Original Article

B-Natriuretic Peptide Level as a Predictor for the Severity of LV Dysfunction

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Summary:

Background:
B -Natriuretic peptide is a neurohormone normally synthesized in ventricular heart muscle and known to be released in situations when left ventricular wall stress increases, it has a variety of physiological functions on its own, that are thought to be compensatory.

Objective:
The aim of this study was to apply B-natriuretic peptide (BNP) as a biomarker and to correlate its levels with the severity of heart failure using certain selected parameters as indicators of cardiac function.

Patients and Methods
Forty Six (46) patients with provisional diagnosis of heart failure were chosen for this work, thirty six (36) males and ten (10) Females, their age ranged between 33 and 80 Years. All underwent complete physical examination and ECG tracing together with ECHO/DOPPLER examination for heart failure.

Eleven (11) healthy Subjects were chosen as control group for purpose of comparison.

The patients were divided into groups, according to Age , Gender, BMI, whether they had the following selected associated diseases: (IHD, hypertension, and diabetes mellitus), smoking habit, Drugs intake, cardiac chambers dilatation including (LV in systole and diastole, RV, and LA), EF%, FS%, degree of diastolic impairment, LV Segmental wall motion abnormalities.

Five ml (5ml) specimen of venous blood were aspirated from each patient, and also the control group for estimation of BNP level, using ELIZA technique.

Results
There was a significant difference in mean serum BNP levels between cases of congestive heart failure and control group. Considering the subject as a positive for heart failure if his BNP level was ≥ 375pmol/l, at this cutoff value there will be a sensitivity of 80.4% and specificity of 100%. Also the study showed highest values of mean BNP in those patients having restrictive pattern of diastolic dysfunction.

Conclusion:
BNP was used as a biomarker for the first time in Iraq to diagnose congestive heart failure. The role of BNP as a guide to determine the severity of heart failure and the efficacy of treatment was promising, so BNP fulfill most of the criteria in patients with suspected heart failure.

At this point it was found that the mean of the right ventricular dimensions were significantly higher in the group with highest BNP quartile compared to lowest quartile BNP group, probably reflecting more severe form of impaired cardiac function and heart failure, a finding which has not been mentioned in any earlier studies in the same field.

Keywords: BNP, LV-Dysfunction, heart failure

Fac Med Baghdad 2007; Vol.49, No.4
Received July 2006
Accepted Jun.2007

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Introduction:

Natriuretic peptide hormones are a family of vassoactive peptides with many favorable physiological properties. They have been emerged as important candidates for the development of diagnostic tools and therapeutic agents in cardiovascular diseases for the particular diagnosis of heart failure and left ventricular dysfunction. Circulating BNP and its N-terminal fragment ANP are the best active representatives of this family [(1)].

The existences of various natriuretic hormones have been postulated for some time. Two of these are secreted by the heart, in the atria and ventricles that contain secretary granules which usually increase in number when sodium chloride is increased and the extra cellular fluid expanded leading to natriusis[(2)].

In 1990, a third member of this family was identified and called C-type natriuretic peptide (CNP) which is structurally distinct from ANP and BNP, and expressed two much greater extent in the central nervous system and vascular tissues than the heart[(3)].

The stimulus for ANP and BNP release is myocyte stretch rather than transmural pressure. Both hormones are synthesized as amino acid precursor proteins and undergo intracellular modifications to pro hormones [(4)].

Although ANP concentrations are more closely related to left arterial pressure and BNP to left ventricular pressure and volume indices [(5)]. Some overlap between sites of release exists.

In addition to primary regulation via myocyte stretch natriuretic peptide synthesis can be augmented by tachycardia [(6)], glucocorticoides[(7)], thyroid hormones and vassoactive peptides such as endothelin-1 and angiotensin-II.

BNP predicts disease state and prognosis better than ANP or N-terminal ANP[(8)]. N-terminal BNP seems to provide much the same information as BNP and assays for N-terminal BNP are also now available commercially[(9)].

