

Brain Natriuretic Peptide and NT-proBNP Levels Reflect Pulmonary Artery Systolic Pressure in Trekkers at High Altitude

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Summary

Our objective was to evaluate the utility of the natriuretic peptides BNP (brain natriuretic peptide) and NT-proBNP as markers of pulmonary artery systolic pressure (PASP) in trekkers ascending to high altitude (HA). 20 participants had BNP and NT-proBNP assayed and simultaneous echocardiographic assessment of PASP performed during a trek to 5150 m. PASP increased significantly ($p=0.006$) with ascent from 24 ± 4 to 39 ± 11 mm Hg at 5150 m. At 5150 m those with a $PASP\geq 40$ mm Hg ($n=8$) (versus those with $PASP<40$ mm Hg) had higher post-exercise BNP (pg/ml): 54.5 ± 36 vs. 13.4 ± 17 ($p=0.012$). Their resting BNP at 5150 m was also higher: 57.3 ± 43.4 vs. 12.6 ± 13 ($p=0.017$). In those with a pathological (≥ 400 pg/ml) rise in NT-proBNP at 5150 m ($n=4$) PASP was significantly higher: 45.9 ± 7.5 vs. 32.2 ± 6.2 mm Hg ($p=0.015$). BNP and NT-proBNP may reflect elevated PASP, a central feature of high altitude pulmonary oedema, at HA.

Key words

Hypoxia • Altitude • BNP • NT-proBNP • Pulmonary artery systolic pressure

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Introduction

Large numbers of people trek to high altitude

(HA) each year, of which a significant number develop pulmonary hypertension and succumb to HA illnesses such as high altitude pulmonary oedema (HAPE). Currently there is no useful bed-side blood test that can aid in the diagnosis of pulmonary hypertension or HAPE.

The cardiac natriuretic peptides, BNP (active) and NT-proBNP (inactive), are derived from a prohormone, proBNP, stored in cardiomyocytes (Hall 2005). Their release is stimulated primarily by myocardial wall tension related to cardiomyocyte stretch and as such they are classically associated with congestive cardiac failure (CCF) secondary to left ventricular dysfunction (LVD) (Hall 2005). However, it is increasingly recognized that hypoxia may also stimulate their release (Casals *et al.* 2009, Due-Andersen *et al.* 2008) and we have recently reported a rise in BNP (Woods *et al.* 2011a) and NT-proBNP (Woods *et al.* 2012) at high altitude (HA). Further, they may also be elevated in conditions associated with pulmonary artery hypertension at sea-level (SL) (Blyth *et al.* 2007) and have been correlated with pulmonary artery systolic pressure (PASP) pre- and post-exercise (Kerr *et al.* 2008).

The hypoxia of HA leads to pulmonary vasoconstriction, which in turn contributes to an increase in PASP, which may be associated with elevated natriuretic peptides at SL. An exaggerated pulmonary vascular response is of central importance in the development of high altitude pulmonary oedema (HAPE) (Bartsch *et al.* 2005, Maggiorini *et al.* 2001) but symptoms of HAPE can

be difficult to distinguish in the early stages. Progressive shortness of breath with a dry cough may occur but is difficult to distinguish from that which commonly occurs at HA (Hall *et al.* 2011). Inspiratory lung crackles are a later feature of HAPE but again are not pathognomic (Hall *et al.* 2011). Only as the disease progresses with orthopnoea through to the typical pink frothy sputum of frank pulmonary oedema does the diagnosis become obvious. Early detection of HAPE is therefore challenging and any simple test with the potential to facilitate early diagnosis and treatment could be life-saving.

Conventionally, assessment of PASP either requires invasive assessment, not practical in the field, or non-invasive assessment using trans-thoracic echocardiography that requires a skilled operator and expensive equipment not usually available on conventional expeditions to HA. BNP and NT-proBNP can be assayed on a small venous blood sample and BNP results can be readily available in the field with little expertise using a point-of-care (POC) testing device.

Although we have previously reported an association between BNP and NT-proBNP and acute mountain sickness (AMS) (Woods *et al.* 2011a, Woods *et al.* 2012) the evidence above prompted us to establish if NT-proBNP/BNP could also be driven by, and act as a marker for, an elevated PASP in previously healthy individuals exposed to HA.

Methods

The study was approved by the Ministry of Defence Research Ethics Committee (MODREC), UK and conformed to the standards set in the Declaration of Helsinki. All participants gave written informed consent.

