ARTICLE IN PRESS
+ MODEL
Respiratory Medicine (2015) xx, 1–11

Available online at www.sciencedirect.com
ScienceDirect
journal homepage: www.elsevier.com/locate/rmed

Associations of circulating natriuretic peptides with haemodynamics in precapillary pulmonary hypertension

Ralf Kaiser [a,*], Katharina Grotemeyer [b], Philipp Lepper [a], Caroline Stokes [b], Robert Bals [a], Heinrike Wilkens [a]

[a] *Saarland University, Dep. of Internal Medicine V, Pulmonology, Allergology, Respiratory Intensive Care Medicine, Kirrberger Strasse, D-66424, Homburg/Saar, Germany*
[b] *Saarland University, Dep. of Gastroenterology, Germany*

Received 29 October 2014; accepted 23 February 2015

KEYWORDS
Pulmonary hypertension;
Haemodynamics;
Renal function;
Natriuretic peptides

Summary
Background: While N-terminal B-type natriuretic peptide (NT-proBNP) has been examined extensively in pulmonary hypertension (PH), limited data exists on the subtype A, C and D. The aim of this prospective pilot study was a head-to-head comparison of NPs in respect to haemodynamic parameters and the influence of renal function.
Methods: Plasma samples were drawn during routine right heart catheterization in 62 patients with precapillary PH and 20 control patients. MR-proANP measurements were performed on the automated Kryptor platform, NT-proBNP by CLIA, NT-proCNP and DNP levels by ELISA. Results are expressed as median [range] and tested non-parametrically. Non-parametric locally linear multiple regression was performed to determine the influence of renal function on NP levels. P-values <0.05 were considered significant.
Results: Patients with PH had significantly higher MR-proANP and NT-proBNP levels. NT-proCNP showed a trend to higher levels, while DNP did not differ from control subjects. Both MR-proANP and NT-proBNP were associated with cardiac index (CI), right atrial pressure (RAP), mean pulmonary artery pressure (PAPm) and pulmonary vascular resistance index (PVRI). NT-proCNP was associated with RAP, while DNP showed no associations with haemodynamic variables. Associations of haemodynamic parameters with NPs were weakened in patients with in elevated serum creatinine and showed increased regression slopes.
Conclusion: MR-proANP demonstrated equivalent associations with haemodynamics compared

Abbreviation: MR-proANP, mid-regional pro-A-type natriuretic peptide; NT-proBNP, N-terminal pro-B-Type natriuretic peptide; NT-proCNP, N-terminal pro-C-type natriuretic peptide; DNP, D-type natriuretic peptide; NP, natriuretic peptide; PH, pulmonary hypertension; PAH, pulmonary arterial hypertension; LD, lung disease associated PH; CTEPH, chronic thrombembolic PH; CKD, chronic kidney disease; cGMP, cyclic guanylyl mono-phosphate; RAAS, renin-angiotensin-aldosteron system.

* Corresponding author. Tel.: +49 6841 1623619; fax: +49 6841 1623645.
E-mail address: ralfkaiser@gmx.net (R. Kaiser).

http://dx.doi.org/10.1016/j.rmed.2015.02.014

Please cite this article in press as: Kaiser R, et al., Associations of circulating natriuretic peptides with haemodynamics in precapillary pulmonary hypertension, Respiratory Medicine (2015), http://dx.doi.org/10.1016/j.rmed.2015.02.014

to NT-proBNP, but both markers depend on intact renal function. NT-proCNP was correlated with RAP and renal function, while DNP showed no associations. Larger studies should evaluate MR-proANP as candidate prognostic biomarker in PH.

Introduction

Natriuretic peptides (NP) are mediators in the regulation of fluid balance in the circulation. Triggers of incretion are transmural wallstress of the heart as well as hypoxia. So far, four subtypes A to D have been identified in humans, demonstrating specific binding characteristics to three NP receptors NPR-A, NPR-B and NPR-C. Natriuretic peptides are synthesized from pro-peptides by intracellular cleavage. Diagnostic tests for natriuretic peptides vary in respect to the target region used as antigen and include the N-terminus (NT), mid-regional (MR) or C-terminus (CT) of the peptide.

