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Original research article

Study of N Terminal Pro Bnp Levels in Congestive Heart Failure

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Abstract

Background: Heart failure is one of the leading causes of morbidity and mortality in the populations across the globe, as it is a common end point of many diseases viz. coronary artery diseases, cardiomyopathies, hypertension and many others enumerated in the forthcoming sections. So methodical management of this ailment will play a vital role in preventing unnecessary mortality and morbidity.

Methods: Patients admitted in cardiology ward, All India Institute of medical sciences New Delhi, Study period Between September 2019 To June 2022 with reduced left ventricular ejection fraction on 2D echocardiography, were selected as cases. Forty patients diagnosed with congestive cardiac failure were selected as the cases. 40 subjects with normal 2D echocardiography with normal renal function tests, normal Hb%, normal BMI were selected as controls.

Conclusion: This study emphasizes the role of NT pro BNP in the diagnosis of congestive heartfailure. The level of NT proBNP rises exponentially with the onset of heart failure in contrast to BNP. So this creates a gross difference in blood values of NT proBNP in patients with congestive heart failure as compared to those without congestive failure.

Keywords: NT-proBNP; Congestive heart failure; NYHA; LVEF.

Introduction

Heart failure is one of the leading cause of morbidity and mortality in the populations across the globe, as it is a common end point of many diseases viz coronary artery diseases, cardiomyopathies, hypertension and many others enumerated in the forthcoming sections. So methodical management of this ailment will play a vital role in preventing unnecessary mortality and morbidity. Lot of research has been done in relation to better understanding of thepathophysiology of this disease as well as in the diagnostic and therapeutictechniques related to heart failure, till date. Echocardiography in particular has revolutionised the diagnosis of heart failure.

In the forthcoming sections we are focussing on a very simple and quick method of diagnosis of heart failure viz. NT-proBNP level estimation, which neither needs the echocardiography gadgets nor a skilled echotechnician/ cardiologist to interpret the echocardiographic images. This might prove very handy especially in situations where cardiologists and echocardiography are not accessible. Apart from diagnosis it may as well be used for follow up as well asfor prognostication. So, our efforts are towards making diagnosis of heart failure more simpler.

Objectives

To look for correlation of the NT-proBNP levels and the NYHA class of Heartfailure.
To look for the role of other variables, such as age, on the levels of NT-proBNPin a patient with heart failure.

Review of Literature

Heart failure, a complex clinical syndrome, arises from a process of ventricular dysfunction (acute or chronic), where the venous return to the heart is normal but the heart is unable to pump sufficient blood to meet the body's metabolic needs at normal filling pressures. Ventricular systolic dysfunction is characterized by a loss of contractile strength of the myocardium accompanied by "compensatory" ventricular hypertrophy and/or dilatation (ventricular remodeling). Systolic ventricular dysfunction due to focal loss of contraction can be dynamic and transient, as may occur with acute ischemia. With restoration of metabolic requirements of an ischemic segment of myocardium, either from restoring adequate coronary flow or reducing oxygen requirements, myocardial contraction may be restored. Sometimes restoration is delayed, so-called stunning. Chronically reduced coronary flow may be inadequate to preserve contraction but adequate for myocardial survival. Such persistent depression of the myocardium has been termed hibernation; with reperfusion, contractility may recover over time. As ventricular dysfunction proceeds, there is activation of the sympathetic and renin-angiotensin-aldosterone systems; this, although meant to physiologically augment contractility and heart rate in the former system and to preserve salt and water balance in the latter, contributes to further cardiac remodeling, peripheral vasoconstriction with sodium retention, and progressive cardiomegaly. Heart failure is also generally associated with a very poor prognosis, even when symptoms are mild. Systolic left ventricular (LV)dysfunction or failure reflects a decrease in normal emptying capacity [usually with an ejection fraction (EF) of45 percent or less] that is usually associated with a compensatory increase in diastolic volume. Isolated diastolic ventricular dysfunction or failure is present when the filling of one or both ventricles is impaired while the emptying capacity is normal. Despite many recent advances in the evaluation and management of HF, the development of symptomatic HF still carries a poor prognosis. Community- based studies indicate that 30-40% of patients die within 1 year of diagnosis and 60–70% die within 5 years, mainly from worsening HF or as a sudden event(probably because of a ventricular arrhythmia). Although it is difficult to predict prognosis in an individual, patients with symptoms at rest [New York Heart Association (NYHA) class IV] have a 30–70% annual mortality rate, whereas patients with symptoms with moderate activity (NYHA class II) have an annual mortality rate of 5-10%. Thus, functional status is an important predictor of patient outcome.[1,2] In mice BNP gene knockout leads to cardiac fibrosis, gene over-expression to hypotension and bone malformations. BNP is cleared from plasma through binding to the natriuretic peptide clearance receptor type C, but it seems relatively resistant to proteolysis by neutral endopeptidase NEP 24.11. Clearance mechanisms for NT-proBNP await further study. While the plasma concentrationof NT-proBNP and BNP is approximately equal in normal controls, NT-proBNP plasma concentration is 2–10 times higher than BNP in patients with heart ailure.