As previously described (Woods *et al.* 2012) twenty healthy participants from the UK military participating in Exercise Khumbu Ramble, a trek in Nepal were studied. Five of the subjects had been trekking at high altitude previously, not in the preceding 6 months, and none were HAPE-susceptible. The group flew from Kathmandu (Kat) to Lukla (2840 m) by light aircraft and commenced trekking on day 1. Three main altitudes were used to study participants: 3440 m (day 2); 4270 m (day 6) and 5150 m after ascent of Kala Patthar (5643 m) on day 10. Participants were studied immediately on arrival after a day of trekking ("post-exercise") and the following morning at rest.

Echocardiography and venous blood samples (from antecubital fossa) were performed post-exercise

and at rest at the main study altitudes. Oxygen saturation (digitally on warm hands at rest) was measured using a Nellcor NP-20 pulse oximeter (Covidian, MA, USA). BNP was assayed using a point-of-care analyzer (Biosite Triage Meter with BNP tests strips, Alere Ltd, Cheshire, UK) in the field and NT-proBNP was assayed on frozen samples on return to the UK using the Roche NT-proBNP assay (Roche Diagnostics, Mannheim, Germany). As NT-proBNP is renally cleared renal function was assessed by serum creatinine. PASP was estimated from the maximum velocity of the trans-tricuspid gradient using continuous wave Doppler imaging added to a fixed value of 5 mm Hg as previously validated (Yock and Popp 1984). Further off line processing was carried out by a consultant cardiologist (CB), who was blinded to any of the other data, to ascertain PASP.

For statistical calculations the software package SPSS 14.0 was used. Parametric or non-parametric statistical tests were applied after performing the Shapiro-Wilks statistic.

Changes in dependent variables between altitudes were initially tested by Student's paired t test or Wilcoxon signed ranks test. For independent variables an independent-samples t test or Mann Whitney test was used. Either a within participants ANOVA or a Friedman test was performed to investigate any serial changes in measures (e.g. PASP or BNP) with ascent. BNP and NT-proBNP levels were also interrogated according to a PASP \geq 40 mm Hg or <40 mm since the maximal PASP response in healthy participants to hypoxia is considered 40 mm Hg (Grunig *et al.* 2000). Spearman's rank correlation between BNP, NT-proBNP and PASP was performed, as was a ROC (receiver operating characteristic) analysis to investigate the utility of the natriuretic peptides in identifying a PASP>40 mm Hg.

A p value <0.05 was considered significant throughout. All data are reported as mean \pm SD (\pm range where appropriate) except for Figure 2 (mean \pm SEM).

Participants were excluded from analysis once they took drugs to aid acclimatization.

Results

Patient demographics have been previously reported (Woods *et al.* 2012), in brief the 20 subjects (9 female, 11 male) were 36.1 \pm 1.9 years old (range 22-51 yrs); 174.5 \pm 1.7 cm high and weighed 76.8 \pm 3.1 kg (all data mean \pm SEM). One subject had taken drugs known to affect acclimatization by 4270 m, and 5 participants by 5150 m.

Table 1. Oxygen saturation, PASP, BNP and NT-proBNP with ascent to 5150 m in the Khumbu valley, Nepal (n=20 at 1300 and 3400 m, n=19 at 4270 m and n=15 at 5150 m). The BNP and NT-proBNP data have previously been reported (Woods *et al.* 2012) but not in the context of PASP.

Altitude	SpO ₂ (%)	PASP (mm Hg) (mean±SD, range)	NT-proBNP (mean±SD, range)	BNP (mean±SD, range)
Kat (1300 m) (rest)	96±0.5	24.1±4.1 (18-32)	37±30 (9.4-111)	9.2±2 (5-35)
3400 m (post-exercise)		36.8±8.2 (23-56)	111.2±96 (35-379)	N/A
3400 m (rest)	87.5±1.2	31.6±8 (21-53)	334.8±541 (27-2081)	N/A
4270 m (post-exercise)		38.6±9.2 (25-62)	152±238 (18-994)	16.6±4 (5-56)
4270 m (rest)	85.1±1.2	34.8±7.7 (25-52)	207±291 (18-1045)	28.9±9 (5-101)
5150 m (post-exercise)		39.4±10.5 (25-57)	301±408 (15-1539)	32.3±8.8 (5-95.6)
5150 m (rest)	73.8±2	35.7±8.4 (25-53)	259±346 (18-1109)	33.3±9.7 (5-123)

