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# Relationship between plasma BNP levels and left ventricular diastolic function as measured by radionuclide ventriculography in patients with coronary artery disease

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## Abstract

BACKGROUND: Radionuclide ventriculography enables such parameters of the left ventricular (LV) function as the ejection fraction (EF), ejection rate (ER) and filling rate (FR) to be measured correctly. The impairment of the LV function in coronary artery disease (CAD) results in an increase in plasma brain natriuretic peptide (BNP). The aim of this study was to check whether the reduction of the average filling rate (AFR) leads to an increase in plasma BNP levels in patients with CAD and nEF and whether that increase is comparable to that occurring in subjects with a reduced PER.

MATERIAL AND METHODS: The study population comprised 69 patients with CAD and 18 healthy subjects — a control group (CG). In all cases radionuclide ventriculography was performed at rest and the plasma BNP level was estimated.

RESULTS: The plasma BNP concentration was significantly higher in the group with CAD than in those with CG . In patients with CAD and a decreased LVEF (dEF), the BNP level was significantly higher than in those with normal LVEF (nEF). In the subgroup with nEF and an AFR ≤ 1.04 EDV/s, the level of plasma BNP was significantly higher than in that with an AFR >1.04. In the total CAD group, a significant correlation was found between plasma BNP concentrations and the LVEF, PER and AFR. In patients with nEF, the level of plasma BNP correlated only with the AFR.

CONCLUSIONS: It is concluded that the diastolic dysfunction of the left ventricle in patients with CAD leads to an elevation of plasma BNP concentrations despite the normal ejection fraction. A diastolic dysfunction of the left ventricle affects the BNP plasma concentration to a greater degree than a systolic dysfunction.

**Key words: radionuclide ventriculography, BNP, LV diastolic function, CAD**

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## Introduction

As it is commonly known, radioisotope examinations permit one to assess the phenomena occurring during the heart cycle which are connected with the change of the left ventricular vo-

lume. Among these methods, equilibrium gated radionuclide ventriculography is regarded as the most important. This method allows the ejection fraction as well as the left ventricular filling and emptying rates to be assessed correctly [1–3]. The significant advantage of this method is the fact that no geometrical assumptions are used to determine the left ventricular volume and its changes during the cardiac cycle.

Coronary artery disease is one of the pathological processes leading to an impairment of myocardial contractility which can be assessed successfully by radionuclide ventriculography.

It has been proved in many earlier studies that in coronary artery disease (CAD) the myocardial relaxation and the left ventricular filling are disturbed relatively early and prior to the deterioration of the systolic function and decrease in the left ventricular ejection fraction (LVEF) [4–9]. The enlargement of the left ventricle and the reduction of the ejection fraction point to a relatively serious impairment of the heart function.

The impairment of the heart function leads to an increase in the blood concentrations of some biologically active substances, like atrial natriuretic peptide (ANP), vascular natriuretic peptide type C (CNP) and brain natriuretic peptide (BNP) [10–21], the last one considered to be the most important among them [22, 23, 17].

Brain natriuretic peptyde was discovered in 1988 by Sudah et al [24]. It is released mainly from the ventricular myocytes in answer to pressure or volume overload. Smaller amounts of BNP are produced also in the atrial myocardium. Its main role is to neutralize the effects of stimulation of the renin-angiotensin-aldosterone system. Besides this, it regulates the blood pressure, increases diuresis and natriuresis and regulates both the volume of the vascular bed and the water balance of the body [22–25].

The BNP level increases predominantly in such cardiovascular disorders that lead to left ventricular overload. High BNP levels were observed in patients with heart failure, left ventricular hypertrophy and arterial hypertension. It has been proven that the plasma BNP level increases also in patients with coronary artery disease, particularly in those with decreased ejection fraction [10–13, 15, 16, 18, 19, 21–24].

Because of this relationship, BNP plasma level measurement is recommended by the European Society of Cardiology as one of the basic laboratory tests in patients with suspected heart failure. Above all, this recommendation concerns high risk patients with coronary artery disease [16].

Despite the numerous publications on plasma BNP in heart diseases, the usefulness of this peptide in patients with isolated systolic or diastolic dysfunction and with normal ejection fraction is still not quite clear and is still intensely discussed [26–33].

In our previous study we showed that the BNP plasma level increases in CAD not only in patients with decreased ejection fraction but also in those with normal ejection fraction but an impaired ejection rate [34].

The aim of this study was to check whether the deterioration of the left ventricular volume changes the rate during diastole as measured by radionuclide ventriculography as a reduced filling rate leads to an increase in BNP plasma levels in patients with normal ejection fraction (EF) and whether this increase is comparable to that occurring in subjects with a reduced ejection rate.