Recently measurement of circulating levels of BNP has become available as means of identifying patient with elevated left ventricular filling pressure that are likely to exhibit signs and symptoms of heat failure. However BNP has been widely investigated as a biochemical marker of morbidity and mortality with known heart failure and as aid in differentiating dyspnia due to other causes in an emergency setting[(10)].

The aim of this study is to use B-natriuretic peptide (BNP) as a biomarker and to correlate its levels with the severity of heart failure using certain selected parameters as indicators of cardiac function and in comparison with control group trying to find a cutoff value that can differentiates between patients with congestive heart failure and those who have other diseases that mimic heart failure in symptoms and signs.

Subjects and methods

Data of this study were obtained from 46 patients with heart failure who underwent complete physical examination and ECG tracing by physicians at the Medical City Teaching Hospital. They were selected from 294 examined patients who only satisfied the criterion of having EF<35% to get the optimized results.

Thirty six of the patients were male and 10 were females. Their ages ranged between 33 and 80 years with a mean age of 57±23 years. Eleven healthy subjects were chosen as control subjects all of them were males and their ages ranged between 32-75 years with a mean age of 56±21 years.

The patients were divided into groups, according to Age, Gender, BMI, whether They have the following Selected associated diseases, (IHD, hypertension, and diabetes mellitus), smoking habit, Drugs intake, cardiac chambers dilatation including The (LV in systole and diastole, RV, and LA), EF%, FS%, degree of diastolic impairment, LV Segmental wall motion abnormalities, secondary findings (including mitral valve regurge, tricuspid valve regurge, aortic regurge and pericardial effusion).

Five mls specimen of venous blood were aspirated from each patients and control subject for estimation of BNP level using ELISA technique. The kit was supplied by Biomedica-Viena

ECHOCARDIOGRAPHIC test (figure 1): imaging was done for each subject using commercial instruments , with electronic phased array transducer 2.5MHz , Voluson 530D type supplied by Kretz technique company.

Transthoracic 2-D guided M-mode and Doppler Echocardiograms were recorded, all

patients were examined in the left lateral decubitus position, Measurements were obtained by way of standards recommended by the American Society of Echocardiography[11].

Measuring the left ventricle internal dimensions in end diastole and end systole. The fractional shortening (FS %), ejection fraction (EF %). LV volumes at end systole and diastole were obtained.

The M-mode method can be used only in patients with symmetrically contracting ventricle as the M-mode samples only the septum and free wall at mid ventricle level.

