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Brain Natriuretic Peptide Clearance in Patients with Obesity and Insulin Resistance - a Mechanistic Study

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Abstract

Introduction: Brain Natriuretic Peptide (BNP) is secreted from cardiac myocytes in response to the wall stress. BNP is eliminated via Natriuretic Peptide Receptor C (NPR-C) and degradation by extracellular proteases including neprilysin (NEP). Obesity and insulin resistance predispose to lower circulating natriuretic peptide levels. Raised NEP activity and an elevated NPR-C gene expression have been described in obese individuals with insulin resistance and lower circulating levels of natriuretic peptide.

Methods: We assessed the relationship between markers of peptide production and pulmonary clearance with indices of insulin resistance and body weight. The cardiac, peripheral and pulmonary Extraction Ratio (ER) has been quantified to assess BNP synthesis and clearance. Twenty one individuals admitted for EP study were consented. Simultaneous sampling of serum BNP level was performed from femoral artery and vein, coronary sinus and femoral artery and pulmonary artery and pulmonary wedge position.

Results: The mean serum BNP level was 37 ng/L. The mean cardiac ER was 1.20, pulmonary and peripheral ER was 0.13. There was a tendency for lower cardiac and pulmonary ER in males. Pulmonary ER correlated with age (r=0.495, p=0.023) and systolic BP (r=0.58, p=0.006) only. However there was no correlation between cardiac and pulmonary ER with BMI, waist circumference and HOMA-IR.

Conclusions: We found no correlation between the marker of BNP pulmonary clearance with body size and insulin resistance. Induction of the adipose tissue specific NPR-C pathway (rather than NEP clearance) is more likely the cause of the lower level of BNP in patients with obesity and insulin resistance.

Keywords: Brain natriuretic peptide; BNP Metabolism; Obesity; Insulin resistance

Introduction

The Brain Natriuretic Peptide (BNP) belongs to the family of natriuretic hormones (including ANP and to lesser degree CNP) which are secreted from cardiac myocytes (atria and ventricles) in response to the wall stress. BNP plays an important role in the regulation of blood pressure, intravascular volume, and cardiac remodelling and its level is elevated in patients with cardiac disease [1-5].

Metabolic syndrome is a complex disorder defined by a coexistence of factors that markedly increase the risk of cardiovascular diseases and type 2 diabetes mellitus. Obesity and insulin resistance, integral components of the syndrome, predispose to lower circulating natriuretic peptide levels [6-12]. The imbalance between synthesis (lower production) and elimination (higher degradation) of the peptides is likely the cause [13]. BNP is metabolised utilising two main mechanisms: tissue specific elimination via Natriuretic Peptide Receptor C (NPR-C) and systemic degradation by extracellular proteases including neprilysin (NEP) [14-16]. Both a raised NEP activity and an elevated NPR-C gene expression (in the adipose tissue) have been described in obese individuals with insulin resistance and lower circulating levels of natriuretic peptide [17,18]. However the prevailing mechanism of the higher peptide clearance (NEP vs. NPR-C pathways) remains unknown.

Materials and Methods

We studied 21 consecutive patients (6 males, 15 females) with isolated cardiac arrhythmia (SVT and atrial flutter without structural cardiac abnormality) admitted for an elective Electrophysiology Study to the Princess Alexandra Hospital in Brisbane.

Patient characteristics including gender, age, weight, BMI, waist circumference and cardiac risk factors are shown in Table 1. Before the procedure baseline investigations including fasting lipid profile, glucose and insulin were performed and HOMA-IR was calculated for each individual patient (Table 2).

Procedural Details

The usual approach via femoral access (vein and artery) with the

Variable	Total	Male n -6	Feinale n - 25	P value
Cardiac catheterization				
H8	/6 tit.	H ± 18	/8 t 16	0.53
S31,	149 t 25	154 t 26	10 t 15	0.61
03P	74 t 15	791:24	73 ± 10	0.33
MAP	99 ± 1.4	95 t 5	100 ± 17	0.73
18:WP	9 r 3	1U t 3	8 t 3	0.23
kW	3/ ± 10	35.1t11	3/./ ± 113	1135
Perlphera En	0.13 tO CH	pia 0.05	013 t 0.03	0.31
Car8lac ER	1.201.0.6	1.16 ,--- 0.2	1.22 ± 0.7	0.51
Pulmonve LH	0.13 ± 0.01	0.073 0.03	0.15 ± 0.01	0.19

Table 1: Characteristics of the study group – baseline measurements.

