# Relation between Brain Natriuretic Peptide (BNP) and Congestive Heart Failure among Hypertensive Patients in Gaza Strip.

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## Abstract:
Brain natriuretic peptide (BNP) has been established as a new and reliable laboratory marker for congestive heart failure (CHF). BNP is a neurohormone secreted by the cardiac ventricles in response to volume expansion and pressure overload. This study aimed to ascertain whether an association exists between the level of BNP hormone and CHF among hypertensive patients. Retrospective design (case–control study) was used to collect data from 75 patients with CHF and history of hypertension (case group), and 75 patients with history of hypertension only (control group). CHF subjects consisted of fourteen subjects with acute heart failure, and fifty six subjects with chronic heart failure. CHF group was also classified into four classes; the diagnosis and classification of CHF were done according to the New York Heart Association (NYHA) by two cardiologists. Self report structure interview and Ethylenediamine tetracetic acid (EDTA) blood samples were obtained from both groups. In this study we used Abbott AxSYM in conjunction with a recently available immunoassay kit for BNP hormone MEIA (Microparticles Enzyme Immuno Assay) system. T-test, Kruskal-Wallis and ANOVA-I were used to analyze the data. The results of the study showed a significant relationship between BNP hormone and CHF (P value = 0.00). The obtained data suggest that the measurement of BNP levels may be helpful in the diagnosis and prognosis of CHF and in selecting patients for further evaluation.

**Key words: Brain natriuretic peptide, congestive heart failure, hypertension.**

## العلاقة بين الهرمون البيبتيدي المدر للصوديوم نوع "ب" (BNP) و فشل القلب الاحتقاني عند مرضى ضغط الدم المرتفع في قطاع غزة.

**يعتبر الهرمون البيبتيدي المدر للصوديوم نوع "ب" (BNP) مؤشر مخبري جديد للكشف عن فشل القلب الاحتقاني. ويفرز هذا الهرمون من بطيني القلب كاستجابة لتضخم القلب وارتفاع الضغط على القلب. وتأتي هذه الدراسة للتحقق من العلاقة بين مستوى هذا الهرمون وحدوث فشل القلب الاحتقاني لدى مرضى ضغط الدم المرتفع.**
**شملت الدراسة مجموعتين: الاولى (عينة الدراسة) تكونت من ٧٥ مريض يعانون من فشل القلب الاحتقاني وضغط دم مرتفع، والمجموعة الثانية (العينة الضابطة) تالفت من ٧٥ مريض يعانون من ضغط دم مرتفع. عينة الدراسة تضمنت ١٤ مريض فشل قلب احتقاني حاد و٥٦ فشل قلب احتقاني مزمن. كما تم تصنيف عينة الدراسة إلى أربع اقسام وفقا لتصنيف جمعية نيويورك للقلب من قبل طبيبين مختصين في الموضوع.**
**تم جمع البيانات اللازمة من خلال مقابلة المرضى وتعبئة استبانه. وتم سحب عينات دم من جميع المرضى لفحص الهرمون. تم قياس مستوى هرمون (BNP) باستخدام جهاز (AXSYM) وبنظام (MEIA).**

**تم تحليل البيانات والنتائج باستخدام الاختبارات الإحصائية اللازمة وأظهرت النتائج وجود علاقة ذات دلالة إحصائية بين مستوى هرمون (BNP) ومرض فشل القلب الاحتقاني وبذلك أظهرت الدراسة أهمية قياس هرمون (BNP) في تشخيص ومتابعة تطور هذا المرض وتحديد المرضى للمتابعة والتقييم.**

**الكلمات المفتاحية: الهرمون البيبتيدي المدر للصوديوم "ب"، فشل القلب الاحتقاني، ضغط دم مرتفع.**

## Introduction:

Plasma brain natriuretic peptide (BNP) is a novel cardiac hormone which was first isolated from the porcine brain and subsequently from the cardiac tissue of many species including humans. Although plasma brain natriuretic peptide (BNP) and atrial natriuretic peptide (ANP) have similar structures and functions, BNP is predominantly produced by the left ventricle, whereas ANP is mainly released from the atria. BNP plays an important role in the regulation of blood pressure and body fluid volume by its diuretic and natriuretic action as well as by arterial dilation and inhibition of the renin-angiotensin system. Plasma BNP concentration has been shown to be elevated in pathological conditions associated with pressure and volume overload, such as congestive heart failure (CHF) or essential hypertension, and the secretion of these natriuretic peptides is stimulated by cardiac wall stretch due to cardiac load [1].