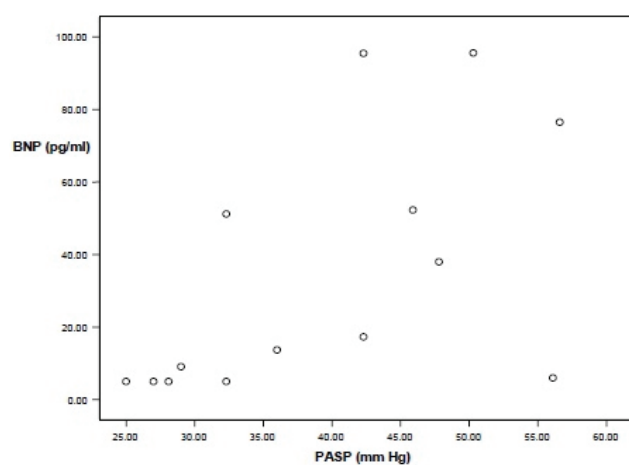


Fig. 1. At 5150 m post-exercise there was a significant correlation between BNP and PASP ($\rho=0.7$, $p=0.005$).

PASP rose significantly ($p=0.006$) with altitude from 24 ± 4 at baseline to 39 ± 11 mm Hg at 5150 m (Table 1). Overall BNP significantly correlated with PASP ($\rho=0.45$, $p<0.001$) as did NT-proBNP ($\rho=0.508$, $p<0.001$). The correlation between BNP and PASP was strongest at 5150 m post-exercise ($\rho=0.7$, $p=0.005$) (Fig. 1).

At 5150 m post-exercise those with a PASP ≥ 40 mm Hg ($n=8$) (versus those with PASP <40 mm Hg) had higher post-exercise BNP (pg/ml): 54.5 ± 36 vs. 13.4 ± 17 ($p=0.012$). Their resting BNP at 5150 m was also higher: 57.3 ± 43.4 vs. 12.6 ± 13 ($p=0.017$) (Fig. 2). In the same participants there were non-significant differences in NT-proBNP (pg/ml) at 5150 m: 500 ± 516 vs. 146 ± 251 (post-exercise, $p=0.083$) and 433 ± 432 vs. 117 ± 162 (resting, $p=0.19$). BNP and NT-proBNP had been significantly higher in these participants at the previous altitude of 4270 m (BNP: 40 ± 38.5 vs. 16.3 ± 27 , $p=0.02$, NT-

proBNP: 308 ± 356 vs. 117 ± 207 , $p=0.028$). In those with a pathological (≥ 400 pg/ml) rise in NT-proBNP at 5150 m ($n=4$) PASP was significantly higher than those without: 45.9 ± 7.5 vs. 32.2 ± 6.2 mm Hg ($p=0.015$) (Fig. 3).

ROC analysis (to investigate the utility of BNP and NT-proBNP measured at HA in identifying a PASP >40 mm Hg) revealed an AUC of 0.741 (95 % CI 0.591-0.850, $p=0.001$) and 0.743 (95 % CI 0.612-0.874, $p<0.001$) for BNP and NT-proBNP respectively. An NT-proBNP cut-off of 133 pg/ml gave a sensitivity of 70 % and a specificity of 83 % for identifying a high PASP.

Serum creatinine ($\mu\text{mol/l}$, mean±SD, (range)) at baseline was 78.11 ± 8.8 (63-95) and at 5150 m 94.3 ± 16.4 (76-142) ($p<0.001$).

Discussion

The main, novel, finding of this study is that at HA those with a markedly elevated PASP appear to have higher BNP and NT-proBNP than those with a more moderate PASP.

An abnormally high PASP is a key feature in the pathophysiology of HAPE (Bartsch *et al.* 2005, Maggiorini *et al.* 2001) It has been suggested that the maximal PASP response to hypoxia (FiO₂ 12 %) in healthy participants is 40 mm Hg (Grunig *et al.* 2000) Indeed, HAPE susceptible participants under hypoxic conditions have a much higher PASP than non-susceptible participants (33 ± 6 vs. 50 ± 9 mm Hg) (Berger *et al.* 2005) that can be further exacerbated by an exercise stimulus (Dehnert *et al.* 2005).