## Material and methods

The study population comprised 69 patients with confirmed CAD, aged 30–79 years (mean 57.5 yrs), among them 10 women and 59 men. Thirty-two patients had had a myocardial infarction in the past, 27 had been treated for arterial hypertension, 16 cases were after percutaneous transluminal coronary angioplasty (PTCA), and another 10 patients had undergone coronary artery by-pass grafting (CABG). Myocardial single photon emission computer tomography (SPECT) revealed perfusion abnormalities at rest in 61 cases, in which all but 2 cases, increased during exercise. In the remaining 8 subjects under study, regional blood flow defects were observed only during physical stress. None of the patients had any other medical conditions which might influence cardiac function. All patients agreed in writing to be included in the experiment. The study project was approved by The Bioethics Committee at the Medical University of Lublin.

All subjects underwent equilibrium gated radionuclide ventriculography at rest, with 99mTc-erythrocytes, labeled in vivo. For this purpose the patients were injected intravenously with stannous pyrophosphate, and 25–30 min later with 740 MBq (20 mCi) technetium 99mTc pertechnetate. Data acquisition was started 15 minutes after the injection of radioactive technetium. During the examination, the patient was in a horizontal position. The activity was measured using a Picker gamma camera (Picker Int., Clevland, USA) connected to the Max Delta computer system (Siemens, Erlangen, Germany). The detector of the camera was equipped with an all purpose, low-energy collimator and positioned over the cardiac area in a 30–40° left anterior oblique (LAO) projection. The heart cycle was divided into 26 sequences. The measured data were collected on the 64 × 64 computer matrix. During the data processing the left ventricular regions were drawn in end-diastole and end-systole and the area of background activity was defined. From the data collected, a time activity curve was constructed and such parameters of the left ventricular function as the left ventricular ejection fraction (LVEF), the peak ejection rate (PER) and the average filling rate (AFR) were calculated. The ejection fraction was determined as a difference between the average activity in the end-diastole and that in the end-systole, expressed as a percentage of the average activity in the end-diastole. The left ventricular peak ejection rate was defined as a maximum change in the count rate per second occurring between the end-diastole and the end-systole (EDV/s). The mean filling rate was defined as an average change in the count number per second between the end-systole and the end-diastole (EDV/s).

The plasma BNP levels were estimated in the blood samples (8–10 ml) collected from patients under study between 8 am and 10 am following an overnight fast. Immediately after withdrawal, blood samples were put into disposable polypropylene tubes containing aprotinin in the amount of 500 KIU/ml of plasma and ethylene diamine tetraacetic acid (EDTA) in the amount of 1 mg/ml of plasma. Plasma samples were rapidly separated by centrifugation for 10 min at 4° C and then frozen and stored at –20° C in 1 ml aliquots until an assay was performed. The plasma BNP level was measured in duplicate along with the immumoradiometric method, by a SHIONO-RIA kit supplied by CIS Bio International (Schering S.A., Gif-Sur-Yvette CEDEX, France). In accordance with the manufacturer's recommen-

dations, a BNP level of 18.4 pg/ml was accepted as the upper limit of the normal range.

Additionally, the plasma BNP concentrations were determined in blood samples collected from 18 healthy subjects (control group), among them 5 men and 13 women, aged 25–67, on average 38.8 years.

A statistical analysis was applied to the obtained results. The plasma BNP concentrations in patients with CAD were compared with those in the control group. In patients with CAD, the results of plasma BNP measurements were examined in relation to the radionuclide ventriculography. The relationships between plasma BNP levels and left ventricular function parameters were analyzed in the total material and after dividing the study population into groups.

Two subgroups were created according to the LV ejection fraction: group nLVEF (normal LVEF), with an LVEF ≥ 50% consisted of 52 subjects, and group dLVEF (decreased LVEF), with an LVEF < 50% contained 17 subjects.

Subjects with a normal LVEF (nLVEF) were divided into 2 subgroups, based on the median value (ME) estimated for the mean left ventricular filling rate (ME AFR = 1.04 EDV/s).

Additionally, the nLVEF group was divided into 4 subgroups, taking as a criterion the median values of both the mean filling rate and the peak ejection rate (ME PER = 2.33 EDV/s). Accordingly, the A group consisted of the cases with the PER greater than the median value (PER > 2.33 EDV/s) and a mean filling rate greater than the median value (AFR > 1.04 EDV/s); group B contained subjects with a PER > 2.33 EDV/s and an AFR ≤ 1.04 EDV/s; group C — those with a PER ≤ 2.33 EDV/s and an AFR > 1.04 EDV/s; and group D — patients with a PER ≤ 2.33 EDV/s and an AFR ≤ 1.04 EDV/s.

