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ORIGINAL ARTICLE

Correlation of N-terminal fragments of Atrial Natriuretic Neuropeptides (NT-ProANP) with Left Ventricle Ejection Fraction in Cases with Acute Myocardial Infarction

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Abstract

Background This study aimed to assess the correlation of natriuretic neuropeptides (NT-ProANP) with the left ventricular ejection fraction (LVEF) in patients with acute myocardial (AMI).

Materials and Methods This case-control study composed of 120 patients was recruited from the cardiac center in Babylon, Iraq. The plasma levels of NT-ProANP and echocardiographic measure of the left ventricle ejection fraction percentage (LVEF%) for both patients and controls as well as demographic data were taken.

Results The mean ages were 61.9 ± 13.2 and 33.1 ± 8.3 years for patients and control, respectively, 80.8% of the candidates were male. The differences in NT-ProANP serum levels between AMI patients and controls were highly significant p-0.001. There was a good diagnostic ability of NT-ProANP to predict patients with AMI from the healthy subjects by ROC-curve analysis: AUC=0.957, sensitivity=0.961, specificity=0.962, 95%CI=0.927 – 0.987, and p>0.05. Whereas, there was a poor diagnostic performance of NT-ProANP to predict LVEF%: AUC=0.438, sensitivity=0.438, specificity=0.519, 95%CI=0.285 – 0.598, and p>0.05. Serum concentrations of NT-ProANP showed no significant correlation with the measures of left ventricular EF%, age, and BMI among AMI patients. The serum levels of NT-ProANP revealed no significant variations between AMI patients with low and those with preserved LV functions

Conclusion The study suggests that the measurement of NT-ProANP was not correlated to LVEF%, although its levels were significantly higher among patients with AMI compared to the healthy controls.

Keywords: NT-ProANP; LVEF%; AMI; N-terminal fragment; atrial wall stress.

1 Introduction

Advances in the analytical capability in contemporary medicine present various biomarkers for diagnosing acute myocardial infarction (AMI) [1–7]. Still, assessing troponin-I in the blood remains the "gold-standard" laboratory test to diagnose acute myocardial infarction [8, 9]. This is because troponin-I is exclusively expressed in cardiomyocytes making it highly specific and sensitive to cardiac necrosis [8–10] The "atrial natriuretic peptide" (ANP) is a peptide neurohormone secreted from the left atrium, although it can be produced from the ventricular cells under certain conditions too. ANP is produced initially as a pre-prohormone precursor "pre-proANP" [11], and then modified to prohormone (proANP), which is deposited in specific granules of atriomyocytes and finally cleaved into the "98 amino-acid N-terminal fragments (NT-ProANP) and the 28 amino-acid active ANP neurohormone". NT-ProANP precursors have longer shelf-life,

higher molecular weight, and plasma measures compared to ANP [8, 12]. ANP exerts protective cardiac activity. Reduced circulatory ANP levels were frequently linked with obesity and/or diabetes mellitus type 2, hypertension, and cardiac failure [13].

A plethora of evidence from well-conducted studies supports NT-ProANP as a sensitive, low-priced biomarker capable of improving the prognostication of AMI and cardiac failure [14]. Raised plasma levels of NT-ProANP are correlated with higher mortality in left ventricle systolic dysfunction, congestive cardiac failure, and patients with unstable angina [15]. Nonetheless, various plasma-half-lives, altered hemodynamics, and thus altered time intervals from the prodromal symptom up to the admission, govern various circulatory courses of NT-ProANP [16].

A substantial ratio of AMI patients has negative or minor non-significant troponin-I elevations at admission, with a consequent rise in late hematogenous samples. In some infarcted patients, troponin-I values remain modest, even after consecutive samples. As a result, a "cutter sward" marker of cardiac necrosis has been strongly needed. Hence, some candidate biomarkers have lately been assessed [12, 17]. "Left ventricular ejection fraction% (LVEF%)" is broadly used as a factor to evaluate ventricular pumping proficiency, though it has some recognizable restrictions [14].

2 Material and method

The entire 120 patients were included in this case-control, single-center study were referred for appointed elective coronary angiography. The AMI patients were recruited from Shaheedul-Mihrab cardiac center in Merjan Medical City, Babylon, Iraq. The physicians identified the patients as AMI based on history, clinical examination, laboratory tests, ECGs, & echocardiogram studies. All the study patients had Extensive coronary disease and Viability in at least 4 dysfunctional myocardial segments. The excluded patients are with decompensated heart failure, Aged <18 years,eGFR < 25 ml/min, unless established on dialysis, and pregnant women. The healthy control group comprised 88 healthy (selected from the visitors or attendants of the patients) free from any cardiac illnesses. Blood samples were collected from all applicants for NT-ProANP estimation. Venous sampling was performed through the antecubital vein 24-36 hours after the onset of the symptoms. Plasma NT-ProANP measures were assessed using "Human Elabscience® ELISA-kit, China". The laboratory workers, physicians, echocardiography examiners, and cardiologists were unaware of the study protocol, or the NT-ProANP activities. Verbal permission was taken from every patient (or attendant) at the beginning of the questionnaire. The ethical committee legalized the entire study procedure for research at the cardiac center and from the Babil health directorate. The study adapts all the principles outlined in the Helsinki Declaration.