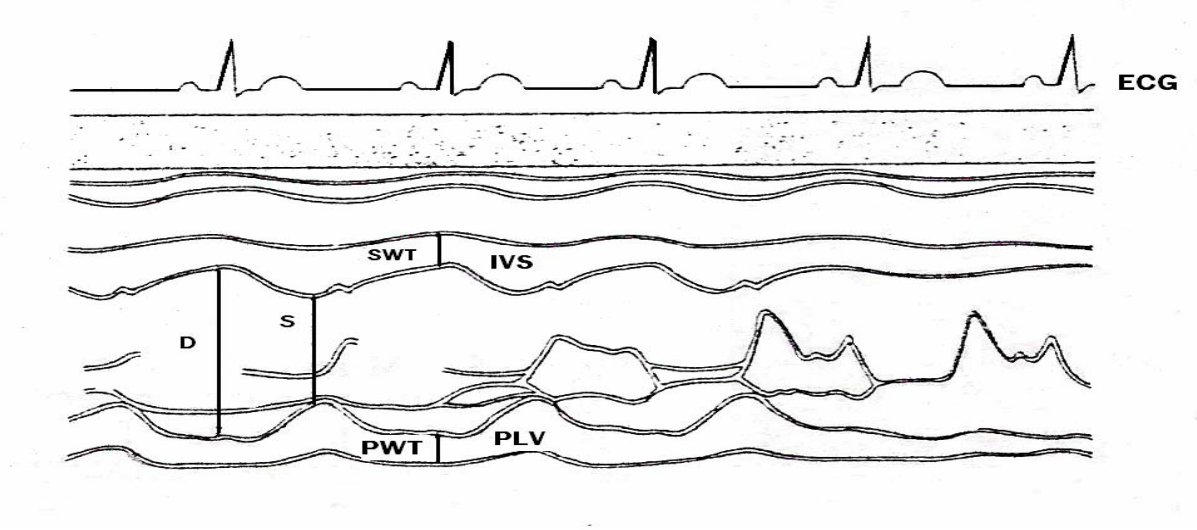

Figure 1: Diagram of M-mode ECG demonstrating the LV measurements as recommended by American Society of ECG.

D=LV diastolic dimension; S=LV systolic dimension; SWT=septal wall thickness; IVS= interventricuar septum PWT= posterior LV wall thickness; PLV= posterior LV wall [11].

In this study we used the four chambers view, for asymmetrically Contracting Ventricle (in IHD), by tracing the endocardium of the LV at end systole and end diastole, and Estimating the Maximal length of LV (figure 2).

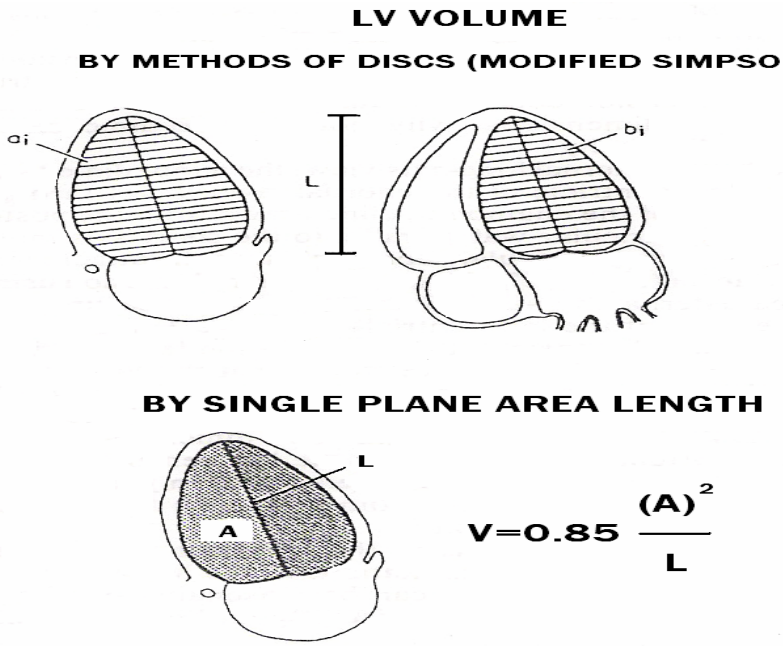

Figure 2:
Diagram demonstrating how LV volume can be measured using the modified Simpson's rule technique and by single plain area length method[11].

Pulsed wave Doppler examination of the mitral valve is used. The transducer is at /or slightly medial to the apex, directed backward slightly medially and upward.

The two-dimensional echocardiogram is an apical of two or four chambers views. The examination is optimized for the best possible Doppler recording, then the degree of diastolic impairment (mainly estimating the E/A ratio, and E deceleration time) would be assessed.

The presence of associated secondary findings including mitral, tricuspid and aortic valves regurge, color flow mapping in the same views is used.

All statistical analysis have been made by applying the excel program 2002 (10.2614.2625), t-test was applied to estimate the significancy. P value was taken to the closest ($P<0.05$).