Heart failure is a major public health problem in the United States. It affects nearly 5 million Americans and is responsible for approximately 1 million hospitalizations and 50,000 deaths each year [2]. The prevalence of symptomatic heart failure in Europe is estimated to be about 0.4–2% [3]. Heart diseases were the leading causes of death among Palestinian people aged 60 years and above with a proportion of 29.6% and hypertension disease with a proportion of 10.7% of total deaths. [4]. The aim of the present study was to ascertain whether an association exists between the level of BNP hormone and CHF among hypertensive patients.

## Materials and Methods:

This study presents a case-control study design in which the case group was CHF patients with hypertension (HTN) and the control group was hypertensive patients only. We studied three groups of subjects; the first group was a healthy subjects group that consisted of 20 healthy individuals (13 males and 7 females; with a mean age of 43.6 years). All subjects were free from acute diseases and denied any serious disease in the past as well as the use of any drug for at least 3 weeks prior to the study. Those subjects were used to test the method and to examine clarity of the questionnaire. The second group was a case group which consisted of 75 subjects aged 40 to 75 years with CHF and history of hypertension (35 males with a mean age of ~60.9 years and 40 females with a mean age of ~61.7 years) without history of other diseases particularly diabetes mellitus and renal failure. The last group was a control group and consisted of 75 subjects aged 40 to 75 years, with a mean age of 60.7 years with hypertension only (35 males with a mean age of ~60.6 years and 40 females with a mean age of ~59.3 years) without history of other diseases particularly diabetes mellitus and renal failure.

**Sample and sampling method:** One hundred seventy subjects participated in the study, 20 healthy subjects, 75 case group (CHF with a history of HTN) and 75 control group (HTN without history of other diseases) selected by simple random sample from the three main governmental hospitals in Gaza Strip which are Al-Shifa (63 patients), Nasir (10 patients) and the European Gaza Hospital "EGH" (2 patients). This number was determined on basis of data on CHF admission or readmission in CCU of the participating hospitals for heart failure. It was found that about 300 CHF subjects were admitted to CCU at Shifa Hospital during the period from 01/05/2003 –01/05/2005. According to patient information provided in the CCU record book, more than 200 subjects were excluded from the study due to different reasons.

Table 1 shows that the subjects in the case group consisted of 34 males (45.3%) and 41 females (54.7%). The control group was matched by age and gender with the case group in order to decrease confounding variables. The sample was divided into two categories according to age: 81.3% of the case group and 78.7% of the control group were older than 51 years and this classification is in agreement with most of the studies which proved that age is an important factor in CHF and HTN.

**Table 1:** Distribution of the case and control groups by age and gender.

| The Characteristic | | Case group | | Control group | |
|---|---|---|---|---|---|
| | | Number of subjects | % | Number of subjects | % |
| Gender | Male | 34 | 45.3 | 34 | 45.3 |
| | Female | 41 | 54.7 | 41 | 54.7 |
| Total | | 75 | 100 | 75 | 100 |
| Age | Less than 50 | 14 | 18.7 | 16 | 21.3 |
| | More than 51 | 61 | 81.3 | 59 | 78.7 |
| Total | | 75 | 100 | 75 | 100 |

**Ethical Considerations:** Objectives of the study were fully explained to all human subjects who participated in the study. Blood samples and patient information dealt with in the study were collected with informed consent of the participants and following clearance from the Helsinki Ethical Committee in Gaza.

