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ARTICLE

B-type natriuretic peptide (BNP) affects the initial response to intravenous glucose: a randomised placebo-controlled cross-over study in healthy men

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Abstract
Aims/hypothesis B-type natriuretic peptide (BNP) is a hormone released from cardiomyocytes in response to cell stretching and elevated in heart failure. Recent observations indicate a distinct connection between chronic heart failure and diabetes mellitus. This study investigated the role of BNP on glucose metabolism.
Methods Ten healthy volunteers (25±1 years; BMI 23±1 kg/m^2; fasting glucose 4.6±0.1 mmol/l) were recruited to a participant-blinded investigator-open placebo-controlled cross-over study, performed at a university medical centre. They were randomly assigned (sequentially numbered opaque sealed envelopes) to receive either placebo or 3 pmol kg^{-1} min^{-1} BNP-32 intravenously during 4 h on study day 1 or 2. One hour after beginning the BNP/placebo infusion, a 3 h intravenous glucose tolerance test (0.33 g/kg glucose + 0.03 U/kg insulin at 20 min) was performed. Plasma glucose, insulin and C-peptide were frequently measured.
Results Ten volunteers per group were analysed. BNP increased the initial glucose distribution volume (13±1% body weight vs 11±1%, $p<0.002$), leading to an overall reduction in glucose concentration ($p<0.001$), particularly during the initial 20 min of the test ($p=0.001$), accompanied by a reduction in the initial C-peptide levels (1.42±0.13 vs 1.62±0.10 nmol/l, $p=0.015$). BNP had no impact on beta cell function, insulin clearance or insulin sensitivity and induced no adverse effects.
Conclusions/interpretation Intravenous administration of BNP increases glucose initial distribution volume and lowers plasma glucose concentrations following a glucose load, without affecting beta cell function or insulin sensitivity. These data support the theory that BNP has no diabetogenic properties, but improves metabolic status in men, and suggest new questions regarding BNP-induced differences in glucose availability and signalling in various organs/tissues.
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Keywords BNP · C-peptide · Diabetes · Glucose · Heart failure · Healthy volunteers · Insulin sensitivity · IVGTT

Abbreviations

BNP	B-type natriuretic peptide
CSI	Index of insulin sensitivity
dACPRg	Acute C-peptide response to glucose
dAIRg	Acute insulin response to glucose
dGLUC	Incremental glucose concentration
G_0	Theoretical zero intercept of the glucose concentration

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Introduction

Recent observations indicate a bilateral connection between chronic heart failure and diabetes mellitus. Patients with diabetes have a 2.5-fold increased risk of developing heart failure [1]. On the other hand, heart failure is an independent risk factor for the development of diabetes [2–4]. Changes in heart function are associated with alterations in glucose metabolism [5, 6] and whole-body insulin resistance is prevalent in chronic heart failure patients [7].

The mechanisms underlying these findings are not fully understood. Interestingly, the restoration of normal cardiac output after the implantation of a left ventricular assist device improves the control of diabetes in patients with heart failure [8]. Although these changes in glucose metabolism might also be partially attributed to changes in concomitant medications, this evidence emphasises the fact that the impact of heart failure on diabetes depends on left ventricular function and is, at least partially, reversible.

The extent of heart failure can be evaluated not only by measuring ventricular function using ultrasound, but also by determining the circulating concentrations of B-type natriuretic peptide (BNP) [9]. BNP is a peptide released from cardiomyocytes in response to myocyte stress and stretching [10–12]; it has vasodilatory properties and helps to reduce the preload. BNP is therefore one of the main messengers indicating the burden of the left ventricle in heart failure, and might also influence other processes, such as glucose metabolism.

BNP concentration increases with hyperglycaemia and is not influenced by hyperinsulinaemia [13, 14]. A few studies have addressed a positive association between BNP and adiponectin, a protein considered to be a marker of insulin sensitivity [15, 16]. However, up to now, only a few studies have investigated the relationship between BNP and glucose metabolism in detail. Since BNP levels rise with the degree of cardiac dysfunction, and insulin resistance correlates with the degree of cardiomyopathy, we hypothesised a direct influence of BNP on glucose metabolism in healthy men. Thus, the aim of this study was to investigate the effects of a continuous intravenous BNP infusion on beta cell function and insulin sensitivity in a placebo-controlled cross-over trial in healthy volunteers.

