

Comorbidities and natriuretic peptide plasma levels

Edoardo Gambuti, Franco Alfano, Fabio Fabbian

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is the N-terminal part of a 108 amino acids prohormone called proBNP, and its gene is located on chromosome 1. It is produced when cardiac disease occurs especially in patients with heart failure (HF). Cardiac wall stress is the main stimulus for proBNP production and secretion. Once in the circulation, the prohormone is split into BNP (32 amino acids) and NT-proBNP (76 amino acids) [1]. Natriuretic peptide constitutes an endogenous compensatory system that acts to counter excess cardiac load and volume expansion and its actions include natriuresis, diuresis, vasodilatation, and lusitropism, plus direct suppression of volume-retaining, vasoconstricting system including the renin-angiotensin-aldosterone and sympathetic nervous system. Natriuretic peptide also has trophic actions opposing cardiac hypertrophy and fibrosis [2]. Thus, the main effect of natriuretic peptide is on the cardio-renal axis, and its actions are targeted in order to treat HF as in the case of sacubitril-valsartan [3]. In clinical practice, this peptide is used to identify people who require further cardiac investigation because HF is suspected [4]. In acute setting of HF, NT-proBNP cutoff point should be set at 300 pg/ml whilst in chronic HF instead, the optimal cutoff is below 125 pg/ml. The clinical strength of natriuretic peptide is to permit a rule out diagnosis of HF [4]. If low concentrations are detected, negative predictive values is high (0.94-0.98) in both acute and non-acute setting. Moreover, the positive predictive values are lower both in the acute setting (0.66-0.67) and in the non-acute setting (0.44-0.57) [4]. It should be underlined that natriuretic peptides plasma

levels could be modified by other conditions different from HF. Richards et al. reported that natriuretic peptide plasma levels could be altered by several heart diseases such as acute coronary syndromes, atrial fibrillation, valvular heart disease, cardiomyopathies, myocarditis, left ventricular hypertrophy and procedures such as cardioversion, and non-heart conditions such as age, renal impairment, pulmonary embolism, severe pneumonia, obstructive sleep apnea, bacterial sepsis, severe burns, cancer chemotherapy, toxic and metabolic diseases [2]. Therefore, relationship between NT-proBNP plasma levels, comorbidity and diagnostic cutoff is still a matter of debate. Guo et al. [5] evaluated the role of plasma NT-proBNP in diagnosing elderly patients with acute exacerbation of chronic obstructive pulmonary disease (COPD) and HF. They concluded that NT-proBNP diagnostic cutoff of 1,677 ng/L is suggestive of presence of HF associated with COPD. In order to ameliorate clinical performance of NT-proBNP in HF diagnosis, patients with serum creatinine >2.8 mg/dl were excluded, selecting however a population with an average serum creatinine of 1.3 ± 1.1 mg/dL. On the other hand, glomerular filtration rate (GFR) was not estimated. Moreover, other comorbidities were not considered such as atrial fibrillation and chronic kidney disease (CKD). Choosing this stratification, they did not take into consideration a fourth group including only HF patients. Richards et al. [2] analyzed NT-proBNP values, setting an optimal cutoff point, based on patient age, and in elderly patients there was a raise in concentrations of natriuretic peptide altering the classic rule out point of 300 pg/ml. NT-proBNP clearance is renal, therefore, it is important to evaluate the impact of GFR in interpreting natriuretic peptide plasma concentrations [4]. A cohort of consecutive patients admitted because of HF suspicion to an internal medicine unit aged 65 to 90 years was evaluated and it was found that NT-proBNP was independently associated with hemoglobin levels and pulmonary disease, including in the definition of pulmonary disease infections and COPD. $GFR < 60$ ml/min/1.73 m² was related to high NT-proBNP levels and NT-proBNP levels increased following CKD stages, starting from a mean value of 1,897 pg/ml. Moreover, prevalence of atrial fibrillation was higher in patients with high NT-proBNP [6]. Jannuzzi et al. [7] suggested that upper normal value of NT-proBNP in subjects aged >75 years should be 1,800 pg/ml. NT-proBNP plasma levels have been related to different stages

