h. This peculiar temporal behavior of BNP was shared by all study groups. Patients with the longest edema resolution showed the highest BNP level 8 and 12 h after admission.

Conclusions: In acute pulmonary edema, BNP increased up to 12 h after emergency admission regardless of dyspnea recovery time, making BNP quantitative meaning in the acute phase of pulmonary edema uncertain.

1. Introduction

According to the most popular and applied guidelines, natriuretic peptides should be used for distinguishing between cardiac and non-cardiac acute dyspnea [1,2]. This is done using a single B-type Natriuretic peptide (BNP) determination usually performed at patient arrival at the emergency room [3,4]. Indeed, BNP increases in the presence of acute hemodynamic impairment [1,2,5,6]. BNP measurement is also recommended before hospital discharge in patients hospitalized for heart failure to assess prognosis and the likelihood of the necessity for a re-hospitalization for heart failure due to further decompensation in the near future [4,7–12]. Indeed, a reduction of elevated BNP with heart failure treatment is considered as a relevant sign of a favorable prognosis [1,2,5,6].Indeed BNP at discharge or its reduction during hospitalization have a strong prognostic capability [13–15]. Viceversa BNP at acute heart failure onset has a limited long term prognostic value [15] but it is unknown whether BNP value in the first hours of acute heart failure is stable or how quickly it follows the hemodynamic status.

In chronic heart failure patients, exercise is frequently associated to the occurrence of dyspnea, hemodynamic impairment, and transient BNP increase [16–18]. However, with the cessation of exercise, hemodynamic impairment and dyspnea quickly disappear, and BNP returns to pre-exercise levels within a short time [18]. Also acute pulmonary edema is associated with life-threatening hemodynamic impairment and severe dyspnea, but the time course of BNP behavior during acute pulmonary edema is unknown.

The present study was therefore undertaken to assess the temporal

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behavior of BNP plasma level during acute pulmonary edema recovery. Indeed we hypothesized that in the acute phase of heart failure plasma BNP has some degree of temporal variability, making its assessment for prognosis of uncertain value.

2. Methods

2.1. Patient population

We studied 50 consecutive patients with acute cardiogenic pulmonary edema admitted at the emergency room of a tertiary hospital with a heart failure referring unit. Study inclusion criteria were acute pulmonary edema and known chronic heart failure. Exclusion criteria were acute coronary syndrome, acute cardiogenic shock (systolic blood pressure < 100 mm Hg), need of cardiopulmonary resuscitation, acute pulmonary embolism, known lung diseases, pneumonia or COPD exacerbation, moderate to severe aortic stenosis, and neurological disorders including dementia and known or acute cerebrovascular accidents or BNP levels < 350 [1] at emergency admission. Patients with acute pulmonary edema associated with relevant pericardial effusion were also excluded [19], as were excluded patients successfully treated outside the hospital so that dyspnea regressed before arriving at the emergency room regardless of BNP level. Patients' characteristics are reported in Table 1.

At emergency room arrival, patients were treated according to current guidelines and as suggested by the medical personnel in charge [1,2]. Emergency treatments are reported in Table 2. Several patients received some sort of treatment before arrival at the emergency room by paramedic intervention. Dyspnea severity was assessed every few minutes as clinically appropriate by directly questioning patients using an arbitrary numerical, 1 to 100, scale. A 50% reduction of the dyspnea reported at arrival was considered as the sign of clinical improvement and, at least partial, edema resolution. All emergency room medical personal was instructed about the present research protocol and received detailed information about dyspnea assessment.

Table 1
Demographic and clinical characteristics of study population.