Methods

Participants The study protocol was approved by the Ethics Committee of the Medical University of Vienna and adheres to the Declaration of Helsinki. Participants were informed about the aims, procedures and possible risks of the study, and gave written informed consent. A sample size calculation, according to the recommendations given by Stolley and Strom [17] was performed. Ten healthy male volunteers (25±1 years; BMI 23±1 kg/m^2, fasting glucose 4.6±0.1 mmol/l) were recruited after a prescreening examination. Inclusion criteria were normal body weight (i.e., body mass index between 17 and 27 kg/m^2), normal OGTT, normal electrocardiogram and echocardiography, normal blood pressure and plasma BNP concentrations within the normal range. Exclusion criteria were concomitant acute or chronic disease, regular intake of medications or food supplements, or abnormal clinical chemistry or haematological results.

Study design and assays A prospective, single-blinded (participants were blinded to treatment), randomised, placebo-controlled, cross-over study was performed on two different study days separated by a washout period of at least 3 weeks (see the flow diagram in Fig. 1). Study days started at 08:00 hours; participants had been fasting since 18:00 hours the previous day and remained in that condition until the end of the study day. Participants were randomly assigned to receive active treatment or placebo on day 1 or day 2, respectively. Either placebo (0.9% NaCl) or 3 pmol kg^{-1} min^{-1} human BNP-32 (American Peptide, Sunnyvale, CA, USA) was infused for 4 h (from −60 to 180 min during the IVGTT) in order to achieve a plateau of 400–500 pg/ml at the beginning of the IVGTT. At time 0, a bolus of glucose (330 mg/kg of glucose 33%, Mayrhofer Pharmaceutics, Leonding, Austria) was administered intrave-

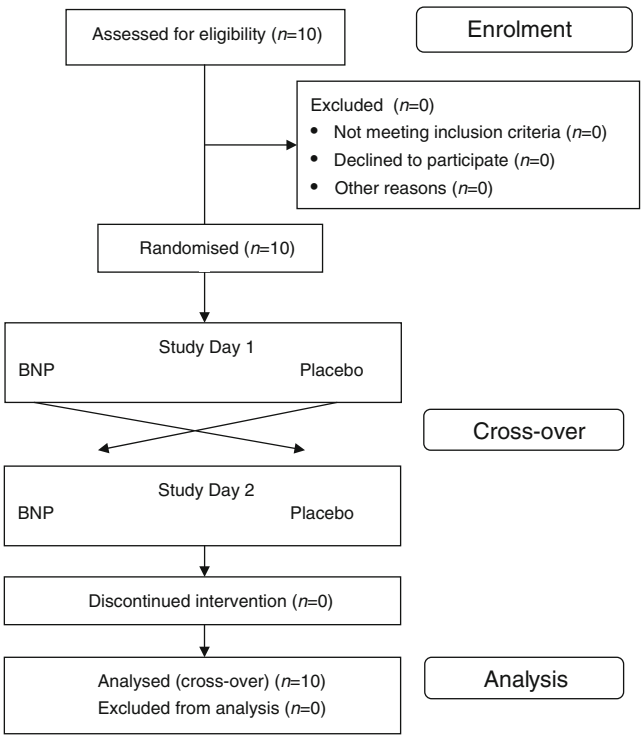

Fig. 1 Flow diagram

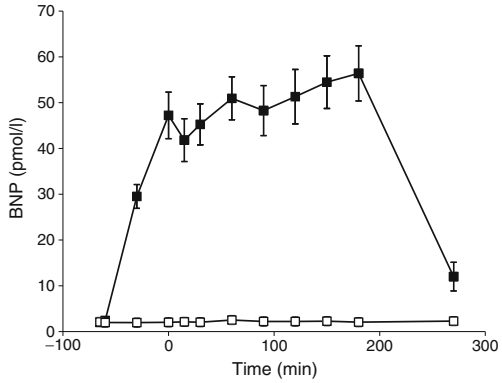

Fig. 2 Plasma BNP concentrations. Either placebo (white squares) or 3 pmol kg^{-1} min^{-1} BNP (black squares) was infused from time point −60 to 180 min