2.1 Echocardiography study

Two echocardiography examiners using Vivid®-III standard two-D thoracic (GE ultrasound system) performed the echocardiographic study at the cardiac center. "Modified Simpson's method" was applied to calculate LVEF, and a cutoff limit of LVEF less than 40% was selected to define systolic LV dysfunction. Therefore, AMI subjects were categorized into LVEF $\leq 40\%$ set against $> 40\%$ [18].

2.2 Statistical analysis

Statistical analysis was concluded with SPSS software, V/21. Variations across two groups were scrutinized by chi-square for dichotomous variables. T-tests were applied for independent samples to compare the continuous data (given as means). Relations of NT-ProANP, LVEF%, and demographic characteristics were studied by Spearman correlation. When the p-value reaches less than 5%, it will reflect a statistical significance.

Table 1: Baseline characteristic features of the studied participants (N-304).

Variables		Acute coronary patients N=120	Healthy controls N=88	P-value
Age (years)		61.9 ± 13.2	33.1± 8.3	0.05
BMI (kg/m2)		27.2 ± 7.1	26.2 ± 11.3	NS
Gender	Females (N-40)	28 (70%)	12 (30%)	0.05
	Males (N-168)	92 (54.8%)	76 (45.2%)	
Current smokers No (%)		36 (30%)	39 (44.3%)	0.05
Left ventricle EF %		49.8 ± 30.4	67.9 ± .1	0.05
NT-ProANP (pmol/l)		357.9 ± 165.3	174.8 ± 28.3	0.001
Hypertension No. (%)		37 (30.8%)	7 (7.8%)	0.05
Diabetes No. (%)		30 (22.4%)	4 (4.5%)	0.05

In the current study, the sex revealed no significant changes in the study variables except significant (p-0.001) higher female NT-ProANP levels Table 2.

Table 2: Distribution of the study variables in patients with acute myocardial infarction according to the gender .

Characteristics	Age	LVEF%	BMI	NT-ProANP
Male No (mean)	58.2 ± (31.9)	49.3 ± 13	27.2 ± 5.1	228.6 ± 132.2
Female No (mean)	61.4 ± (21.1)	52.7 ± 8.9	26.2 ± 4.6	320.3 ± 234.2
Significance	NS	NS	NS	0.001

There was a good diagnostic ability of NT-ProANP to predict patients with AMI from the

healthy subjects as indicated by ROC-curve analysis: AUC=0.957, sensitivity=0.961, specificity=0.962, 95%CI=0.927 – 0.987, and p>0.05. Whereas, there was a poor diagnostic performance of NT-ProANP to predict LVEF%: AUC=0.438, sensitivity=0.438, specificity=0.519, 95%CI=0.285 – 0.598, and p>0.05, Table 3.

Table 3: ROC-curve assays of NT-ProANP to differentiate AMI from healthy subjects and to predict poor LVEF% .

Predictability	AUC	P-value	Sensitivity	Specificity	95% CI
The ability of NT-ProANP to predict AMI patients from healthy	0.957	0.001	0.961	0.962	0.927 – 0.987
The ability of NT-ProANP to predict poor LVEF%	0.438	>0.05	0.519	0.539	0.285 – 0.598

Serum concentrations of NT-ProANP showed no significant correlation with the measures of left ventricular EF%, age, and BMI among the AMI patients, Table 4.

Table 4: Correlation of NT-ProANP serum levels with LVEF%, ages, and BMI in AMI patients .

Variables	r	P
LVEF %	0.122	0.3
Age (years)	0.293	0.053
BMI (kg/m^2)	0.221	0.4

The serum levels of NT-ProANP revealed no significant variations between AMI patients with low and those with preserved LV functions Table 5.

Table 5: Comparison of the serum mean concentrations of NT-ProANP according to two categories of LVEF%.

	LVEF Category	Mean	Std. Deviation	P-value
NT-ProANP	>40%	338.0	158.2	>0.05
	<40%	368.3	188.7	

The levels of circulatory NT-ProANP did not differ significantly between those with hypertension and diabetes individually and those without not.

Table 6: Differences in the serum mean concentrations of NT-ProANP according to the presence of hypertension and diabetes mellitus.

Variable		No.	Mean	Std. Deviation	Significance
Hypertension	Positive	44	392.9	184.2	>0.05
	Negative	164	321.8	159.5	
Diabetes	Positive	34	327.7	148.1	>0.05
	Negative	174	379.3	190.7	

3 Discussions

In the current study, we inspected the neurohormone levels of cardiac origin NT-ProANP and its association with LV performance in terms of LVEF% among patients with AMI compared to healthy subjects. The authors selected to measure the NT-ProANP peptide rather than ANP because it is more advantageous as it has an extended plasma half-life and thus higher levels, which offers easy usage and analysis.

