

Original Research Article

The Role of NT- Probnp in The Diagnostic Workup of Patient with Chronic Dyspnea of Unexplained Etiology

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Abstract

Dyspnea is a common clinical complaint of diverse causes, it may be of acute or chronic onset. Diagnosis of dyspnea should depend on good history, proper physical examination with the logistic use of laboratory & radiological investigation. Yet some time, especially in patient with chronic dyspnea, we may be left with patient without clear clinical diagnosis.

NT- proBNP is which is a hormone produced from the heart whenever there is stretch of cardiac muscle is proved of diagnostic value in acute dyspnea.

This study is to examine the diagnostic value of NT-proBNP in the etiology of chronic dyspnea with unapparent clinical cause.

From 425 patient presented complaining of chronic dyspnea, after full history, physical examination & conventional investigation, Sixty-two patient have no evident cause for their dyspnea. Those patients were studied to assess the value of NT- proBNP in the work up for the cause of their dyspnea & its relation to their BMI, age, HT, DM & IHD. Significant high level of NT- proBNP was found in patient who have higher grade of dyspnea & in those with chronic disease as HT, DM & IHD especially if they have IHD. Although many of the patient have high BMI but it does not significantly related to the level of dyspnea.

NT- proBNP is a helpful diagnostic mean in patient with chronic dyspnea although other limitation factors as age, sex & BMI should considered.

Keywords: NT-proBNP, Chronic Dyspnea

Abbreviations: BNP= Brain natriuretic peptide, NT- proBNP = N terminal Pro brain natriuretic peptide, HT=hypertension, DM=diabetes mellitus, IHD=ischemic heart disease , HF=heart failure

الدور التشخيصي لهرمون NT- proBNP في البحث عن مسببات عسرة التنفس المزمنة المبهمة

الخلاصة

ان عسرة التنفس هي شكاوى شائعة وذات مسببات متنوعة وقد تكون حادة او قد تكون مزمنة. ان تشخيصها يعتمد على معرفة التاريخ المرضي بشكل مفصل مع الفحص السريري ويدعم بالفحوصات المختبرية والشعاعية. ومع ذلك ينبغي هناك قسم من حالات عسرة التنفس وخاصة المزمن منها غير بيئية التشخيص.

لقد تبين ان هورمون (NT- proBNP) واذا يفرز من خلايا القلب عند تعرضها للامتداد له قيمه تشخيصيه لتفريق حالات عسرة التنفس الحاده الناتجة عن عجز القلب من المسببات الاخرى لهذه العسره. هذه الدراسه اجرت للتحري عن دراسه القيمه التشخيصيه لهذا الهرمون لحالات عسرة التنفس المزمنة والتي لم تشخص بالطرق التشخيصيه التقليديه ومدى علاقه مع العمر والجنس والوزن وحالات المراضه المرافقه.

من بين ٤٢٥ مريضاً يشكون من عسرة تنفس مزمنة وبعد اخذ التاريخ المرضي لهم واجراء الفحص السريري والاطلاع على فحوصاتهم القديمة واجراء الفحوصات التقليديه بقي ٦٢ مريض غير مشخص سبب عسرة التنفس لديهم. على هذه العينه المتبقية درس الدور التشخيصي لهرمون NT-proBNP لمعرفة سبب عسرة. بينت نتائج الدراسه ان الدور التشخيصي لهرمون NT-proBNP يكون ذو فائده لدى المرضى اللذين يشكون من امراض اخرى مرافقه كداء السكر وعدم كفاية الشرايين التاجيه وارتفاع ضغط الدم، كما ان هناك عوامل محدده للفائده التشخيصيه للهرمون لتاثيره بعوامل اخرى كالعمر والجنس والوزن.

Introduction

Dyspnea is defined as abnormal or uncomfortable breathing in the context of what is normal for a person according to his or her level of fitness and exertional threshold for breathlessness [1- 5].

The differential diagnosis of dyspnea is composed of four general categories: cardiac, pulmonary, mixed cardiac or pulmonary, and non-cardiac or non-pulmonary. Dyspnea may be acute which occurs within minutes to few hours or chronic dyspnea which is shortness of breath that lasts more than one month [6].