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of renal function assessed with different methods in older adult subjects admitted because of dyspnea. Patients were classified into the five K/DOQI stages of CKD and median NT-proBNP values were calculated evaluating their relationship with GFR. The latter was calculated with different equations, the four variables MDRD equations, Mayo Clinic Quadratic formula, and the CKD-EPI formula, and NT-proBNP plasma levels progressively increased with worsening of renal function. GFR assessed with the Mayo Clinic Quadratic formula appeared to better stratify NT-proBNP in older adult subjects [8]. Schaub et al. [9] reviewed systematic relationship between renal dysfunction and NT-proBNP in acute decompensated heart failure (ADHF). In patients with an estimated GFR < 60 ml/min/1.73 m², the area under the curve (AUC) for NT-proBNP ranged from 0.66 to 0.89 and the median cutoff point was 1,980 pg/ml. They concluded that NT-proBNP was useful in diagnosing ADHF in patients with renal dysfunction adopting higher cutoff. Without a correct evaluation of GFR, the relationship between HF and pulmonary diseases could be misunderstood. At the time of the interpreting NT-proBNP levels, considering a stratification for comorbidities is important. A study enrolling 94 patients confirmed the effect of renal dysfunction on NT-proBNP showing that average natriuretic peptide plasma levels significantly differed in different stages of CKD [10]. From stage I to IV, NT-proBNP levels rised exponentially from 424 to 8.075 pg/ml [10]. Moreover, considering left ventricular ejection fraction (LVEF), Perez-Downes et al. [11] underlined how "LVEF is the most critical variable influencing mortality and NT-proBNP". Di Castelnuovo et al. [12] analyzed a data of 58,173 participants (50% men, mean age 52 years) in order to evaluate the association between NT-proBNP and stroke. The aim of this study was to consider the relationship between predictive values of NT-proBNP and stroke risk. The results established a solid connection between NT-proBNP and ischemic stroke. Besides natriuretic peptide represented a strong predictor of in-hospital mortality, 90-day and 60-month mortality in patients with sepsis [13]. High natriuretic peptide plasma levels are related not only to HF but also to outcomes in different non-heart related diseases. In conclusion, there are different conditions that could affect NT-pro BNP plasma levels, which need to be considered separately in patients with only HF, and other multi-morbid patients. Thus, in order to better define relationship between NT-proBNP cutoff and multimorbidity, further studies must be conducted in elderly populations.

Keywords: Comorbidities, Heart failure, Natriuretic peptide, Renal dysfunction

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Edoardo Gambuti – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Franco Alfano – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Data Availability

All relevant data are within the paper and its Supporting Information files.

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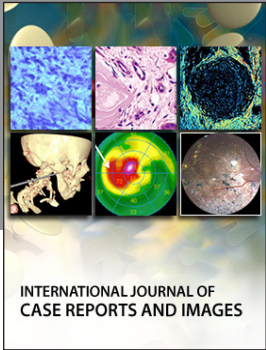
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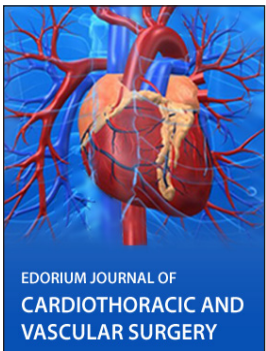
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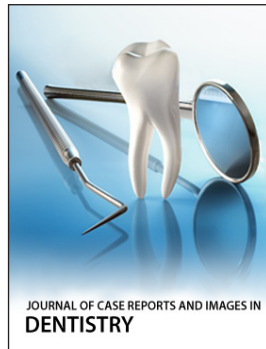
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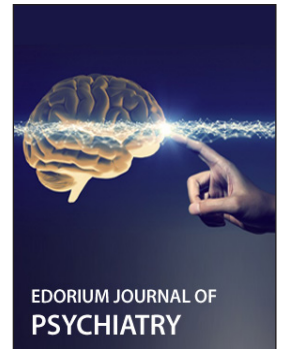
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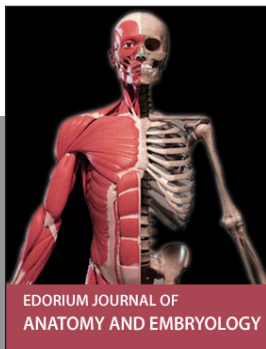
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