**Instrument and measurement system**
Blood samples for testing BNP and face to face structural interviews were used to collect data from both patients and their families. In this study we used Abbott AxSYM kit, a recently developed immunoassay for BNP, based on **M**icroparticles **E**nzyme **I**mmuno **A**ssay (**MEIA**) and using dedicated instrumentation (Ax-SYM_Plus System, Abbott Laboratories, Diagnostic Division, Abbott Park, IL, USA). MEIA is a non-competitive immuno-enzymatic method (with clinical sensitivity and specificity of 74.17 and 91.46%, respectively), using two anti-BNP mouse monoclonal antibodies, one coated on microparticles and the other conjugated to alkaline phosphatase. The assay was performed following the manufacturer's instructions.

**Data analysis:** All the data obtained from the questionnaire and BNP

measurements were entered in SPSS 11 software and analyzed using one-way analysis of variance (ANOVA) in order to examine the relationships between the various study parameters and CHF and HTN. The t-test was employed in order to detect significant variations among up to two parameters in CHF. Additionally, Chi square, Scheffe test and non-parametric Kruskal-Wallis test were used to test the correlation between the case group or control group and variables that affect their occurrence.

## Results:

Patients with CHF showed a mean of BNP of 796.8 pg/ml which is greater than that of HTN patients (69.3 pg/ml). Additionally the mean BNP value of HTN is greater than that of the normal individuals (9.7 pg/ml). This indicates a statistically significant difference in the BNP level between the CHF and controls. The BNP mean difference was also significant between CHF and normal subjects from one side and between the HTN (controls) and normal subjects from the other side ($p = 0.001$).

The results revealed that patients with acute heart failure (AHF) have a mean BNP of 2011.9 pg/ml, which is greater than that of chronic heart failure (292.4 pg/ml). Moreover, the mean value of BNP of chronic heart failure, was greater than that of HTN (69.3 pg/ml), and that of HTN was greater than the mean BNP value of normal individuals (9.7 pg/ml). The test results showed a significant difference between BNP hormone and heart failure subgroups as evidenced by a p value of 0.001. In addition, Scheffe test was used to investigate the relation between BNP and heart failure (HF) subgroups. It showed a significant difference between the means of AHF and the means of CHF from one side and increased blood pressure or normal subjects from the other side. On the other hand the results showed a significant difference between HTN and normal subjects, as evidenced by p value (0.001).

Regarding the relation between BNP and severity of CHF (NYHA classes), the results revealed significant differences between the means of BNP and NYHA classes (Table 2). Post hoc analysis test shows a significant difference between NYHA classes and BNP (i.e., between class 1 and class 2, class 1 and class 3 and so on) as evidenced by the p-values of less than 0.05. The results thus proved that, the mean value of BNP increases with the severity of the disease, i.e., the higher the BNP level the greater the severity of heart failure.

**Table 2:** The relation between BNP and NYHA classes among the case group population**.**

| | NYHA Class | Sample Size (n) | Mean BNP pg/ml | SD | SEM | F-test Value | P-Value |
|---|---|---|---|---|---|---|---|
| BNP | Class I | 23 | 77.96 | 44.25 | 9.22 | 105.4 | 0.001 |
| | Class II | 30 | 456.87 | 264.96 | 48.37 | | |
| | Class III | 8 | 1189.11 | 133.92 | 47.34 | | |
| | Class IV | 14 | 2482.13 | 896.11 | 239.49 | | |

Table 3 shows a Post hoc and Scheffe test analyses and indicate that there is a significant difference between each class and BNP hormone, (class 1 and class 2, class 1 and class 3 and so on) as evidenced by the statistically significant

p-values. Patients with class 4 have a mean of BNP more than those with class 3, 2 and 1. Patients with class 3 have a mean of BNP more than those with class 2 and 1. Patients with class 2 have a mean of BNP more than those with class 1.