Results

The mean serum BNP level of 550.3pmol/l in cases with heart failure is significantly higher than control 220.5pmol/l. Table (1)

Table 1: The case –control difference in mean BNP(pmol./l)

	Serum BNP			
Groups	range	mean	SD	N
Control	95-350	220.5	78.2	11
patients	200-900	550.3	192.6	46

Table 2 shows the differences in mean BNP in cases with heart failure by selected explanatory variables.

Table 2: The difference in mean BNP in cases with heart failure by selected explanatory variables

	Serum BNP level (pmol./l)		
Age in years	Range	Mean±SD	N
<50	300-875	556.3±186.5	8
50-59	200-750	429.3±163.2	15

60+	200-900	627.2±178	23
Gender			
Female	300-900	567.5±216	10
Male	200-875	545.6±188.7	36
IHD			
Negative	200-900	580.1±181.6	35
Positive	200-750	455.5±204.5	11
Hypertension			
Negative	200-875	547.9±189.4	40
Positive	300-900	566.7±231.7	6
DM			
Negative	200-900	561±183	40
Positive	200-875	479.2±256.1	6
Smoking habit			
X-smoker	200-875	486±203.3	10
Non-smoker	200-900	570.4±200.4	26
Heavy smoker	250-750	562.5±163.4	10

Table 3 shows the difference in mean BNP in cases with heart failure by type of drug intake

Table 3: The difference in mean BNP in cases with heart failure by type of drug intake

	Serum BNP level (pmol./l)		
Drug intake	Range	Mean±SD	N
Negative	400-875	623.2±142.4	11
Positive	200-900	527.4±202.2	35
Anti-anginal drugs (nitroglycerines)			
Negative	200-900	581.4±179.2	36
Positive	200-750	438.5±206.9	10
Diuretics in general			
Negative	200-900	560.4±190.3	27
Positive	200-875	536.1±200.1	19
ACE inhibitors			
Negative	200-900	593.1±214.7	27
Positive	250-750	489.5±139.8	19
Aspirin			
Negative	300-900	587.7±155.2	30
Positive	200-875	480.3±238.2	16
Digoxin			
Negative	200-875	551±186.7	41
Positive	200-900	545±262.4	5

Table 4: The relative frequency of selected LV wall motion abnormalities patters as shown by ECG in a sample of cases with heart failure

Abnormal cardiac motility pattern (n=46)	N	%
Hypokinesia	13	28.3
Akinesia	4	8.7
Dyskinesia	2	4.3
Any of the above 3 abnormalities	15	32.6

Table 5: The difference in mean BNP in cases with heart failure by selected explanatory variables

	Serum BNP level (pmol./l)		
Severe diastolic impairment (E-declaration time < 150ms)	Range	Mean±SD	N
Negative	200-750	534.4±187.9	31
Positive	200-900	583.3±204.6	15
Restriction pattern (E/A ratio > 2)			
Negative	200-875	478.2±172.3	25
Positive	260-900	636.2±183.3	21
Wall motion abnormalities			
Negative	200-900	584.8±192.1	31
Positive	200-875	479±179.1	15

Table 6: The difference in mean BNP in cases with heart failure by E-declaration time and E/A ratio

	Serum BNP level (pmol./l)		
E-declaration time (ms)	Range	Mean±SD	N
Abnormally low (< 150)	200-900	583.3±204.6	15
Within normal	200-875	553.1±186.8	27
Abnormally high (>240)	250-600	407.5±161.9	4
E/A ratio			
Abnormally low (< 1)	200-750	472.7±169.4	11
Within normal (1-2)	200-875	482.5±180.9	14
Abnormally high (>2)	260-900	636.2±183.3	21

From the ROC (receiver operator characteristics) curve (figure 3) the optimum cutoff value for separation between cases and control was 375pmol/l.