nously over 1.5 min. A bolus of insulin (0.03 U/kg, Actrapid, Novo Nordisk, Bagsværd, Denmark) was given at 20 min [18]. Blood was frequently withdrawn for the measurement of glucose, insulin and C-peptide. Samples were immediately cooled, centrifuged at 3,500 rpm and frozen at −20°C for later analysis. Circulating glucose was measured via routine laboratory techniques (www.kimcl.at). Insulin and C-peptide were measured using a commercial radioimmunoassay (Linco, St Charles, MO, USA) with inter- and intra-assay CV being, respectively, 2.5% and 3% for insulin and both 4.4% for C-peptide. The IVGTT was chosen because it is considered to be a reliable, simple tool for directly assessing beta cell function, as it bypasses gastro-intestinal effects associated with oral glucose intake. In addition, the insulin-modified IVGTT protocol also guarantees an accurate calculation of insulin sensitivity [19]. At −65, −60, −30, 0, 30, 60, 90, 120, 150 and 180 min, BNP plasma concentrations were measured by using the commercially available ARCHITECT BNP immunoassay on the ARCHITECT System (Abbott Laboratories, Vienna, Austria).

Calculations The AUCs for glucose, insulin and C-peptide concentration were calculated using the trapezoidal rule in the first 10 min for a comprehensive description of the very early phase, when the perturbation of the steady state is maximal. IVGTT glucose and insulin data were analysed using a simplified minimal model method [20] that provides a validated index of insulin sensitivity (CSI), and which describes the action of insulin on glucose disappearance following the glucose load, and the theoretical zero intercept of the glucose concentration (G_0). Acute incremental insulin (dAIRg) and C-peptide (dACPRg) responses were calculated as the mean suprabasal concentration during the time interval 3–10 min to avoid possible influences from the glucose mixing phase. Given the exogenous insulin infusion at 20 min, the total insulin delivery could be evaluated during the whole test only with the C-peptide AUC. Early beta cell function was calculated as the ratio of dACPRg to the incremental glucose concentration (dGLUC) in the same time interval. In addition, hepatic insulin extraction could be calculated as previously described [21], but only during the first 20 min. The pharmacokinetic approach was used for evaluating the glucose distribution volume (litres), calculated as the glucose dose divided by G_0, and the insulin clearance, calculated as the insulin dose divided by the insulin AUC from 20 to 180 min [22]. The disposition index was calculated as CSI × dAIRg and reflects the effect of peripheral insulin in allowing glucose disposal with regard to the prevailing insulin resistance [23].

Differences in circulating BNP concentrations were tested by repeated measurements ANOVA, followed by post hoc statistics for specific time points. Differences between variables were tested by paired *t* test after checking for normality. SPSS (Chicago, IL, USA) was used as the statistical software; data and results are presented as means ±SE unless otherwise indicated; $p<0.05$ is considered to be statistically significant.

Results

BNP infusion significantly increased plasma BNP levels within 30 min ($p<0.001$) to a plateau of 47–56 pmol/l (corresponding

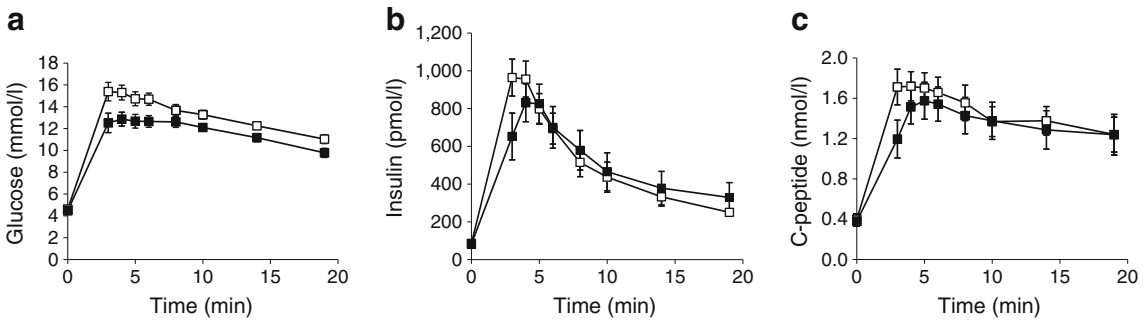

Fig. 3 Plasma concentrations of glucose (**a**), insulin (**b**) and C-peptide (**c**) during the IVGTT, immediately following the glucose bolus and before the start of the insulin infusion (time point 0 min is 1 h after the start of BNP/placebo infusion; placebo, white squares; 3 pmol kg^{-1} min^{-1} BNP, black squares)