The clinical presentation alone is adequate to make a diagnosis in 66 percent of patients with dyspnea. Patient descriptions of the sensation of dyspnea with full history and physical examination with findings of jugular venous distention, decreased breath sounds or wheezing, pleural rub, clubbing may be helpful in making the diagnosis [7].

Initial testing in patients with chronic dyspnea includes chest radiography, electrocardiography, echocardiography, spirometry, complete blood count, and basic metabolic panel may uncover the cause for it. However sometimes more sophisticated test may be used as high-resolution computed tomography, holter monitor, radionuclide study, ventilation-perfusion (V/Q) scan [6].

BNP is synthesized in the cardiac myocytes as a 134-amino acid prohormone (preproBNP), removal of the 25-residue N-terminal signal peptide generates the prohormone proBNP which is stored intracellularly; proBNP is subsequently cleaved into the biologically active 32-amino acid polypeptide BNP-32& the N-

terminal 76 amino-acid NT-proBNP that is released from cardiac ventricles in response to increased wall stress and volume overload [8, 29].

In patients with dyspnea plasma NT-proBNP concentrations are increased in left ventricular dilatation, hypertrophy, systolic dysfunction, or diastolic dysfunction, but not by pulmonary dysfunction [9].

In acute setting BNP and N-terminal Pro-BNP levels can be used to distinguish between patients with dyspnea due to heart failure from pulmonary causes of dyspnea [10, 11].

Elevated concentrations of BNP or NT-proBNP are powerfully associated with the presence of HF; however, there is no value for either that is 100% diagnostic for HF. Both BNP and NT-proBNP may be elevated in a number of other disease states, and patient factors may influence results [12].

In patients with acute dyspnea BNP or NT-proBNP is, in conjunction with other clinical information, as rapid measurement is useful in establishing or excluding the diagnosis of congestive heart failure [13]. but in In ambulatory patients with dyspnea, measurement of BNP or N-terminal pro-B-type natriuretic peptide (NT-proBNP) is useful to support clinical decision making regarding the diagnosis of HF, especially in the setting of clinical uncertainty [14].

There are many patient with chronic dyspnea for whom neither history or physical examination nor conventional investigation explain the underlying cause of their dyspnea ,so we have to do more sophisticated investigations which may be costive [6].

As a laboratory specimen, NT-proBNP is more stable during storage than BNP, NT-proBNP samples are stable at room temperature for 72 hours, versus less than 4 hours for BNP samples [15, 16].

We choose to measure the NT-Pro BNP in those patients & see if it is of diagnostic value in the workup of patients with chronic dyspnea without apparent cause as it is easy to do & it is less costive.

Patients and Methods

In the period between 1st June 2013 to 5th May 2014, 425 patients 289 were female & 149 male, age 18-86 year who were presented with chronic dyspnea for variable period were studied.

Those patient was evaluated by two physician including where full history, physical examination and their previous investigation were reviewed. The patients who was smokers or had history of chronic respiratory disease, or have renal failure, severe anemia, and uncontrolled hypertension, previous diagnosis of heart failure or renal failure were excluded. The patients who have no clear explanation for their dyspnea were studied.

They undergo the following investigations full blood picture, ECG, Echocardiography, pulse oximetry, blood urea, serum creatinine, CXR and pulmonary function test. After the revision of the workup of the investigations those for whom a cause for dyspnea was found were also excluded from the study.

We are left with 62 patient, age 21-76 yrs. Mean age 51.9, 16 male (25.8%) and 46 female (74.2%) without clear diagnosis for their dyspnea. For whom NT-ProBNP measurement was done.

The NT-proBNP measurement procedure using Biomerieux kits. with calibration of 2 levels of 2 mL included in the kit, calibration verification done every 28 days, with a measuring range 20- 25,000 pg/mL & traceability ROCHE ELECSYS® NT-proBNP. , Sample volume 200 µL of the

patient serum was used. Minividas –B analyzer used for the study. The test takes 20 minutes to get the results.

