ORIGINAL ARTICLE

# N-terminal pro-B-type Natriuretic Peptide with fractional excretion and clearance of sodium in relation to cardiovascular events after elective cervical spine surgery

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## Abstract

**OBJECTIVES:** N-terminal pro-B-type Natriuretic Peptide (NT-proBNP) is increasingly being used as a biomarker of cardiovascular risk. To date neither its cut-off for postoperative period in noncardiac surgery nor whether the cardiovascular risk has any relation to natriuresis has been assessed.

**DESIGN:** The prospective observational study evaluated postoperative serum levels of NT-proBNP with fractional excretion of sodium ($FENa^+$) and sodium clearance ($CNa^+$) in relation to the occurrence of cardiovascular events in patients after elective cervical spine surgery.

**METHODS:** In 27 otherwise healthy patients after elective cervical spine surgery we prospectively measured serum NT-proBNP and serum sodium immediately after the operation (day 1) and on day two. We correlated both NT-proBNP with $FENa^+$, $CNa^+$, diuresis and intake of fluids and sodium, which were assessed from the beginning of the operation until day two. We followed the incidence of myocardial infarction, heart failure and cardiac death postoperatively to 1 year.

**RESULTS:** Immediate postoperative NT-proBNP values were within the reference range (mean 4.53 ± 2.48 pmol/l), but they increased significantly on the second day (mean 23.57 ± 12.27 pmol/l, $p<0.001$). Significantly elevated $CNa^+$ (0.033 ± 0.014 ml/s, $p<0.001$), $FENa^+$ (0.018 ± 0.008, $p<0.001$) and $fUNa^+$ (mean 326.9 ± 125.2 mmol, $p<0.01$) were found. There was a significant positive correlation between the two values of NT-proBNP (r=0.47, $p=0.014$), but we did not find any correlation between NT-proBNP and the further measured parameters. None of the patients had any cardiovascular events from operation until 1 year.

**CONCLUSIONS:** The significant postoperative elevation of NT-proBNP had no relationship with the rise in $FENa^+$, $CNa^+$ or $fUNa^+$ and was not connected with any occurrence of cardiovascular events in patients after elective cervical spine surgery.

**Abbreviations:**

| | |
|---|---|
| ACDF | anterior cervical discectomy and fusion |
| APACHE | Acute Physiology and Chronic Health Evaluation |
| BNP | B-type natriuretic peptide (pmol/l) |
| $CNa^+$ | sodium clearance (ml/s) |
| CCr | creatinine clearance (ml/s) |
| ECLIA | electrochemiluminscence immunoassay |
| $FENa^+$ | fractional excretion of sodium |
| $fUNa^+$ | urinary loss of sodium (mmol) |
| NT-proBNP | N-terminal pro-B-type Natriuretic Peptide (pmol/l) |
| NYHA | New York Heart Association |
| RAAS | renin-angiotensin-aldosterone system |
| $SNa^+$ | serum sodium (mmol/l) |
| SCr | serum creatinine (μmol/l) |
| UCr | urinary concentration of creatinine (mmol/l) |
| $UNa^+$ | urinary concentration of sodium (mmol/l) |
| V | urine volume (litres) |

## INTRODUCTION

N-terminal pro-B-type Natriuretic Peptide (NT-proBNP) is widly used as a diagnostic and prognostic cardiac biomarker. It is a 76-amino terminal fragment, hormonally inactive part of prohormone (proBNP) which remains after separating the active hormone BNP (Hall 2004, Vanderheyden *et al.* 2004).

B-type natriuretic peptide (BNP) is a hormone with protective functions in increasing wall stretch of the ventricular myocardium. It causes vasodilation in vessels, increases diuresis and natriuresis and inhibits the renin-angiotensin-aldosterone system (RAAS), (Ruskoaho *et al.* 1997). BNP is a biologically active 32-amino acid natriuretic hormone, first isolated from porcine brain tissue in 1988 (Sudoh *et al.* 1988), but in humans it is primarily secreted by the cardiac ventricular myocytes (Hosoda *et al.* 1991). The main stimulus for its synthesis and secretion is cardiac wall stretch (Ruskoaho *et al.* 1997, Wiese *et al.* 2000). The diuretic and natriuretic effect of BNP increases fractional excretion of sodium (Jensen *et al.* 1998).

NT-proBNP is part of cardiological guidelines in diagnosing heart failure. BNP is the most sensitive marker of left ventricular dysfunction and an independent predictor of high left ventricular and-diastolic pressure and volume (Choy *et al.* 1994; Davis *et al.* 1994; Cowie *et al.* 1997; McDonagh *et al.* 1997; 2004; Richards *et al.* 1998; Maisel *et al.* 2002; Morrison *et al.* 2002; Lainchbury *et al.* 2003; Hobbs *et al.* 2005). NT-proBNP is used for screening cardiac dysfunctions in critically ill patients (McLean & Huang 2005; Phua *et al.* 2005). Its use is becoming more widespread for assessing cardiac risk in cardiac and noncardiac surgery. Preoperative elevated serum levels of NT-proBNP are independent predictors of outcome after cardiac and noncardiac surgery (Cuthbertson *et al.* 2009; Oscarsson *et al.* 2009; Ryding *et al.* 2009; Schutt *et al.* 2009; Choi *et al.* 2010). However, neither the cut-off for the postoperative period in noncardiac surgery nor whether the cardiovascular risk has any relation to natriuresis is known.