Table 1 Metabolic variables during IVGTT on placebo- and BNP-study days in ten participants during the cross-over trial

Variable	Placebo	BNP	*p* value
dGLUC (3–10) (mmol/l)	9.7±0.5	8.0±0.5	0.003
$AUC_{Glucose}$ (0–10) (mmol/l×[10 min])	130±5	114±5	0.002
dAIRg (3–10) (pmol/l)	641±78	592±98	0.344
$AUC_{Insulin}$ (0–10) ($\times10^{-3}$ pmol/l×[10 min])	6.32±0.72	5.76±0.90	0.238
dACPRg (3–10) (nmol/l)	1.21±0.11	1.03±0.13	0.015
$AUC_{C\text{-}peptide}$ (0–10) (nmol/l×[10 min])	14.4±1.5	12.6±1.6	0.033
$AUC_{C\text{-}peptide}$ (0–180) (nmol/l×[3 h])	115±18	114±17	0.881
Glucose initial distribution volume (l)	7.8±0.3	9.3±0.5	0.001
Hepatic insulin extraction (0–20) (%)	65.2±5.9	67.6±3.0	0.530
Insulin clearance (ml min^{-1} kg^{-1})	8.3±0.7	8.7±1.1	0.734
Insulin sensitivity ($\times10^{-4}$ min^{-1}[μU/ml]$^{-1}$)[a]	9.45±1.59	10.14±1.25	0.672
Beta cell function (3–10) ($pmol_{C\text{-}peptide}/mmol_{Glucose}$)	124±11	129±17	0.637
Disposition index (10^{-2} min^{-1})	7.65±1.12	7.70±0.99	0.976

Values are mean±SE

The time interval over which the variable is calculated is given in parentheses (min)

[a]To convert values to SI units (μmol m^{-2} min^{-1}[pmol/l]$^{-1}$) multiply by 0.167

to 350–480 pg/ml) (Fig. 2); thereafter, BNP concentration remained constantly elevated.

Circulating glucose concentration was lower during the first 20 min of the IVGTT with BNP compared with the placebo control ($p<0.001$; Fig. 3). During the first 10 min, C-peptide was reduced compared with the control (1.42±0.13 vs 1.62±0.10 nmol/l, $p=0.015$). No differences were detected between BNP and placebo for insulin and C-peptide over the remaining period of the test; furthermore, insulin sensitivity, insulin release (dAIRg), insulin clearance, hepatic insulin extraction and the disposition index remained unchanged (Table 1).

Modelling analysis ascribed the initial lower glucose concentration to a 20% increase in the initial glucose distribution volume observed with BNP (increment of ~2% body weight from 11±1% body weight to 13±1%, $p<0.002$). The total distribution volume was, in both cases, approximately 26% body weight.

Participants had no significant changes in blood pressure throughout the study period. Heart rate was significantly higher during BNP infusion compared with placebo at time points 60, 180 and 270 min ($p<0.05$) and significantly lower during the BNP infusion from time point −60 to −30 min ($p<0.05$) (Table 2).

Discussion

The main finding of this study is that BNP infusion decreases circulating glucose concentrations achieved during a glucose tolerance test, without affecting insulin secretion and clearance. Circulating glucose remained lower with BNP treatment during the early phase of the IVGTT, and our analysis quantified an acute increase in the glucose initial distribution volume of approximately 20%. The decrease in C-peptide during the initial phase was accompanied by lower levels of glucose, and therefore the beta cell function remained unchanged.

The study participants remained lying down and fasted throughout the study, and exhibited, in agreement with

Table 2 Blood pressure and heart rate

Time point	Systolic BP (mmHg)		Diastolic BP (mmHg)		Heart rate (bpm)	
	Placebo	BNP	Placebo	BNP	Placebo	BNP
−60	129±12	131±11	74±8	79±10	65±13	69±16
−30	125±10	129±6	75±8	76±3	66±13	64±11
0	129±14	129±7	77±7	77±6	66±12	65±11
30	125±14	131±10	74±5	76±8	64±13	65±10
60	127±8	125±11	73±7	74±11	61±9	70±12*
90	126±12	128±11	73±7	73±9	59±6	64±6
120	121±13	124±13	73±7	73±10	60±6	62±8
150	120±10	121±12	72±8	72±9	63±6	65±8
180	123±12	121±12	72±7	71±8	61±7	68±7*
270	121±9	128±21	71±6	74±7	60±6	73±15*