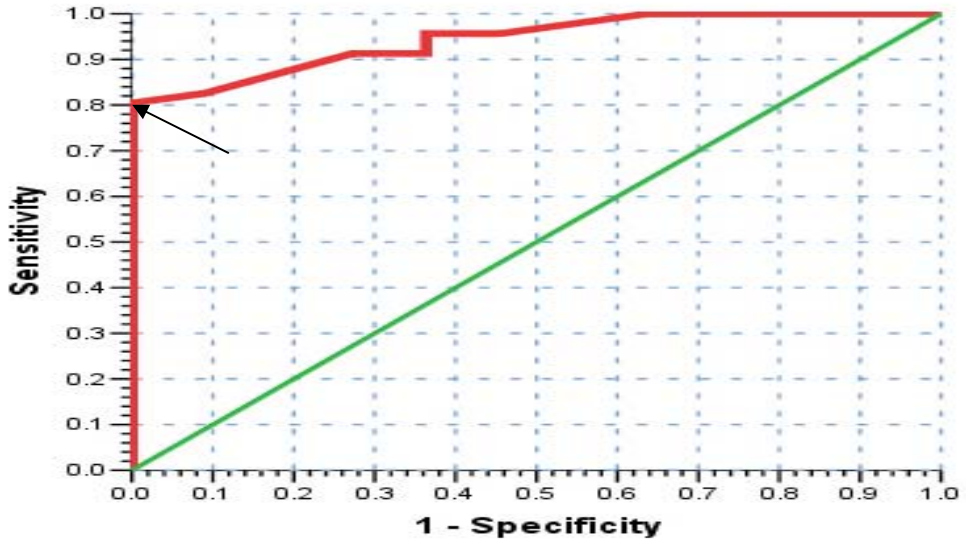

Figure 3:ROC curve showing the trade-off between sensitivity (rate of true positive) and rate of false negative (1-specificity) for serum BNP in differentiating between cases with severe heart failure and controls.

Area under the ROC = 0.94 P<0.001

This curve shows the relation between sensitivity (rate of true positive) and rate of false negative (1-specificity) for serum BNP in differentiating between cases with heart failure and healthy controls. The figure also shows valid parameters of serum BNP in differentiating between cases with heart failure and healthy control groups. A positive test of this cutoff value would establish diagnosis of heart failure with 100% confidence at any pre test probability (any level of clinical suspicion of heart failure). A negative test result would exclude the possibility of heart failure. in clinical situation of uncertainty (50% pre test probability , negative predictive value), this parameter would give 83.6 confidence to exclude heart failure with 100% confidence a subject would have a BNP level less than 190 pmol/l .

An area of overlap is present between cases and control groups and are limited between 190-375pmol/l of serum BNP levels. As shown in figure 4. In this area we may find less sever cases of cardiac failure.