Although markedly elevated levels of BNP and NT-proBNP are used as a marker of CCF they are also moderately elevated in pulmonary hypertension at SL

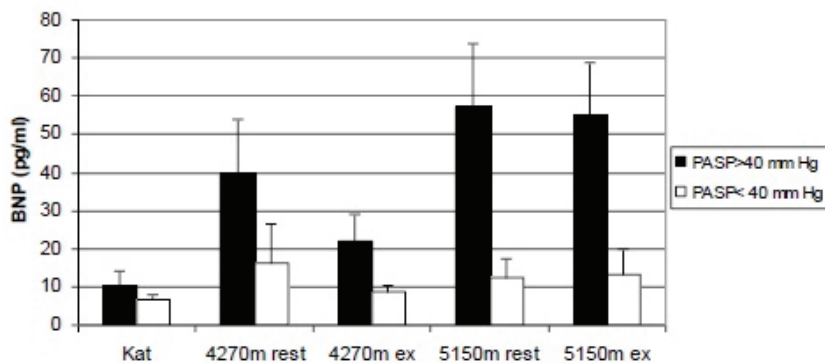


Fig. 2. BNP (mean±SEM) with ascent according to a PASP≥40 mm Hg (n=8) vs. <40 mm Hg at 5150 m post-exercise (n=20 at 1300 and 3400 m, n=19 at 4270 m and n=15 at 5150 m). Those with a PASP≥40 mm Hg had post-exercise BNP (pg/ml) that was significantly ($p=0.012$) higher (54.5 ± 36 vs. 13.4 ± 17) as was resting BNP at 5150 m (BNP: 57.3 ± 43.4 vs. 12.6 ± 13 $p=0.017$).

(Blyth *et al.* 2007) There is a significant difference between their “normal” levels {median BNP in a healthy population age <45 years is 7.7 pg/ml, (Alere Triage BNP test product insert); median NT-proBNP in a healthy population age <50 years is 60.5 pg/ml (Bernstein *et al.* 2011)} and those conventionally used to diagnose CCF (>100 and >400 pg/ml respectively). The levels we report associated with PASP≥40 mm Hg are above the normal range, occasionally above the diagnostic level for CCF, and consistent with those seen in other states of pulmonary hypertension.

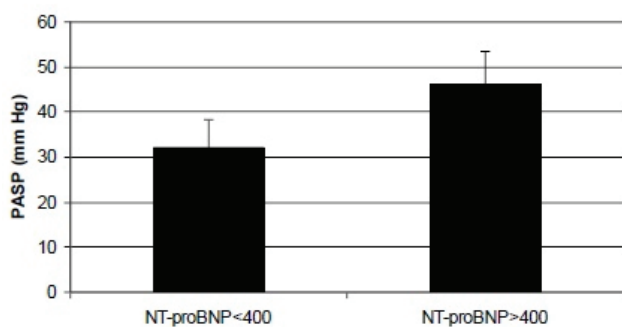


Fig. 3. In those with a pathological (≥ 400 pg/ml) rise in NT-proBNP at 5150 m (n=4) PASP (mean±SD) was significantly higher than those with a NT-proBNP <400 pg/ml (n=11): 45.9 ± 7.5 vs. 32.2 ± 6.2 mm Hg ($p=0.015$).

Only one previous study has examined the relationship between NT-proBNP and PASP at HA (Toshner *et al.* 2008). This study reported no rise in NT-proBNP on arrival at 5200 m following 5 days acclimatization at 3600 m despite a rise in PASP from 16.1 mm Hg to 39.4 mm Hg. They reported an NT-proBNP of 12.9 pg/ml on arrival compared to the 301 pg/ml we recorded at a very similar altitude using the same assay. A critical difference between these studies may be the exercise stimulus involved: our participants trekked to 5150 m, as opposed to arriving at 5200 m by

vehicle (Toshner *et al.* 2008). The fact that they reported very similar PASP to that which we observed suggests that exercise, which also increases PASP, may be a key factor in the rise in NT-proBNP at altitude. This is supported by our group’s previous work that has shown no rise in BNP during acute hypobaric hypoxia with minimal exertion (<5 min) (Boos *et al.* 2012, Woods *et al.* 2011b) despite inducing a rise in PASP from 24.3 to 35 mm Hg (Boos *et al.* 2012).

Prolonged exertion at SL has been associated with a rise in natriuretic peptides (Leers *et al.* 2006, Neumayr *et al.* 2005, Scharhag *et al.* 2008) that has recently been suggested may relate to ventriculo-arterial mismatch (Sahlén *et al.* 2012). Conversely, short duration exercise is generally not associated with a rise in natriuretic peptides (Marumoto *et al.* 1995, Nishikimi *et al.* 1997). Increases in BNP and NT-proBNP under normoxic conditions have been noted to resolve within several to 24 hours (Leers *et al.* 2006, Neumayr *et al.* 2005, Scharhag *et al.* 2008) and may explain why no rise was previously documented in trekkers at HA when samples were only taken the following day at rest (Feddersen *et al.* 2009).