The physiological effects of natriuretic peptides include elimination of water via renal receptors to maintain fluid balance and decrease of pulmonary vascular resistance by direct interaction with vascular smooth muscle cells.

Precapillary pulmonary hypertension (PH) is characterized by an increase of pulmonary vascular resistance and therefore increased right ventricular afterload and pulmonary artery pressure. Consequently, dyspnea, venous congestion, exercise intolerance and syncope develop. As the disease progresses, the right ventricle begins to fail and therefore limits the life expectancy to a three year survival rate of 73.9% under current guideline therapy [1]. In this context, BNP emerged as an established biomarker for therapy guidance and risk estimation [2].

A-type natriuretic peptide (ANP) is attributed to atrial synthesis in the heart. As most cardiac disease is related to ventricular damage, ANP was neglected in this area of research as being less sensitive compared to alternative biomarkers [3]. Nevertheless, tests for its C-terminal, mid-regional and N-terminal fragments have been developed and compared mainly in acute cardiac disease [4]. Data concerning ANP in PH is very limited [5]. The recent development of MR-proANP for an automated validated test platform lead to new data in the area of cardiovascular research [6,7], but has not been evaluated for patients with PH.

BNP has been used extensively in daily practice to evaluate patients with congestive heart failure. While therapy guidance remains controversial for left heart disease [8—10], NT-proBNP has evolved as an established marker in the diagnostic procedure and evaluation of PH [11—13].

The principal source of C-type natriuretic peptide (CNP) is the vascular endothelium and therefore contrasts ANP and BNP. Shear stress has been shown to increase its expression in vascular endothelial cells [14]. Furthermore, significant production of CNP was measured in the failing heart [15—17]. The pathophysiological function of CNP is less well understood compared to ANP and BNP as result of a broader range of organs CNP is acting on. So far, no data has been published on CNP in the field of PH.

D-type natriuretic peptide (DNP) was found in the venom of Dendroaspis angusticeps — the green mamba, and is therefore named in the literature also as dendroaspis natriuretic peptide. Its presence in human plasma and vessels was soon discovered and an elevation demonstrated in patients with heart disease [18]. Its interaction with fluid balance and vascular tone has not been examined in patients with PH.

The aim of this study was to examine the associations of MR-proANP, NT-proBNP, NT-proCNP and DNP with invasive haemodynamic parameters in patients with PH and elaborates the influence of renal function.

Methods and design

Participants

Between June 2007 and December 2011, we enrolled prospectively 20 control subjects and 68 patients the Department of Pulmonology of the Saarland University Hospital (Homburg/Saar, Germany). The control group consisted of 9 subjects with invasive exclusion of PH and 11 volunteers without history of cardiovascular or pulmonary disease, with bland non-invasive work-up. Six subjects from the patient cohort were excluded due to missing data, compromised blood sampling or development of significant left heart disease. The remaining 62 patients are characterized in Tables 1 and 2, consisting of both incident and prevalent PH. The patient group with PAH consisted of 24 patients with idiopathic PAH, 9 patients with connective tissue disease associated PAH, two patients with Eisenmenger syndrome and one of each HIV-PAH, porto-pulmonary PH, M. Osler and familial PAH. The patients with lung disease associated PH (LD) consisted of 17 patients. Included were six patients with interstitial lung disease (ILD), five patients with idiopathic pulmonary fibrosis (IPF), four patients with endstage COPD and two had silicosis. All patients had either pulmonary angiograms and/or ventilation-perfusion szintigraphy to distinguish CTEPH from PAH. Patients with post-capillary PH, significant heart disease, and malignancies were excluded from the study. Patients were at least two months haemodynamically stable during enrollment.

Study design

Blood was drawn during right heart catheterization in pulmonary artery position. The samples were processed immediately, aliquoted and stored at −80 °C. Diagnosis of PH was based on a mean pulmonary artery pressure above

Please cite this article in press as: Kaiser R, et al., Associations of circulating natriuretic peptides with haemodynamics in precapillary pulmonary hypertension, Respiratory Medicine (2015), http://dx.doi.org/10.1016/j.rmed.2015.02.014