This relative change in peptide levels may be explained by shifts in cardiac secretion and/or clearance mechanisms.[3,4,5,6,7] Due to better stability in circulating blood, measurement of N-terminal proBNP (NT-proBNP) may be a more discerning marker for the detection and evaluation of chronic heart failure. The half-life of BNP is only 22 min, whereasthe half-life of NT-proBNP is much longer, ~120 min with a normal glomerular filtration rate.[8] Heart failure. Among those with acute heart failure, a presentingNT pro-BNP concentration of >5180 pg/ml was strongly predictive of death by76 days.[9] Another study, showed that a raised NT pro BNP (>357 pmol/L) identified patients with acute LVF of <40% with a sensitivity of 73% and specificity of 82%. The negative predictive value of having a NT pro BNP concentration below 357 pmol/L was 98%.[10] A study showed that at cut points of >450 pg/ml for patients <50 years ofage and >900 pg/ml for patients >50 years of age were highly sensitive and specific for diagnosis of acute CHF ($p<0.001$). An NT-proBNP level < 300 pg/ml was optimal for ruling out acute CHF, with negative predictive value of 99%. NT-proBNP testing alone was superior to clinical judgement alone for diagnosing acute CHF.($p <0.001$).[11] NT-proBNP plus clinical judgement was superior to NT-proBNP or clinical judgement alone. So it concluded that NT-proBNP measurement is a valuable addition to standard clinical assessment for the identification and exclusion of acute CHF in the emergency department setting.[12] In a pooled analysis from a large sample of 3051 subjects, out of which10% (305) had significant LV dysfunction and 1% had heart failure, the median concentrations of NT-proBNP in normals was 20 pg/ml, 117.3 pg/ml in those with significant LV dysfunction, 269.6 pg/ml in those with heart failure ($p< 0.001$).[13] A study revealed 1 year mortality rates of 7.0% and 21.6% in patient with NT-proBNP levels <1767 and >1767 pg/ml respectively. Thus, the risk of deathwas 2.7 fold higher for the patients with baseline NT-proBNP values above the median (95% CI, $p=0.001$).[14] As eGFR decreases with age, old age too causes comparatively higher levels of NT-proBNP than in younger patients.[15,16] Another drawback in taking NT-proBNP as a marker of LVdysfunction is that it can be raised even in pure RV failure as well as in pulmonary embolism.[24] Critically ill patients with sepsis also have elevated NT-proBNP levels.[17,18]

Material and methods

Simple random sampling, Patients admitted in cardiology ward, All India Institute of medical sciences, new Delhi. with reduced left ventricular ejection fraction on 2D echocardiography, were selected as cases. 40 patients diagnosed with congestive cardiac failure wereselected as the cases. 40 subjects with normal 2D echocardiography with normal renal function tests, normal Hb%, normal BMI were selected as controls.

Inclusion Criteria

Patients admitted in AIIMS, New delhi, diagnosed with clinical evidence of congestive heart failure with confirmation on 2D echocardiography.

Exclusion Criteria

Patients with abnormal renal function tests.
Obesity
Anemia

Data were collected in a pre tested proforma, including detailed history, clinical examination, and relevant investigations after consent.