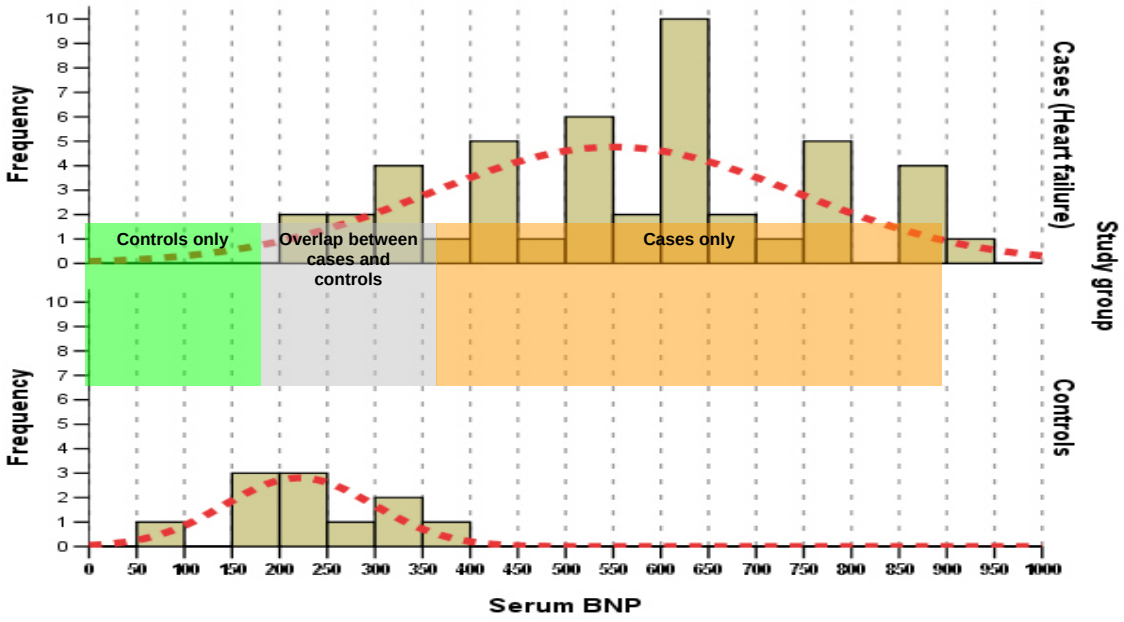

Figure 4: Validity of parameters of serum BNP in differentiating between cases with heart failure and healthy control groups.

Table 7 shows the variations of selected parameters among different gradients of serum BNP levels with heart failure. This table shows the relation of serum BNP level with the following parameters:

Left atrium (LA), left ventricular end diastolic dimension (LVEDD), left ventricular end systolic dimension (LVESD), ejection fraction (EF%), fractional shortening FS% BMI and right ventricular dimension. The patients' groups were divided according to their BNP levels into, lowest quartile BNP<400pmol/l their number was 9, interqurtile BNP level 400-649pmol/l the pateints' number was (24) and highest quartile (BNP≥650pmol/l the pateints' number was (13). It is found from this table that there is no significant correlation between BNP levels and estimated parameters except the mean of the right ventricular dimension. They were significantly higher (29mm) in the group with highest BNP quartile to lowest quartile BNP group (24.7mm)

Table 7: The difference in mean of selected parameters between different gradients of serum BNP in cases with heart failure

	Serum BNP level (pmol./l)		
	lowest quartile <400 (n=9)	interqurtile 400-649 (n=24)	highest quartile ≥650 (n=13)
Fractional shortening %			
Range	12-17	11-17	12-16
Mean±SD	14.4±1.9	14.2±1.6	14±1.4
Left atrial dimension(mm)			
Range	43-60	32-64	32-64
Mean±SD	49±5.2	49±7	51.2±9.7

Left ventricle end diastolic dimension (mm)			
Range	59-83	57-84	59-78
Mean±SD	68.7±8	69.3±7.5	66.2±6
Left ventricle end systolic dimension (mm)			
Range	49-72	49-75	50-68
Mean±SD	58.4±7.5	59.1±7.2	56.6±5.6
Ejection fraction%			
Range	26-35	24-35	26-32
Mean±SD	30±3.5	30±3.3	29.2±2.3
Right ventricle dimension(mm)			
Range	22-29	23-41	23-40
Mean±SD	24.7±1.9	27.9±4.6	29±5.2
Body Mass Index (BMI)			
Range	21-32.8	17.7-40.5	19.5-41.7
Mean±SD	27.4±3.9	26.4±4.9	25.5±6.1

Discussion

Currently, identification of heart failure is based on comprehensive history and physical examination combined with diagnostic tests such as ECG , chest X-ray and an assessment of left ventricular function[12] .

A simple, rapid cost effective test for the accurate diagnosis of heart failure based on symptoms of dyspnea, fatigue and signs of fluid overload remain a major clinical challenge.

Natriuretic peptide hormones, a family of vasso active peptides have emerged as important candidate for development of diagnostic tools and therapeutic agents in cardiovascular diseases for diagnosis of heart failure and left ventricular dysfunction, where few focus on the measurement of circulation BNP and its N-terminal fragment of pro-hormone[13].