## Results

It was found that the BNP plasma concentration was significantly higher in the CAD group, than in the normal group (Table 1).

In patients with CAD, the BNP level was significantly higher in the group with decreased ejection fraction as compared with the nLVEF group (Table 2).

In the nLVEF group with an AFR ≤ 1.04 EDV/s, the BNP concentration was significantly higher and the elevated values were distinctly more frequent than in that with AFR > 1.04 EDV/s (Table 3).

An analysis of the subgroups created according to the median values of both the PER and AFR revealed the highest BNP concentration in both groups with an AFR ≤ 1.04 EDV/s (group B and D). The BNP level was slightly higher in the group with a PER > > 2.33 EDV/s and an AFR ≤ 1.04 EDV/s (group B) as compared to the group with both parameters lower than or equal to the median values (group D).

In the subgroups with an AFR > 1.04 EDV/s (group A and C) the BNP plasma level was slightly elevated compared with the normal values, but significantly lower than in groups with an AFR ≤ ≤ 1.04 EDV/s (groups B and D). However, only the differences between group A and B were statistically significant (Figures 1, 2).

An analysis of the all CAD patients under study, revealed a not very close but highly significant correlation between plasma BNP concentrations on the one hand and the LVEF, PER and AFR on the other (Table 4, Figure 3). In the nLVEF group, the BNP level correlated only with the average filling rate (Table 5, Figure 4) and did not show any significant relationships with the remaining parameters.

**Table 1. Mean BNP and frequency of cases with elevated BNP levels in healthy subjects and in patients with coronary artery disease**

| Groups | n | BNP | | |
|---|---|---|---|---|
| | | (X ± SD) [pg/ml] | $n_l$ | % |
| Control group | 18 | 8.9 ± 6.4 | 1 | 5.5 |
| CAD | 69 | 47.1 ± 55.3 | 40 | 58 |
| *t*-test | | p < 0.01 | p < 0.001 | |

Abbreviations: BNP — brain natriuretic peptyde; CAD — coronary artery disease; n — number of cases; $n_l$ — number of cases with elevated BNP levels; SD — standard deviation from the mean BNP level

**Table 2. Mean BNP and frequency of cases with elevated BNP levels in patients with nomal (nLVEF) and decreased (dLVEF) ejection fraction**

| Groups | n | LVEF (X ± SD) % | BNP | | |
|---|---|---|---|---|---|
| | | | (X ± SD) [pg/ml] | $n_l$ | % |
| dLVEF | 17 | 33.7 ± 14 | 79.1 ± 83.4 | 13 | 76 |
| nLVEF | 52 | 60.3 ± 2.2 | 37.7 ± 38.4 | 27 | 52 |
| *t*-test | | | p < 0.01 | p > 0.05 | |

Abbreviations: LVEF — left ventricular ejection fraction; for other abbreviations see Table 1

**Table 3. Mean BNP and frequency of cases with elevated BNP levels in patients with normal value of average filling rate (nAFR) and decreased value of average filling rate (dAFR) by normal ejection fraction**

| Groups | n | LVEF (X ± SD) % | Filling rate [EDV/s] | (X ± SD) [pg/ml] | BNP % |
|---|---|---|---|---|---|
| dAFR | 21 | 60.3 ± 2.2 | AFR ≤ 1.04 | 56.6 ± 46.3 | 71.4 |
| nAFR | 31 | | AFR > 1.04 | 24.9 ± 25.7 | 38.7 |
| *t*-test | | | | p < 0.01 | p < 0.05 |

AFR — average filling rate; for other abbreviation see Tables 1 and 3

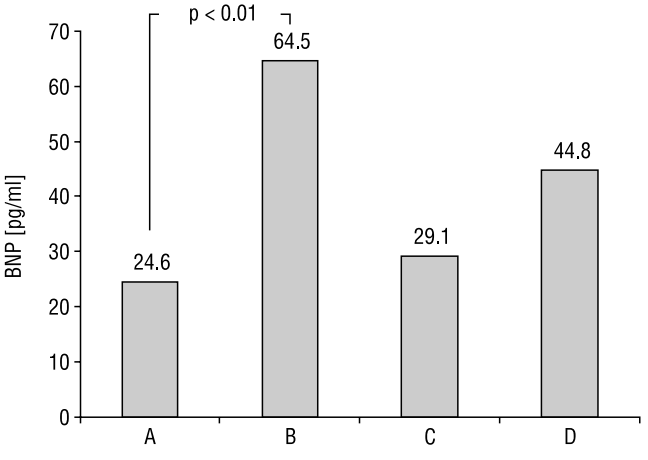


**Figure 1.** BNP levels in group A, B, C and D. Group A — PER > 2.33 EDV/s, AFR > 1.04 EDV/s; Group B — PER > 2.33 EDV/s, AFR ≤ 1.04 EDV/s; Group C — PER ≤ 2.33 EDV/s, AFR > 1.04 EDV/s; Group D — PER ≤ 2.33 EDV/s, AFR ≤ 1.04 EDV/s.