Blood pressure and heart rate (mean±SD) during BNP and placebo infusion

Heart rate was significantly higher during BNP infusion compared with the placebo at time points 60, 180 and 270 min

*$p<0.05$

bpm, beats per min

previous findings, no significant changes in blood pressure [24]. Heart rate was significantly higher during BNP infusion compared with placebo at time points 60, 180 and 270 min ($p<0.05$) (Table 2), which might be due to a non-significant decrease in blood pressure. This increased heart rate is in line with a review by Prahash and Lynch [25], which also showed a higher heart rate following infusion of BNP at 0.1 μg/kg body weight per min compared with placebo.

BNP possesses natriuretic effects; therefore, it is unlikely that it retrieves water within the circulatory system, thereby diluting the available glucose. Due to BNP's vasodilating properties, the decrease in circulating glucose is best explained by the increased glucose distribution volume, indicating a tendency for glucose to fill its total distribution space more quickly in the presence of BNP. There were no changes in the glucose disposal rate and, in addition, no difference in insulin sensitivity could be detected; therefore there was no increase nor decrease in the removal of glucose from the system. We hypothesise that other distribution spaces (e.g. interstitial fluids, intracellular compartments) could be made accessible for glucose, raising questions on possible distribution-modifying effects of BNP, which might also affect the distribution volume of other hormones and drugs. A weakness of the study is the fact that we have no means of evaluating which areas become available to augment the distribution volume. The fact that BNP-induced vasodilatation usually occurs at the capillary level, and that the increased distribution volume goes beyond the contribution of the capillary space, draws attention to other possible distribution spaces, such as the endothelial cells, which are the first to be targeted by hyperglycaemia [26]. BNP could also impact on glucose excretion via the kidneys, inducing local vasodilatation and increasing glucose elimination. It is important to consider that this is an acute effect, which could vanish as soon as the body adjusts to the new situation. To date, it is not clear whether the increase in glucose distribution volume is specific to natriuretic peptides, or is also a property of other vasodilators, such as nitrates. This question remains to be answered in further studies.

The fact that this study was performed in healthy, insulin-sensitive volunteers is one of its limitations. This trial set out to investigate the effects of BNP under 'normal' conditions. Additional trials would be needed to obtain further information on the effects of BNP on glucose metabolism and, particularly, on insulin sensitivity, in patients with impaired glucose tolerance or diabetes.

A second limitation is the fact that we only investigated the acute effects of BNP administration. As the severity of heart failure increases, greater quantities of BNP are secreted, leading to a reduction in the heart work load, and patients with heart failure are exposed to chronic over-secretion of BNP. Low BNP levels are associated with increased metabolic risk factors [27], but to date there have been no trials on the effect of chronic BNP administration on glucose metabolism in humans. Data from rodent studies introduce further evidence on the anti-diabetogenic effects of BNP, as chronic overexpression of BNP protects mice against diet-induced obesity and accompanying insulin resistance [28]. A recent study described lipolytic effects of acute administration of BNP-32 not only in healthy volunteers, but also in patients with heart failure [29].

BNP-32 has a half life of several minutes; therefore we designed the study so as to administer it as a continuous intravenous infusion. NT-proBNP and degradation products have a half life of several hours, and plasma BNP concentrations measured in patients with heart failure correlate best with (biologically inactive) degradation products than with the functional BNP-32 (=BNP(1–32)) [30]. Nevertheless, chronic over-secretion of BNP (including active BNP) in chronic heart failure is indisputable.

Taken together, here we show that acute administration of BNP lowers plasma glucose levels following an IVGTT in men. These results support a non-diabetogenic role of BNP and introduce new questions regarding BNP-induced differences in glucose availability and signalling in several organs and tissues.

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Contribution statement BBH contributed to the conception of the study, analysis of data and article draft; GV contributed to the design of the study, interpretation of data and revision of the article; MRi, BD, TM and MRe contributed to analysis of data and revision of the article; AL contributed to interpretation of data and revision of the article; GP contributed to analysis and interpretation of data and revision of the article; MC contributed to the conception and design of the study, interpretation of data and revision of the article. All authors gave approval of the final version to be published.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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