It was shown that BNP concentrations were highest in those with decompensated heart failure, intermediate in those with known left ventricular dysfunction but with no acute exacerbation, and lowest in those without heart failure of left ventricular dysfunction[10]. This can be seen in table 1, where the mean serum BNP level of patients was 550.3±192.6pmol/l, while the mean value of the control subjects was 220.5±78.2pmol/l. Restriction the analysis to participants of age 55 years old and older improve the sensitivity for cases greater than 60years of age.

BNP concentration falls after treating patients of congestive heart failure with loop diuretics and ACE inhibitors reflecting a reduction in left ventricular filling pressure[14], and that goes with the results of our series. Table (4). Meanwhile patients who had doses of ACE inhibitors titrated to achieve the lower BNP concentration had significantly greater reduction in heart rate than did patients treated traditionally as can be noted in table 3.

This means that BNP could ultimately prove to be useful in helping physicians to select the appropriate drug and dose. On the other hand it was found that in ischemic cardiomypathy, raised plasma concentration of natriuretic peptides where associated with poor long term prognosis, while the presence of contractile reserve is a favorable sign, plasma concentrations of these natriuretic peptides where raised in patients with left ventricular dysfunction which is associated with long term prognosis. Also it was found that in patients with depressed left ventricular function, the

presence of improved function during doputamin infusion (contractile reserve) was thought to be associated with a better prognosis than in patient without contractile reserve. So, it would be of interest to evaluate whether there are differences in plasma levels of natriuretic peptides in patients with heart failure with or without contractile reserve[13].

The findings in table (4) and (5) suggest that there may be still a contractile reserve in those patients and /or complete left ventricular adverse modeling has not occurred. Diastolic dysfunction is involved in estimated 40-50% of patents with heart failure [12] . Although BNP levels increases in both systolic and diastolic heart failure, it dose not clearly differentiate between the two. In general the BNP levels associated with systolic dysfunction run higher than that associated with pure diastolic dysfunction [15]. The highest values of mean BNP were found in those who have restrictive patterns of diastolic dysfunction. while other forms of diastolic impairment as E declaration time and E/A radio have lower levels o mean BNP concentrations reflecting that mean BNP level is heist among more sever forms of impaired diastolic functions as seen in tables 5 and 6.

In the ROC (recover operator characteristics) curve, (figure 3) the optimum cutoff value for separation between cases an control was 375pmol/l, considering a subject as positive for heart failure if his BNP level was equal or less than 375pmol/l. at this cutoff value the test would have a sensitivity of 80.4% and specificity 100%.

In this series, a positive test at this cutoff value would establish a diagnosis of heart failure with 100% confidence at any pre test probability (any level of clinical suspicion of heart failure) a negative test result would exclude the possibility of heart failure.

In clinical situation of uncertainty (50% pre test probability, negative predictive value) this parameter with give 83.6% confidence. to exclude sever heart failure with 100% confidence a subject would have a BNP level less than 190pmol./l while at specificity ≥90.9% the cutoff value would be 325pmol/l, which is close to the figures of other studies[16].

An area of overlap present between patients and control groups are limited between 190-375pmol/l of serum BNP levels in this area we may find cases with lesser severity of cardiac failure , the judgment depending partially on clinical diagnosis whether they are negative predictive e value or positive predictive value at pretest probability.

In conclusion" BNP has been used for the first time in Iraq as a biomarker to diagnose congestive heart failure. For a biomarker to be valuable in clinical practice it should be easily measurable rapidly and accurately at a reasonable coast with a normal value <190pmol/l and a cutoff value of 375pmol/l with a sensitivity of 80.4 % and specificity 100%. Its role as a guide to determine the severity of heart failure and the efficacy of treatment, type of drugs and drug doses is promising. So BNP and N-terminal BNP fulfill most of these criteria in patients with suspected heart failure.

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