Data Management and Statistical Analysis

Results of NT-proBNP over 400pg/dl is regarded significant & suggestive of heart failure [12]. The data was processed using SPSS version 18, with usage of chi square and regarding probability value i.e P value of less than 0.05 is of clinical significant.

Correlation between each factor (age, gender, degree of dyspnea, leg edema, BMI) and NT-ProBNP was tested by means of Kendall's tau_b tests.

Multivariate analyses were performed with cross tabulation with usage of chi square &, to look at the association between the level of NT- ProBNP & co –morbidity (HT, DM, IHD)

Results

From 425 patients with chronic dyspnea, 289 were female and 149 male, there are 62 (14.5%) of them there is no evident diagnosis for their dyspnea, their age is 21 yr-76 yrs. mean age is 51.9 yr, 16 were male (25.8%) and 46 were female (74.2%). Significant NT-proBNP level i.e. over 400pg/dl (with a range from 430-1472pg/dl) was found in 15 patients (24.1%) four were males and eleven were females age range 38-76 year mean age is 59.2yr.

Non-significant level of NT-proBNP i.e. less than 400pg/dl was found in forty- seven patient (75.8%) Thirteen were males and 34 were females. Age range 21-74 yr. mean age is 49.6 yr.

The results of NT-proBNP of those dyspneic patients was studied in relation degree of dyspnea as well to multiple factors as age, gender, body mass index, and, presence of comorbidity as diabetes mellitus, hypertension & ischemic heart disease as explained in the followings paragraphs and seen in table -1.

NT-proBNP and Dyspnea

There is significant correlation between the level of NT-proBNP and the degree of dyspnea, the more dyspneic the patient is the higher the level of NT-proBNP with a P value of 0.014. as seen in figure-1 and table-1 while there is no statistical significant correlation found between the gender of the patient to the degree of dyspnea.

NT-proBNP and age

In the study the effect of age of the dyspneic patient on the level NT-pro BNP shows a significant statistical correlation between the age and the level of NT-pro

BNP. The older age group have more significant NT-pro BNP level with a P value less than 0.003, but the age doesn't carry statistical significance to the degree of dyspnea with a P value of 0.06.

NT-proBNP and BMI

The effect of weight of the patient with dyspnea on the level of NT-pro BNP reveals evidence of significant negative correlation with a P value of 0.01. The more the BMI patient have the lower the level of NT-ProBNP but it does not carry a statistical significant correlation to the degree of dyspnea with P value more than 0.05 ,as seen in the table-1.

Table 1: The relation between NT-ProBNP with age ,gender ,BMI,& dyspnea

			Age	Gender	Body mass index	Dyspnea grade	PRO-BNP category
Kendall's tau_b	Age	Correlation Coefficient	1.000	.087	-.151-	.141	.315**
		Sig. (2-tailed)	.	.416	.087	.155	.003
		N	62	62	62	62	62
	Gender	Correlation Coefficient	.087	1.000	.362**	.030	.010
		Sig. (2-tailed)	.416	.	.001	.801	.941
		N	62	62	62	62	62
	Body mass index	Correlation Coefficient	-.151-	.362**	1.000	-.274- **	-.338- **
		Sig. (2-tailed)	.087	.001	.	.006	.001
		N	62	62	62	62	62
	Dyspnea grade	Correlation Coefficient	.141	.030	-.274- **	1.000	.293*
		Sig. (2-tailed)	.155	.801	.006	.	.014
		N	62	62	62	62	62
	PRO-BNP category	Correlation Coefficient	.315**	.010	-.338- **	.293*	1.000
		Sig. (2-tailed)	.003	.941	.001	.014	.
		N	62	62	62	62	62

** . Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

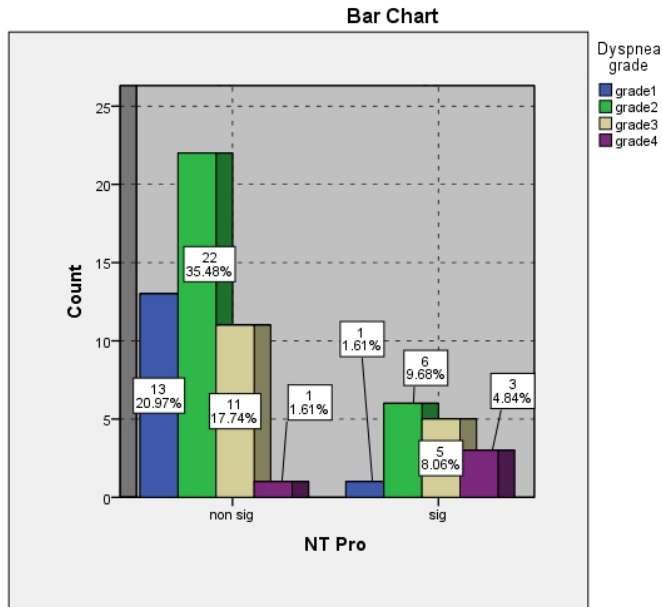


Figure 1 : correlation between NT-proBNP and grades of dyspnea

NT -pro BNP& comorbidity

The correlation between presence of comorbidity of either one or more of the following diseases namely hypertension, diabetes mellitus and ischemic heart disease in patient with significant elevation of NT -pro BNP and those who have non-significant level reveals the followings results & also are seen in table-2:

Of those patient with non-significant NT-proBNP (47 patients) 17 patient has no HT,DM or IHD, 2 have DM only,18 has HT only, 6 has HT and DM , 4 have IHD (two have DM as well and one has HT).

The comorbidity of those patient with significant NT-proBNP level is, 1 have DM only, 2 have HT, 2 have DM& HT. 8 have IHD (either alone or in combination with other disease) and 2 have no HT, IHD or DM.

The result of the study shows significant correlation between significant elevation of NT ProBNP and the presence of one or more of the followings namely diabetes mellitus, hypertension or ischemic heart disease .Patient who have ischemic heart disease has have highest level of NT Pro BNP with P value of 0.01.

Table 2: comorbidity and PRO-BNP category Cross-tabulation

			PRO-BNP category		Total
			none	significant	
comorbidity	normal	Count % within comorbidity	17 89.5%	2 10.5%	19 100.0%
	DM	Count % within comorbidity	2 66.7%	1 33.3%	3 100.0%
	HT	Count % within comorbidity	18 90.0%	2 10.0%	20 100.0%
	IHD	Count % within comorbidity	1 20.0%	4 80.0%	5 100.0%
	DM&HT	Count % within comorbidity	6 75.0%	2 25.0%	8 100.0%
	DM&IHD	Count % within comorbidity	2 40.0%	3 60.0%	5 100.0%
	HT&IHD	Count % within comorbidity	1 100.0%	0 .0%	1 100.0%
	IHD,HT&DM	Count % within comorbidity	0 .0%	1 100.0%	1 100.0%
	Total	Count % within comorbidity	47 75.8%	15 24.2%	62 100.0%