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Variable	Total	Male n = 6	Female n =15	P value
Investigations				
Total cholesterol	4.53 ± 0.97	4.02 ± 1.07	4.74 ± 0.87	0.17
Triglyceride	0.83 ± 0.42	0.98 t 0.48	0.77 t 0.40	0.35
HDL	1.38 ± 0.44	1.12 ± 0.39	1.48 ± 0.42	0.09
LOL	2.80 t 0.90	2.45 t 1.11	2.94 t 0.81	0.44
Fasting glucose	5.3 t 0.9	5.8 ± 1.4	5.1 t 0.6	0.12
Fasting insulin	6.8 ± 3.7	8.9 t 4.7	5.9 ± 2.9	0.28
HOMA-IR	1.68 ± 1.31	2.51 ± 2.08	1.35 ± 0.72	0.11

Table 2: Characteristics of the study group – baseline investigations (mmol/l).

Variable	Total	Male n -6	Feinale n - 25	P value
Cardiac catheterization				
H8	/6 tit.	H ± 18	/8 t 16	0.53
S31,	149 t 25	154 t 26	10 t 15	0.61
03P	74 t 15	791:24	73 ± 10	0.33
MAP	99 ± 1.4	95 t 5	100 ± 17	0.73
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Table 3: Study results including haemodynamic data (mmHg) and venous BNP (ng/l).

use of standard electrophysiology techniques (with the canulation of coronary sinus) was employed. Swan Ganz catheter was used to measure pulmonary artery and pulmonary wedge pressures during procedure and to obtain blood samples from pulmonary artery and from wedge position (assuming that this sample represents an oxygenated pulmonary venous blood).

Blood samples (5 mls) were collected in pairs (femoral vein and artery, coronary sinus and femoral artery, pulmonary artery and wedge) simultaneously by 2 operators to obtain instant gradients (peripheral, cardiac, pulmonary) of the measured peptide. First 2 mls of blood collected from wedge position was discarded as it was likely of arterial (deoxygenated) origin. Blood samples were immediately sent for BNP analysis. NT-pro BNP was not measured during this study.

The ability of an individual organ to remove or secrete molecule from/to the circulation was assessed using the Extraction Ratio (ER). ER was calculated by the following formula which relates the rate of elimination of the molecule to its rate of presentation to the organ of elimination (ER= Ca-Cv/ Cv where Ca=arterial concentration and Cv=venous concentration of the molecule) [19]. The ER was measured for each pair of samples representing the elimination of the peptide in the periphery (peripheral ER) or across lungs (pulmonary ER) or cardiac production (cardiac ER).

Results of serum BNP gradients were cross analysed with baseline data to test for any significant relationship between ER rates, components of metabolic syndrome and indices of insulin resistance.

Results

The results are outlined in Table 3. The mean serum BNP level was 37 ng/l. The mean cardiac ER was 1.20, the mean peripheral and pulmonary ER was 0.13. There was a tendency for lower cardiac and pulmonary ER in males. On further analysis a positive correlation was found between cardiac ER and HDL levels (r=0.671, p=0.001). Peripheral ER correlated with age only (r=0.434, p=0.049). Pulmonary ER correlated with age (r=0.495, p=0.023) and systolic BP (r=0.58, p=0.006).

However we found no relationship between peripheral, pulmonary or cardiac ER and BMI, waist circumference, blood pressure, fasting serum glucose, insulin and HOMA-IR.

Discussion

Obese individuals have lower circulating BNP levels than lean individuals [6-12] and those with established metabolic syndrome and insulin resistance demonstrate an increase in peptide clearance due to a raised NEP activity and an elevated NPR-C gene expression (in the adipose tissue) [17,18].

In this small mechanistic study we assessed BNP production and clearance in individuals with various degree of insulin resistance and other components of metabolic syndrome including elevated body weight, blood pressure and lipids level. We measured directly cardiac synthesis (cardiac ER) and degradation via extracellular NEP (pulmonary ER) without assessing NPR-C gene expression in adipose tissues. We postulated that lower BNP levels in patients with metabolic syndrome and insulin resistance may result from the imbalance between synthesis (lower production) and elimination (higher degradation) of the peptides.

However results of our study did not confirm a direct correlation between markers of BNP synthesis (cardiac ER) and clearance (peripheral and pulmonary ER) with body size (BMI, waist circumference) or markers of insulin resistance (HOMA IR). It is possible that our sample was not adequate and we included patients with lower than expected body size indices and HOMA IR. As a result our findings may not be representative for a cohort of patients with metabolic syndrome described in available literature.

In summary we did not demonstrate a relationship between HOMA IR and pulmonary ER - marker of pulmonary clearance via NEP associated pathway. The adipose tissue specific NPR-C pathway (not assessed in our study) could be the predominant mechanism of increased BNP clearance in patients with obesity and insulin resistance [19].

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