The main findings were (1) the left ventricular EF% significantly deteriorated among the patients with AMI compared to the control, (2) significant high elevation of serum NT-ProANP concentrations of the patients compared to the control, and (3) the good diagnostic ability of NT-ProANP to predict patients with AMI from the healthy subjects, but poor performance to predict poor LVEF%.

Our findings revealed that the stressed infarcted myocardium was not correlated with impaired LV function as estimated by increased NT-ProANP measures among AMI patients compared to healthy subjects. The primary stimulus for the secretion of cardiac neurohormones is the cardiac wall stretch, due to raised atrial pressure and/or volume, like in heart failure, myocardial infarction, or cardiomyopathies [19]. Though ANP levels are more associated with left atrium mural pressure, they can be released from both atria and ventricular tissues in great amounts, in cases of AMI or LV dysfunction [20].

Supporting our findings are those reported by a few studies [21, 22] Increasing evidence confirms that during AMI, a comparable surge in circulating cardiac neuropeptide levels at the sites of the obstructed vessel, getting their plateaus at the maximum grades of intimal stenosis, irrespective of the underlying myocardial stress [23]. This finding contrasts numerous foregoing studies [24, 25].

One probable clarification is the conserved LV function in most cases otherwise caused by cautious and

active reperfusion therapy. Nevertheless, one forgoing study exposed raised neuropeptide values that were also found in AMI subjects with normal ventricle function. Some AMI cases with reduced EF% had a concentration of NT-ProANP within the normal ranges [26]. Probably our patients developed less severe LV impairment with systolic dysfunction.

A likely additional explanation is that high NT-ProANP is caused by cardiac ischemia, simply because ANP synthesis arises not only in ischemic myocardium since the increased secretion can occur also in localized wall stretch or stress in viable atrial myocytes, both within and adjacent, the necrotic area [21].

A further reason for the conserved LV function of most AMI patients might be due to timed and successful reperfusion treatment [27]. Finally, the authors suppose that it is probably that NT-ProANP was not elevated significantly either due to depleted stores of atriomyocytic granules one day after the initial maximal release during the early hours of AMI or due to hemodynamic physiological response that might be so effective and resulting in less atrial wall tension. The third possibility is that the myocardial ischemia was relatively minor and not so extensive, thus inducing only trivial transient alteration in the levels of serum NT-ProANP.

The current study showed no significant gender variation in the study variables apart from NT-ProANP (more in females), similar to the outcomes reported by a couple of studies [24, 28]. Estradiol enhanced the expression and transcription of ANP receptors in the experimental model. Sex-dependent ANP control might induce recognized sex changes in adipose tissue distribution and cardiovascular risk [29].

Consistent with our results as regards no variations in the levels of NT-ProANP with the incidence of DM, was a prior study (although not all recent studies) [22]. Song W. et al., exposed decreased concentrations of ANPs in patients with type-2 DM [13]. However, many reports from other studies had shown a significant link between NT-ProANP measures and DM incidence [22, 27] Likewise, no variations in the levels of NT-ProANP with the incidence of hypertension were observed in the current study, a finding supported by Niccoli G. et al. [22]. In contrast, other studies detected a positive correlation between ANPs and the incidence of hypertension [23, 27] There is a dual relationship between the ANP and systemic blood pressure. Neurohormones reduce blood pressure via several pathways, including increased (natriuresis, renal arterial perfusion, and GFR) and arteriovenous dilation. Also, inhibition of hypophysial antidiuretic hormone, renin-angiotensin-aldosterone system, and sympathetic autonomic NS are potential mechanisms [30]. NT-ProANP concentrations were not correlated with the number and site of the affected coronary arteries in the current study concordant with two other pieces of research [22, 28]. This is expected as NT-ProANP is released in response to increased transmural atrial wall stress or volume rather than coronary vascular changes.

In summary, the ability of NT-proANP to predict LV systolic function among AMI patients is conflicting. The hormonal activities, receptor affinity, and functional roles of ANP are considerably altered during physiological and pathological conditions. The primary study limitation was the relatively small size of patients enrolled. However, the authors believe our outcomes could provide significant supplementary data in this field. Additional future larger cohorts including other parameters like NT-ProBNP, or other mid regional fragments of ANPs, could clarify the precise diagnostic and prognostic role of ANPs among cases with AMI.

4 Conclusion

The study concluded that NT-ProANP hormone measurement was not correlated to LVEF%, although its concentrations were significantly elevated among AMI patients compared to healthy subjects.

Conflict of Interest: No conflicts of interest exist between the authors and the publication of this work.
Ethical consideration: The ethical committee approved the study at Al-Mustaqbal University College, Hillah, Iraq.

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