**Table 3:** Multiple comparisons dependent variable: BNP with NYHA classes by using Scheffe test**.**

| | | **Mean Difference (I-J)** | **Std. Error** | **Sig.** |
|---|---|---|---|---|
| **(I) NYHA** | **(J) NYHA** | | | |
| **CLASS I** | **CLASS II** | -378.92 | 116.96 | .020 |
| | **CLASS III** | -1111.16 | 173.21 | .001 |
| | **CLASS IV** | -2404.17 | 143.05 | .001 |
| **CLASS II** | **CLASS I** | 378.92 | 116.96 | .020 |
| | **CLASS III** | -732.24 | 167.92 | .001 |
| | **CLASS IV** | -2025.25 | 136.59 | .001 |
| **CLASS III** | **CLASS I** | 1111.16 | 173.21 | .001 |
| | **CLASS II** | 732.24 | 167.92 | .001 |
| | **CLASS IV** | -1293.00 | 187.03 | .001 |
| **CLASS IV** | **CLASS I** | 2404.17 | 143.05 | .001 |
| | **CLASS II** | 2025.25 | 136.59 | .001 |
| | **CLASS III** | 1293.01 | 187.03 | .001 |

Figure 1 shows the relation between the diagnosis (on the x-axis) and the mean concentration of BNP (on the y-axis). The mean value of BNP is increasing with the severity of the NYHA classes; all NYHA classes have a mean BNP value over than that of HTN and normal individuals. A significant difference was also encountered between gender and BNP in the case group as evidenced by the p-value (0.040). The results showed that the male population has a significantly higher BNP (mean = 1046.56 pg/ml) than that of females (mean = 589.66 pg/ml). The same, though in the other way around, was also true for the control group population where the mean BNP values were 79.52 for females and 57.03 pg/ml for males (p = 0.044). The difference between BNP mean values and age in the case population, however, was not significant (p = 0.595). In the contrary, the difference was significant in the control group (p = 0.033). Subjects with ages less than 50 years have a mean value of BNP of 38.32 pg/ml, while the mean value of BNP for subjects with ages more than 51 years was 77.73 pg/ml.

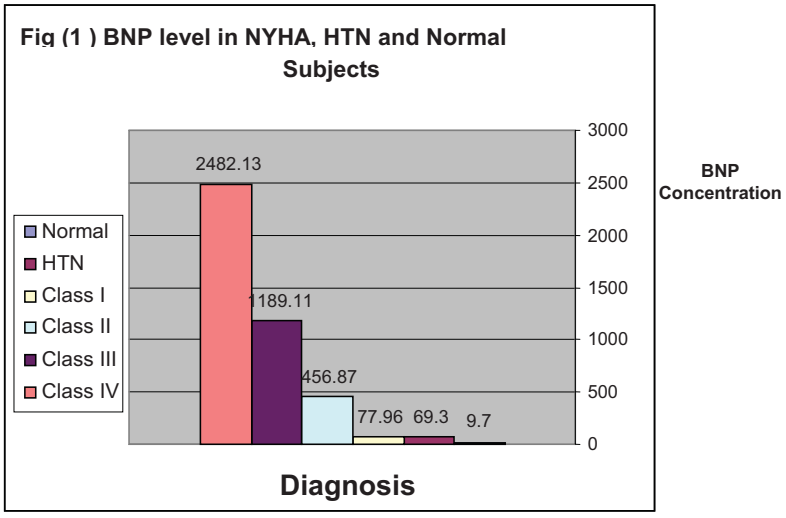


**Figure 1.** BNP level in NYHA classes, HTN and normal subjects.

## Discussion:

The study results showed a significant relation between CHF with age and gender, particularly in men and this is in agreement with most of the studies conducted in this field. Diller *et al* (1999), Ho *et al* (1993) and McMurray *and Stewart* (2000) showed that, the frequency of CHF increased with age for men and women, and the incidence was higher in men compared to women [5,6,7]. Also the results showed a significant relation between gender and BNP among the case group as evidenced by the p-value (0.040). It showed that male population had a significantly higher BNP (mean = 1046.56 pg/dl) than that of females (mean = 589.66 pg/dl). Furthermore, the results did not show significant difference between the means of BNP values and age, as revealed by the p value (0.595), this may be due to misdiagnosis of some subjects in the case group.