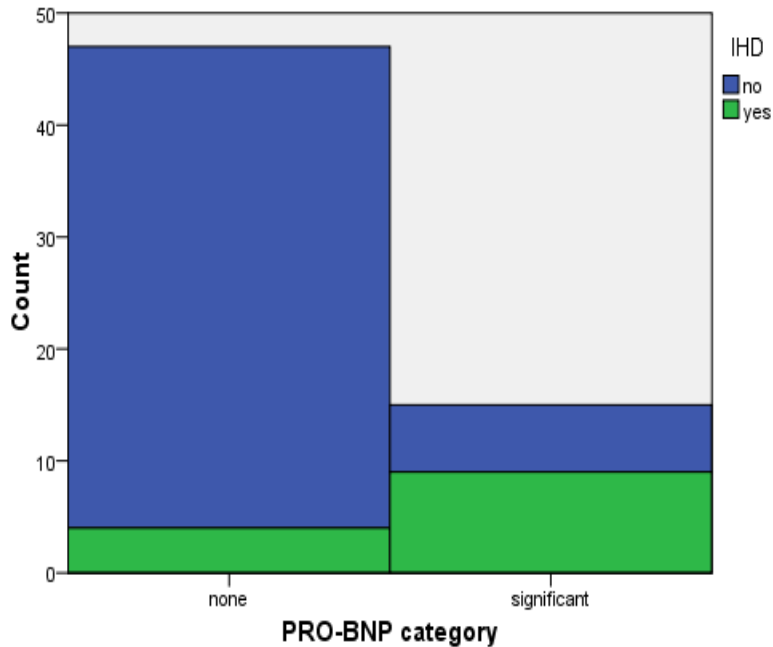


Figure 2: NT- proBNP & ischemic heart disease

Discussion

The results reveals that NT proBNP shows statistically significant positive correlation with the grade of dyspnea and the age of the patient with P value <0.05, although the age of the patient shows no significant correlation to the grade of dyspnea.

In this study older age the patient the higher the ProBNP level .The correlation that we found between increasing age and increasing concentrations of NT-proBNP has been properly established in previous studies [17]. NT-proBNP levels independently predict heart failure and cardiovascular death in older adults [17], although the reason for the age related increase in NT-proBNP is unknown, yet in this study it does not go in parallel with the degree of dyspnea

The sex of the patient shows no statistical significant correlation with NT-proBNP or the dyspnea although in a study done by Carolyn S.P. Lam et al In pair-wise comparisons, men had lower plasma NT-

proBNP than women regardless of menopause status or hormone therapy [18]. But the study does not include the cardiac function state in comparative to the Pro BNP and gender.

In this study we found a negative correlation between BMI&NT pro BNP where the increase in the body weight is associated with lower level of NT-ProBNP which is similar to the finding proved in other studies [19]. but the increase in the BMI shows no statistical significance to the degree of dyspnea with a P value of 0.06.

Obesity is one of the major limitations of HF biomarkers is in obese patients where the relationship between BNP and NT-proBNP levels and myocardial stiffness is complex. Recent data suggest an inverse relationship between BNP and NT-proBNP levels and body mass index.

Given the ever-increasing prevalence of obesity world-wide, it is important to understand the benefits and limitations of HF biomarkers in this population[19] .so

to study NT proBNP as parameter for dyspneic patient of unexplained clinical cause especially if they have high BMI you may need further study to evaluate its clinical significant.

The salient finding is the positive correlation between the level of NT ProBNP of our dyspneic patients & the presence of any of the chronic diseases as hypertension, diabetes or ischemic heart disease either each alone or in combination. It is more evident if the patient has ischemic heart disease.

In relation to diabetes mellitus previous studies demonstrated that NT-proBNP is an excellent predictor of long-term cardiac risk in patients with diabetes mellitus [20-23].

It was found in that there is higher level of NTproBNP in diabetic patients and so NTproBNP can reliably screen diabetic patients for the presence or absence of left ventricular dysfunction [24] so we suggest that this could explain the positive correlation between the dyspnea in our patient and the higher level of NT_ProBNP which could be due to clinically undetected left ventricular dysfunction.

This study reveal that hypertension is also positively correlated with dyspnea & level of NT-ProBNP which may also point out to the possibility that there is left ventricular dysfunction. Previous studies found that BNP and NT-proBNP plasma levels are higher in hypertensive than in normotensive patients [25, 26].

This study shows that the presence of ischemic heart disease in those dyspneic patient is strongly associated with high NT-proBNP level also with degree of dyspnea. This suggest the possibility that those patient have left ventricle dysfunction which is not detected clinically.

Several studies found that elevated levels of NT-proBNP predict cardiovascular morbidity and mortality, independent of

other prognostic markers, and identify at-risk individuals even in the absence of systolic or diastolic dysfunction by echocardiography [27, 28].

Conclusion

NT-proBNP measurement in patient with chronic dyspnea with no clinical evidence on conventional investigation is valuable in patients with underlying chronic disease as diabetes mellitus, hypertension and or ischemic heart disease suggesting that there is ventricular dysfunction. Although other element as age, BMI, sex which may also affect NT-ProBNP should be taken in consideration.

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