Patients were subjected to the following investigations:

Hb%, Total count, ESR, Serum Urea, Serum Creatine, Serum Electrolytes, Liver function tests, Fasting Lipid Pfofile, Urine albumin,sugar and microscopy, Electrocardiography, Chest X ray, 2D echocardiography

Results

A total of 40 cases of CHF were included in the study, out of which 11 were acute CHF and 29 were chronic CHF. Serum NT proBNP levels were measured for all of them. The median value of NT proBNP was 2294 pg/ml in a total of 11 cases of Acute heart failure. The median value was 3450 pg/ml in29 patients with chronic heart failure. The median of acute and chronic heart failure cases taken together was 3193 pg/ml. Among the controls the median value was <20 pg/ml. Clearly the cases had elevated blood levels of NT proBNP as compared to controls. Chronic cases had higher values.

Table 1: Median values of NT-proBNP

Category	values of NT proBNP(in pg/ml)
Acute heart failure	2294
Chronic heart Failure	4422
Acute and chronic failure	3193
Controls	<20

Table 2: Age distribution of cases and controls

Age group (years)	Cases		Controls		Total	
	No.	%	No.	%	No.	%
21-40	3	7.5	6	15	9	11.3
41-60	19	47.5	17	42.5	36	45
60+	18	45	17	42.5	35	43.7
Total	40	100	40	100	80	100

p=0.566

47.5% of the cases were in the range of 41-60 years, 45% were in the rangeof 60 above. Age matched controls were taken for the study.

Table 3: LVEF in cases and controls

LVEF	Cases		Controls		Total	
	No.	%	No.	%	No.	%
<30	21	52.5	0	0	21	26.3
31-40	16	40	0	0	16	20
40+	3	7.5	40	100	43	53.7
Total	40	100	40	100	80	100

p=0.000

52.5% of the cases had left ventricular ejection fraction less than 30%.40% of patients had EF between 31 and 40% and 7.5% patients had EF between 40 and 50%.

Table 4: NT proBNP levels in cases and controls

NT proBNP (pg/ml)	Cases		Controls		Total	
	No.	%	No.	%	No.	%

<1000	7	17.5	40	100	47	58.8
1001-2000	10	25	0	0	10	12.5
2001-10000	15	37.5	0	0	15	18.7
>10000	8	20	0	0	8	10
Total	40	100	40	100	80	100

p=0.000

37.5% of the cases had values of NT pro-BNP between 2000-10,000 pg/ml.25% of cases had values between 1000-2000 pg/ml. 20% of cases had values>10,000 pg/ml. 17.5% of cases had values <1000 pg/ml and among them only onepatient had value less than 100 pg/ml. All controls had values less than 100 pg/ml.

Table 5: Serum NT-proBNP levels and the NYHA grade of CHF

	NT pro- BNP (pg/ml)				**Total**
	< 1000	**1001-2000**	**2001-10000**	**>10000**	
Grade 2 Count % of GRA.H	1 25.0%	1 25.0%	1 25.0%	1 25.0%	4 100.0%
Grade 3 Count % of GRA.H	6 20.7%	7 24.1%	11 37.9%	5 17.2%	29 100.0%
Grade 4 Count % of GRA.H	0 0%	2 28.6%	3 42.9%	2 28.6%	7 100.0%
Total Count % of GRA.H	7 17.5%	10 25.0%	15 37.5%	8 20.0%	40 100.0%

71% of patients with grade 4 NYHA failure had NT pro-BNP values above 2000 pg/ml. 55% of patients with grade 3 NYHA failure had NT pro-BNP valuesof 2000 pg/ml, and 45% of grade 3 NYHA failure had NT pro-BNP values between 100 and 2000 pg/ml. 50% each of patients with grade 2 NYHA failure had values below and above 2000 pg/ml. 78% of the patients with LVEF<30% had NT pro-BNP levels >2000 pg/ml, 22% cases had values < 2000 pg/ml. 37% of patients with EF of 30-40%had >2000 pg/ml, 63% of patients with LVEF 31-40% had NT pro-BNP levels <2000 pg/ml. There were three cases of LVEF >40% in the study and one had <2000 pg/ml while two others had > 2000 pg/ml.