	All (n = 50)
Age (years)	77 ± 9
Sex (woman)	33 (66%)
LVEF (%)	37 ± 11
PAPs (mm Hg)	40 ± 11
K^+ (mEq/l)	4.2 ± 0.8
Na^+ (mEq/l)	138.9 ± 3.4
Creatinine (mg/dl)	1.35 ± 0.72
$PaCO_2$ (mm Hg)	45.5 ± 11.4
PaO_2 (mm Hg)	70.5 ± 28.2
FiO_2 (%)	30 ± 11.4
$SatO_2$ (%)	87.2 ± 10.6
PaO_2/FiO_2	240 ± 9
Permanent AF	17 (34%)
Primary cardiomyopathy	13(26%)
Secondary cardiomyopathy	33 (77%)
CAD	30(60%)
DM	21 (42%)
HBP	38 (76%)
CKD	13 (26%)
ASA	21(42%)
ACE-I	14 (33%)
ARB	15 (30%)
Diuretics	39 (78%)
Nitrates	18 (36%)
β-blockers	30 (60%)

LVEF = Left ventricular ejection fraction.
CAD = Coronary Artery Disease.
PAPs = Pulmonary systolic arterial pressure.
HBP = Arterial hypertension.
FiO_2 = Fraction of inspired Oxygen.
CKD = Chronic kidney disease.
$SatO_2$ = Oxygen saturation.
AF = Atrial fibrillation.
ASA = Acetilsalicilic acid.
ARB = Angiotensin Receptor Blocker.
DM = Diabetes mellitus.
ACE-I = Angiotensin Converting Enzyme-Inhibitor.

Table 2
Pulmonary edema theraphy.

Therapy	All (n = 50)
Diuretics	50 (100%)
Nitrates	36 (73%)
Oxygen	46 (93%)
CPAP	33 (66%)
Others	24 (48%)

CPAP = continuous positive airways pressure.
Others = morphine, antiarrhythmics, digoxin, insulin, bicarbonates.

2.2. Brain natriuretic peptide

Plasma BNP was measured (CMIA, Abbott Point of Care, Princeton, NJ, USA) at patient arrival, and measurements were repeated 4, 8, 12 and 24 h afterwards.

2.3. Statistical analysis

Continuous variables are presented as mean ± SD, and they were compared using *t*-test for independent samples. Variables with skewed distributions are reported as median and interquartile ranges (IQR), and they were log-transformed before analysis. Categorical variables were compared using the chi-square test or the Fisher's exact test, as appropriate.

The difference of variation of BNP within subjects from baseline to the four time points after arrival at the emergency room were assessed by ANOVA for repeated measures followed by paired *t*-test. Between groups comparisons were tested by two-sample *t*-test. All tests were two-sided. P-values < 0.05 were considered statistically significant. Analyses were performed by SAS version 9.4 (SAS Institute Inc., Cary, NC).

The study was conducted following Helsinki declaration [20], approved by the local scientific committee, and financed by Centro Cardiologico IRCCS research founds.

3. Results

The average time to 50% dyspnea recovery was 60 min (IQR 30–120 min). Patients were grouped according to dyspnea recovery time into 3 groups: ≤ 30 min (n = 14 (29%)), 30 to 60 min (n = 19 (39%)), and > 60 min (n = 17 (32%)). At admission, BNP was high in all patients (median 791 pg/ml IQR: 528–1327 pg/ml). No statistically significant difference was observed as regards BNP value at emergency room arrival considering the 3 study groups (≤30 min: 758 pg/ml (IQR: 521–1258 pg/ml); 30 to 60 min: 678 pg/ml (IQR 533–1365 pg/ml), > 60 min: 1197 pg/ml (IQR 527–1467 pg/ml). Atrial fibrillation was present in 34% of cases and equally distributed among groups.

Considering the entire study population, BNP significantly changed over time (p < 0.001). Specifically BNP was elevated but stable comparing arrival vs. hour 4, but it significantly increased at hour 8 and 12, while it decreased at 24 h (Fig. 1). This peculiar kinetics of BNP was shared by all study groups regardless of clinical recovery time (Fig. 2). As a percentage of median value, BNP increased at hour 8 and 12 by 33% (Δ 263 pg/ml; IQR 77–474) and 36% (Δ282 pg/ml; IQR 65–578) in the entire population, by 45% (Δ 338 pg/ml IQR 77–452, p < 0.01)