**Table 4. Relationship of BNP concentration to LVEF, PER and AFR in CAD group**

| y | y ± SD [pg/ml] | X | X ± SD | n | r | p | Regression equation |
|---|---|---|---|---|---|---|---|
| BNP | 47.92 ± 55.39 | LVEF | 53.75 ± 14.58 | 69 | –0.39 | < 0.001 | y = 125.11 – 1.467 x |
| | | AFR | 1.04 ± 0.33 | | –0.40 | < 0.001 | y = 117.05 – 66.63 x |
| | | PER | 2.28 ± 0.67 | | –0.43 | < 0.001 | y = 129.16 – 35.54 x |

Abbreviations: r — correlation coefficient; AFR — average filling rate; PER — peak ejection rate; for other abbreviations see Tables 1 and 2

**Table 5. Relationship of BNP concentration to LVEF, PER and AFR in group with nLVEF**

| y | y ± SD [pg/ml] | X | X ± SD | n | r | p | Regression equation |
|---|---|---|---|---|---|---|---|
| BNP | 37.73 ± 38.4 | LVEF | 60.30 ± 2.18 | 52 | –0.006 | > 0.05 | y = 39.76–0.0337 x |
| | | AFR | 1.16 ± 0.24 | | –0.38 | < 0.01 | y = 107.05–59.76 x |
| | | PER | 2.55 ± 0.45 | | –0.19 | > 0.05 | y = 79.024–16.17 x |

For the abbreviations see Tables 1, 2, 4

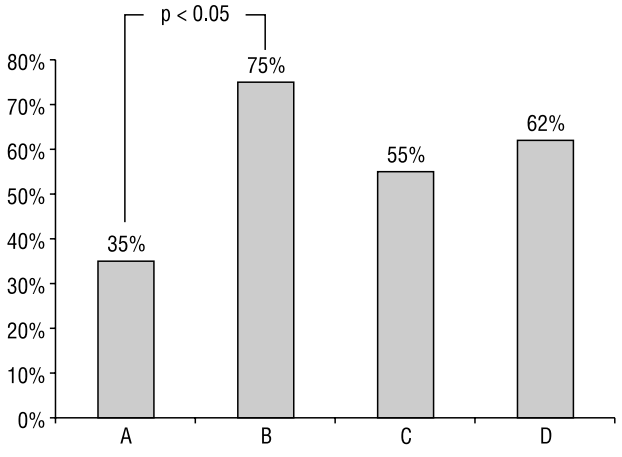


**Figure 2.** Frequency of cases with elevated BNP in group A, B, C and D. Group A — PER > 2.33 EDV/s, AFR > 1.04 EDV/s; Group B — PER > > 2.33 EDV/s, AFR ≤ 1.04 EDV/s; Group C — PER ≤ 2.33 EDV/s, AFR > > 1.04 EDV/s; Group D — PER ≤ 2.33 EDV/s, AFR ≤ 1.04 EDV/s.

## Discussion

Because of its proven diagnostic value, BNP was used as a marker of myocardial function impairment in patients with CAD. In numerous publications, the BNP level has been shown to increase in heart insufficiency, resulting from myocardial ischemia [10–13, 15, 16, 18, 19, 21–24]. An elevation of BNP was observed by various authors in more advanced stages of CAD, with a decreased EF [14, 17, 27, 33, 35]. However, from a clinical point of view it should be considered important to know whether the BNP level increases during earlier stages of myocardial insufficiency resulting from CAD. It has been shown that decreased relaxation and contraction dynamics are the early symptoms of myocardial function impairment, occurring much earlier than the reduction of ejection fraction [4–9].