On the other hand, there is a significant relation between gender and BNP among control group as evidenced by the p-value (0.044). The study showed that the female population has a mean of BNP (79.52 pg/dl) which is greater than that obtained for male (57.03 pg/dl). In addition, it showed significant difference between the means of BNP values and age, as evidenced by the p value (0.033). These results are congruent with those of Redfield *et al.* (2002) who found that BNP increases with age and is higher in women among subjects without cardiovascular disease or cardiac dysfunction [8]. Interestingly, the association of female gender and BNP appears to be in part related to estrogen status, as BNP levels were higher in women using hormone replacement therapy and plasma BNP was 21% higher in females on hormone replacement therapy (HRT) than in those not on HRT [8]. In a prospective study, Maisel *et al.* (2004) also indicated that a significant differences in CHF rates were found on the basis of age (P <.001) and race (P =.020) but not gender (P =.424). BNP levels increased with increasing age (P <.001) [9]. Our study agreed with Maisel *et al*. and Redfield *et al*. studies in relation to age and gender in the control group, but the result of the case

group is not in agreement with those studies with respect to age and consistent with them in terms of gender. Although there is a significant relation between BNP and gender, in both the case and control group, our study shows that the males had a mean BNP concentration higher than that of females, this result did not agree with both the previous studies. The differences in results may be due to that females in Gaza Strip do not have HRT, and most of the patients with AHF in CCU with BNP level more than 1000 pg/ml were males, and the mortality among males was higher than that in females (56.4 % in males vs. 43.6 % in females), with a rate of 60.5 in males and 48.0 in females per 100,000 [10].

Concerning the relationship between BNP and CHF, The results showed that the patients with CHF have a mean of BNP of 796.8 pg/dl which is greater than that in the control group (69.3 pg/ml). Additionally the mean BNP value of control group is greater than that of the normal individuals (9.7 pg/ml). This indicates a significant relation between BNP and diagnosis. On the other hand, the results showed a significant relation between control group and normal subjects regarding BNP, as evidenced by the p value (0.001). Moreover, the results showed that patients with AHF have a mean of BNP of 2011.9 pg/ml, which is greater than that of chronic heart failure (292.4 pg/dl). The present study confirms that circulating BNP progressively increases with the severity of symptomatic CHF. These results and conclusions are consistent with Mukoyama *et al* (1999) who reported that there is an elevation of circulating BNP in humans with CHF [11]. Substantial evidence shows that the BNP test aids in the diagnosis of HF, Davis *et al* showed that the BNP level was higher in patients with HF compared with patients with lung disease and that use of the BNP assay was 93% sensitive and 90% specific for a diagnosis of HF [12].

Furthermore, the results of our study showed that there is a significant relation between the means of BNP hormone and NYHA classes. This finding is in agreement with the study of Wieczorek *et al* (2002) who reported that circulating BNP concentrations determined from the bedside assay increased with CHF severity, as determined by the NYHA classification system, but were only statistically significant (P <.001) between individuals with and without CHF. Individuals without CHF had a median BNP concentration of 9.29 pg/mL. Median BNP values, with their corresponding interquartile ranges for NYHA classification I through IV were 83.1 pg/mL (49.4-137 pg/mL), 235 pg/mL (137-391 pg/mL), 459 pg/mL (200-871 pg/mL), and 1119 pg/mL (728->1300 pg/mL) respectively. With the use of a decision threshold of 100 pg/mL, the assay demonstrated 82% sensitivity and 99% specificity for distinguishing control patients and patients with CHF [13].

In Conclusion, the present study provides strong evidence that BNP measurement is a useful part of the diagnostic work-up for individual patients. BNP levels are sensitive and specific for the diagnosis of abnormal heart function and HF.

**Recommendations :**

- It is recommended to measure BNP in high-risk patients to aid in assessing for CHF and in screening high-risk

subgroups of the population such as patients after MI, and those with angina and acute dyspnea.

- Further studies are needed to investigate the role of BNP in response to treatment and before patient discharge.

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