Discussion

In present study the median concentration of NT proBNP were 2624, 3193 and <20 pg/ml amongst the acute CHF, chronic CHF and controls. Januzzi et al[11]. study showed that for diagnosis of acute CHF cut off of >450 pg/ml and >900 pg/ml for <50 year and >50 year group respectively were highly sensitive and specific. McDonough et al[13]. study had median NT proBNP values of
269.6 pg/ml congestive heart failure.

Table 6: Median serum NT-proBNP levels

	NT proBNP median values (pg/ml)	
	esent study(n=40)	**nough et al study(n=3051)**

CHF	3193	269.6
Controls	<20	20

Yoshihiko et al. showed that blood level of NT proBNP rises exponentially with clinical grade of heart failure: Levels in class II NYHA CHF were 25 times more than in class I NYHA. Levels in Class III NYHA CHF cases were 100 times more than in Class I NYHA. In the present study 29 cases were grade III NYHA, 7 cases were Grade IV NYHA and 4 were Grade II NYHA CHF. The higher median value in the present study thus could be because most of the cases were grade III or IV NYHA congestive heart failures. Among cases 11 cases were acute heart failure, and their median value was 2294 pg/ml. Among the 29 chronic heart failure cases the median was 4422 pg/ml. Thus chronic cases had more median value than the acute cases. There were 7 cases who had values less than 1000 pg/ml, out of which one was acute and others were chronic. This probably could be explained becausemany of the chronic cases were already begun on treatment by the time they were referred to the tertiary centre. Studies have shown that the valuesstart dropping significantly if heart failure is optimally treated. In this study we had higher values of NT proBNP in patients of age above60 years as compared to those below 60 years: 56% of patients below 60 years had values above 2000 pg/ml, whereas 73% of patients aged above 60 years had values above 2000 pg/ml.Bay et al[10]. showed higher values of NT proBNP in elderly patients. The cause of which was attributed to poorer GFR in elderly patients. Thus this justifies that age could behave as a confounding factor provided a different cut off wastaken for elderly and others.

Table 7: Mean serum NT-proBNP in people>60 years and < 60 years

	Present study (n = 40)	Yoshihiko et al (n = 390)	Bay et al (n = 2193)
Mean NT proBNP values in >60 yearsas compared to <60 years	Higher	Higher	Higher

This study had fairly equal proportion of male and female cases. There was no significant difference in the NT proBNP values among males and females for a given NYHA class heart failure and for a given LVEF. Studies done by Yoshihikoet al[5]. showed significant higher values in females for a given class of heart failure. Present study shows correlation between levels of NT proBNP and the duration of exertional breathlessness which is a cardinal symptom of congestiveheart failure. Exertional breathlessness was a presenting complaint in 39 out of the 40 cases in the present study. 60% of patients having breathlessness for more than1 year had NT pro BNP values greater than 2000 pg/ml and majority of them had values >10,000 pg/ml. 57% of patients with breathlessness of duration of 1-12 months had values >2000 pg/ml and majority of them had values between2000 and 10,000 pg/ml. 50% of the patients having breathlessness for 1 to 4 weeks had values between 1000-2000 pg/ml. This prompts at a prospect of using this marker to not only classify severity of heart failure but also as a markerof duration of heart failure. As of now no studies have compared levels of NT proBNP levels in Acute and Chronic heart failure cases.

Table 8: Serum NT-proBNP values in various NYHA grade of CHF

	Grade II NYHA CHF	**Grade III NYHA CHF**	**Grade IV NYHA CHF**

Median NT proBNP levels in present study	2491	2953	7329
Mean NT pro BNP levels in study at Iowa	1666	3029	3465

In the present study there is a correlation between the LVEF and the NT proBNP levels in the plasma. 71% patients having LVEF of <30% had NT pro-BNP levels above 2000 pg/ml, 63% of patients with LVEF of 31-40% had NT pro-BNP levels between 1000 and 2000 pg/ml. These results are in tune with PRIDE study and Yoshihiko et al[5]. study.

Conclusion

Present study emphasizes on the role of NT proBNP in the diagnosis of congestive heart failure. The level of NT proBNP rises exponentially with theonset of heart failure in contrast to BNP. So this creates a gross difference in blood values of NT proBNP in patients with congestive heart failure as compared to those without congestive failure.

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