Equilibrium gated radionuclide ventriculography is a well established method, used to assess left ventricular function and to calculate various functional parameters. In this study radionuclide ventriculography was applied to a group of patients with CAD and the obtained ejection fraction was considered to be the basic para-

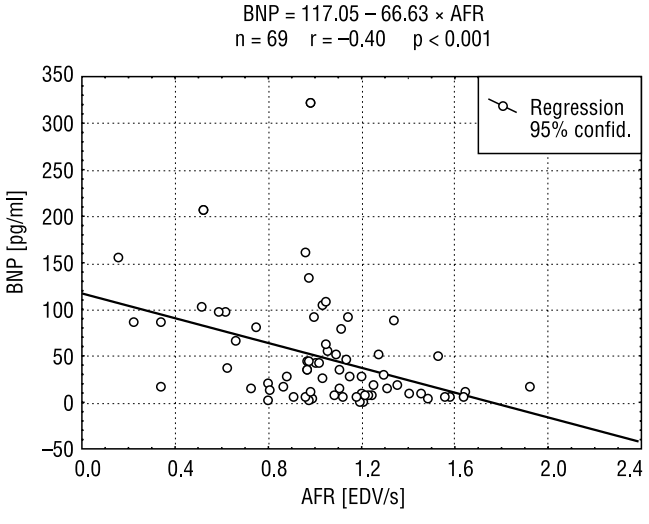


**Figure 3.** Relationship between BNP concentration and AFR in CAD group.

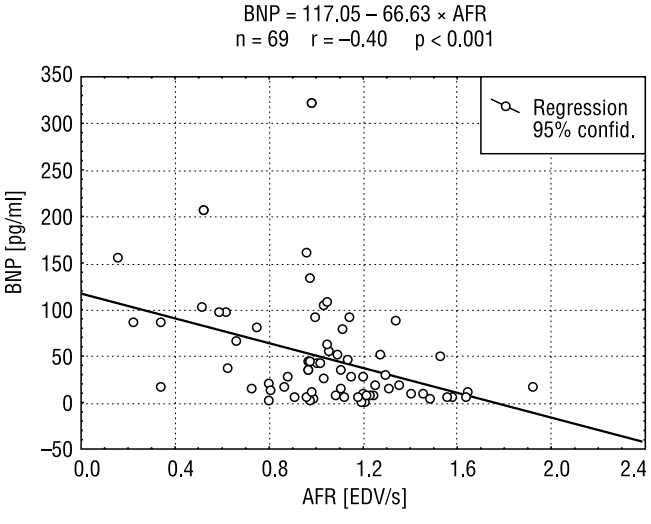


**Figure 4.** Relationship between BNP concentration and AFR in group with nLVEF.

meter. Additionally, such indices of the systolic and diastolic volume changes, as the ejection rate (ER) and filling rate (FR) were calculated. According to the character of the blood ejection process, the maximum rate of the left ventricular emptying (PER) was determined. On the other hand, because of time, as the resolution of the radionuclide ventriculography was proven to be too low to assess the maximum filling rate correctly [36], the average filling rate (AFR) was measured.

The three above parameters of the global left ventricular function obtained by radionuclide ventriculography were compared with the BNP concentrations.

In agreement with the observations by other authors and the results of our previous study, the BNP level was higher in patients with decreased ejection fraction than in patients with normal EF values [14, 17, 27, 33–35]. The close relationship between the ejection fraction and the BNP concentration in CAD was shown in many other studies [14, 17, 27, 33–35].

It was proven in our previous study [34] that in patients with CAD and normal ejection fraction, a decreased contraction rate leads to a rise in the plasma BNP level as well. The present study has shown that in those subjects the decreased dynamics of cardiac relaxation results in a statistically significant increase in BNP plasma levels despite a normal EF. An increased BNP level in patients with isolated diastolic dysfunction has also been observed by other authors [26–33].

It was found that because of normal ejection fraction the rise in BNP concentrations was stronger in patients with a relatively low filling rate than in those with a relatively low ejection rate. Those findings are in agreement with observations by some other authors [26–33].

The above results suggest that the impairment of diastolic function influences BNP concentrations to much greater degree than the impairment of systolic function.

This finding corresponds with results obtained by authors indicating that in CAD the diastolic impairment occurs earlier than that of the systolic [4–9].

The differences in BNP concentrations and in the frequency of patients with elevated BNP levels which were observed between subgroups constructed according to the PER and AFR values were distinct. However, all but one of those differences were statistically insignificant which might be connected with the relatively small numbers of cases. For this reason, the obtained results should be verified on a larger study population.

The results obtained seem to be of practical value as they enable radionuclide ventriculography to be used in diagnosing early stages of heart dysfunction in CAD, when the ejection fraction is still normal but the dynamics of left ventricular filling and emptying is already disordered.

## Conclusions

In conclusion, it should be stated that the diastolic dysfunction of the left ventricle in patients with CAD leads to an elevation of plasma BNP concentrations despite a normal ejection fraction. A diastolic dysfunction of the left ventricle affects BNP plasma concentrations to a greater degree than a systolic dysfunction.

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