In our study the rise in BNP and NT-proBNP seen after exercise at HA not only persisted at rest the following day but had often risen higher despite a fall in PASP. Exercise is likely to exacerbate myocardial hypoxaemia at HA and be a greater stimulus to BNP release than hypoxia alone. In support of this there are hypoxia-responsive elements in the promoter sequence of the BNP gene (Luo *et al.* 2006) and hypoxia is known to stimulate natriuretic peptide release (Due-Andersen *et al.* 2008, Möllmann *et al.* 2010). In isolated human heart muscle (where the mechanical wall stress usually credited with stimulating BNP release has been removed) hypoxia induces a rapid increase in myocardial BNP expression (Möllmann *et al.* 2010). Further, acute myocardial hypoxaemia in pigs induces a marked rise in tissue BNP

mRNA and a premature mRNA BNP followed by rapid release (Goetze *et al.* 2004). We therefore speculate that the initial rise in BNP and NT-proBNP following exercise at SL or HA may be due to release of proBNP from the small stored pool in cardiomyocytes. If there has been sufficient stimulus then in hypoxic conditions there may then be rapid up-regulation of BNP gene transcription that accounts for the persisting and elevated levels at rest.

It also makes physiological sense that the stressed and hypoxic myocardium should release BNP as it induces a natriuresis and is a vasodilator thereby acting to reduce myocardial wall stress. Infused BNP is known to attenuate hypoxaemia-induced increases in PASP and pulmonary vascular resistance (Cargill and Lipwoth 1995) and BNP levels are also employed to guide vasodilator therapy in pulmonary artery hypertension (Yap 2004).

We are not proposing that a high PASP is the sole determinant of a high BNP level at HA. BNP secretion may be stimulated by many factors. Although primarily stimulated by cardiomyocyte stretch and end-diastolic wall stress (Hall 2005) BNP is also stimulated by ischaemia, cardiac hypertrophy and oxidative stress (Nohria 2006). A high BNP may also occur in the context of cardiac transplant rejection where it does not reflect haemodynamic changes but is thought to reflect inflammatory changes within the myocardium (de Bold 2007). In the classical situation of CCF there is still significant heterogeneity in BNP levels. Patients with a similar degree of left ventricular systolic dysfunction demonstrate considerable inter-individual variation in BNP levels (Nohria and Givertz 2006) but this has not prevented BNP from becoming a useful marker of CCF. In a similar fashion we are not proposing that at HA PASP is an isolated stimulus to BNP but that there is some relationship between high PASP and a high BNP or NT-proBNP at HA that may ultimately prove useful in detecting not only high PASP but also cases of HAPE.

Limitations to our study include that although high PASP is a critical factor in the pathophysiology of HAPE our study does not include overt, clinical cases of HAPE. As such this report can only record an association between BNP and NT-proBNP and high PASP. Further work is needed to establish any relationship with subsequent HAPE. In addition, creatinine rose statistically significantly and theoretically a change in

renal function could effect NT-proBNP levels (since NT-proBNP is renally cleared). However, since the absolute rise was marginal and only 1 subject had a creatinine $>125 \mu\text{mol/l}$ ($142 \mu\text{mol/l}$) we feel this is unlikely to have a significant effect on the overall levels of NT-proBNP and the findings of this study.

The correlation between PASP and BNP and NT-proBNP were moderate but highly significant and the ROC analysis suggests that both natriuretic peptides should be further evaluated for their utility in identifying a high PASP at HA in a larger cohort. While an NT-proBNP cut-off of 133 pg/ml that gives a sensitivity of 70 % and a specificity of 83 % for identifying a high PASP may not be perfect, in the context of the cohort studied it is encouraging.

In conclusion, HAPE is a serious condition with an incidence estimated at up to 4 % at 4559 m (Maggiorini *et al.* 2001). The increasing number of visitors to HA represent a significant challenge in the early recognition, treatment, and possible evacuation of those who succumb to HAPE. Pulmonary hypertension, a key feature, is difficult to diagnose without either invasive or non-invasive techniques that require expertise and equipment beyond the realm of most conventional HA expeditions. Any association between high PASP and BNP or NT-proBNP at HA could therefore prove clinically useful in differentiating HAPE from other medical conditions, particularly in the early stages. Our data suggest that BNP and/or NT-proBNP may have potential as a marker of pulmonary hypertension in previously healthy participants at HA and as such, particularly with near-patient testing, may facilitate identification of a pathophysiological state that without appropriate management may be life-threatening.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

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