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ORIGINAL ARTICLE

Inverse Association Between Myocardial B-Type Natriuretic Peptide Release and Functional Capacity in Healthy Humans

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Background B-type natriuretic peptide (BNP) has been found to be inversely related to peak oxygen consumption (peak VO_2) in various patient populations. However, in these studies, circulating plasma BNP, i.e. the net effect of release and elimination, rather than cardiac BNP release has been measured. We assessed the relationship between the transcardiac BNP gradient [ΔBNP_{CS-A}, i.e. the difference between BNP in coronary sinus (BNP_{CS}) and arterial (BNP_A) plasma] and peak VO_2 in healthy subjects with a view to better understanding the regulation of cardiac BNP release in humans.

Methods We studied 10 asymptomatic subjects (age 64 ± 11 years, two females) with preserved left ventricular function (left ventricular ejection fraction 62 ± 5%, averaged early diastolic mitral annular velocity 9 ± 3 cm/s) and low BNP (BNP in venous plasma [BNP_V] <100 ng/l). Subjects underwent measurement of BNP_A and BNP_{CS} for the calculation of ΔBNP_{CS-A}, maximal cardiopulmonary exercise testing, echocardiography and resting and submaximal exercise right heart catheterisation.

Results The median (range) BNP_V, BNP_A, BNP_{CS}, and ΔBNP_{CS-A} were 62 (14, 82), 60 (13, 79), 110 (25, 157), and 44 (1, 103) ng/l. The median peak VO_2 during cardiopulmonary exercise testing was 21.5 (18, 54) ml/min/kg. There was an inverse correlation between higher ΔBNP_{CS-A} and lower peak VO_2 ($r = -0.84$; $p = 0.002$) and oxygen pulse ($r = -0.64$, $p = 0.049$). There was a trend towards an inverse correlation between ΔBNP_{CS-A} and the exercise arteriovenous oxygen content difference ($r = -0.58$; $p = 0.08$).

Conclusions In healthy humans, there is an inverse association between myocardial BNP release and peak VO_2, which may be due to cardiac and non-cardiac mechanisms.

Keywords B-type natriuretic peptide • Myocardial • Transcardiac • Peak oxygen consumption

Introduction

B-type natriuretic peptide (BNP) is an endogenous peptide primarily released from the heart and exhibiting multiple beneficial cardiovascular effects including vasodilation, diuresis and natriuresis [1]. It is thought that various forms of ''cardiac stress'' including (primarily left) ventricular wall stress and myocardial ischaemia trigger cardiac BNP release as an endogenous mechanism to counteract the adverse effects of the activation of the sympathetic nervous system

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and the renin-angiotensin-aldosterone system in presence of cardiac disease, in particular heart failure [1]. Recently, enhancement of these biological effects of BNP by inhibition of BNP degradation has been shown to be clinically highly relevant [2]. However, several aspects of the regulation of cardiac BNP release in humans are still not well understood, one reason being that, in the vast majority of pathophysiological studies, circulating BNP concentrations in peripheral plasma were measured which represent the net effect of cardiac production and extracardiac elimination, rather than the effective cardiac release of BNP [3].

Studies in patients with cardiac and pulmonary disease have shown a significant inverse association between higher BNP plasma concentrations and lower exercise capacity as assessed by measurement of peak oxygen consumption (peak VO_2) [4–6], the latter being the most important parameter reflecting functional capacity in health and disease [7]. This observation might suggest that the regulation of BNP release is more complex than previously thought since peak VO_2 depends on multiple factors including genetics, training, and the function and interaction of heart, lungs, muscles, and blood components (i.e. oxygen transport capacity) [7]. However, it is unknown whether the association between BNP and peak VO_2 is also present in healthy subjects, whether there is really an association between cardiac BNP release (as opposed to plasma BNP) and peak VO_2, and if yes, which component contributing to peak VO_2 is related to the cardiac BNP release. The aim of the present study was therefore to assess the relationship between myocardial BNP release as assessed by transcardiac BNP gradients and peak VO_2 in healthy subjects with a view to better understanding the regulation of cardiac BNP production in humans.

Methods

Subjects and Study Protocol

We studied 10 asymptomatic subjects (median age 65 years, two females) without obvious cardiac disease (i.e., left ventricular ejection fraction [LVEF] >50%, normal left ventricular diastolic function or a pattern of impaired relaxation, no evidence of coronary artery disease based on history, stress testing, and/or coronary angiography, and no more than mild valvular stenosis or regurgitation), normal renal function (i.e., estimated glomerular filtration rate [eGFR] >60 ml/min/1.73 m^2), absence of anaemia (i.e., haemoglobin ≥120 g/l in women and ≥130 g/l in men), absence of a history of pulmonary disease, and low BNP in venous plasma (BNP_V), i.e. $BNP_V < 100$ ng/l. These criteria were applied to ensure inclusion of a population without cardiac and non-cardiac factors with known impact on BNP_V and subjects with a BNP_V spectrum in a relatively normal range. Eight subjects were recruited by advertisement. Two subjects were approached as they were referred for cardiac catheterisation for exclusion of pulmonary hypertension. These two subjects had undergone echocardiography for unspecific symptoms, and based on the peak tricuspid regurgitation velocity possible pulmonary hypertension had been suggested. To clarify the situation in these two subjects who did not have chronic symptoms potentially suggestive of pulmonary hypertension, the treating physicians had made a decision for right heart catheterisation. All subjects underwent detailed transthoracic echocardiography, cardiac catheterisation including arterial catheterisation and coronary sinus catheterisation, assessment of haemodynamics using right heart catheterisation at rest and during exercise, blood sampling to assess BNP_V and transcardiac BNP gradients, and maximal symptom-limited cardiopulmonary exercise testing (CPET). All studies were performed in the non-fasting state. We had previously reported on some these subjects [3]. The study was approved by the Alfred Hospital Ethics and Research Committee, and each of the subjects provided written informed consent.

Echocardiography

Echocardiograms were obtained by one single experienced echocardiographer, using standard techniques in accordance with current guidelines when the study was performed [8,9]. Measurements were performed off-line by a single reader. Measurements were averaged from three cycles. Left ventricular volumes and ejection fraction were calculated using the biplane Simpson method. Pulsed wave Doppler recordings of transmitral inflow were obtained between the mitral leaflet tips from the apical four-chamber view. Peak systolic (s′) and peak early diastolic (e′) mitral annular velocities were measured by pulsed wave tissue Doppler at the septal and lateral annulus, and averaged values are reported. Additional standard measures were performed as previously reported [3].

Cardiac Catheterisation

Cardiac catheterisation was performed immediately after the resting echocardiogram. A 3F arterial line was placed in a radial or brachial artery for blood pressure measurement and blood sampling. Before the haemodynamic measurements a coronary sinus catheter (6F) was inserted via a 7F introducer sheath placed in the right internal jugular or a brachial vein and positioned under fluoroscopic control. The tip of the catheter was positioned at least 2 cm proximal to the orifice of the coronary sinus as confirmed by contrast injection. Blood samples were simultaneously taken from the arterial line and the coronary sinus catheter. After removal of the coronary sinus catheter a balloon-tipped pulmonary artery catheter (7F) was inserted for measurement of right atrial pressure, pulmonary artery pressure, and pulmonary artery wedge pressure (PAWP). The wedge position was confirmed by fluoroscopy and pressure wave form, and the mean PAWP was measured at end-expiration. Cardiac output was measured using thermodilution with measurements taken in triplicate.

Subjects then started to exercise in the supine position on a cycle ergometer mounted to the catheter table at a work rate

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