The aim of this prospective observational study was to evaluate postoperative serum levels of NT-proBNP with sodium renal function parameters (fractional excretion of sodium, $FENa^+$, sodium clearance, $CNa^+$) in relation to the occurrence of cardiovascular events after elective cervical spine surgery.

## PATIENTS AND METHODS

For the purpose of our prospective study we chose elective cervical spine surgery for degenerative disc disease. We observed a group of 27 patients (18 males, 9 females) after anterior cervical discectomy and fusion (ACDF) with mean duration 110 ± 43 minutes. The mean age of patients was 48.3 ± 8.8 years (from 28 to 64 years). The mean Acute Physiology and Chronic Health Evaluation (APACHE) II score after operation was 6.4 ± 2.6 (range 2 to 11).

The observed group of patients was selected according to the following inclusion criteria: 1) elective cervical spine surgery with no complications, 2) otherwise healthy patients, 3) New York Heart Association (NYHA) class I., 4) creatinine clearance within the reference range (1.3–2.5 ml/s), 5) no diuretic or osmotic agents administered.

We measured serum NT-proBNP (cut-off 14.75 pmol/l), serum sodium ($SNa^+$, 135–146 mmol/l) and serum creatinine (SCr, reference range 35–115 μmol/l) immediately after the operation (day one) and at 7 am on day two, approximately 20 hours later. All investigated venous blood samples were taken from an extremity where no infusion was being applied. The following parameters were also evaluated: urinary concentration of sodium ($UNa^+$, mmol/l), urinary concentration of creatinine (UCr, mmol/l), urinary loss of sodium ($fUNa^+$, reference range 100–260 mmol), creatinine clearance, sodium clearance ($CNa^+$, reference range 0.008–0.016 ml/s), fractional excretion of sodium ($FENa^+$, reference range 0.004–0.012) and intake of fluids (ml) and sodium (mmol) and diuresis (ml). For the aforementioned observations we started the collection of urine at the beginning of the operation and continued until 7 am on day two.

NT-proBNP was assessed using the electrochemiluminscence immunoassay ECLIA on the Roche Elecsys 2010 and modular analytics E170 immunoassay analyzers utilizing two-site sandwich principle. Creatinine clearance was calculated according to general formulae for clearance with correction for the body's surface area. Values of urine volume (V) are in litres. For sodium clearance ($CNa^+$) and fractional excretion of sodium ($FENa^+$) we used the following formulae:

$$CNa^+ = UNa^+ \times V / SNa^+$$
$$FENa^+ = UNa^+ / SNa^+ / UCr \times SCr / 1\,000$$

Postoperative cardiovascular events were defined as myocardial infarction, heart failure and cardiac death

recorded by a cardiologist in the period after the operation until 1 year.

Statistical analysis was performed using STATISTICA 9.0 (StatSoft, Inc.). Normality of data was assessed using Kolmogorov-Smirnov tests. For comparison of first and second day values t-test for dependent samples was used. For other group comparisons two sample t-tests were used. For comparison against reference ranges χ-test was used. Pearson's correlation coefficients were used for assessment of dependence between variables.

This study was carried out with the approval of the Regional Hospital Ethical Committee and subsequently of the patients concerned.

**Tab. 1.** The mean values ± standard deviations of all measured parameters.

| Parameter | Unit | Reference range | Mean ± SD |
|---|---|---|---|
| NT-proBNP day 1 | pmol/l | 14.75 | 4.53 ± 2.48 |
| NT-proBNP day 2 | pmol/l | 14.75 | **23.57 ± 12.27** |
| $SNa^+$ day 1 | mmol/l | 135–146 | 139.7 ± 2.0 |
| $SNa^+$ day 2 | mmol/l | 135–146 | 137.6 ± 1.6 |
| $fUNa^+$ | mmol | 100–260 | **326.9 ± 125.2** |
| $CNa^+$ | ml/s | 0.008–0.016 | **0.033 ± 0.014** |
| $FENa^+$ | | 0.004–0.012 | **0.018 ± 0.008** |
| CCr | ml/s | 1.3–2.5 | 1.77 ± 0.29 |
| Diuresis | ml | | 2141 ± 879 |
| Intake of fluids | ml | | 4430 ± 758 |
| Intake of sodium | mmol | | 611.0 ± 108.8 |

NT-proBNP, serum sodium ($SNa^+$), urinary loss of sodium ($fUNa^+$), creatinine clearance (CCr), sodium clearance ($CNa^+$), fractional excretion of sodium ($FENa^+$), diuresis, intake of fluids and intake of sodium. Values in bold are significantly ($p<0.01$) above reference range.

## RESULTS

Immediate postoperative NT-proBNP values in all patients were in the reference range (mean 4.53 ± 2.48 pmol/l), but they rose significantly on day two (mean 23.57 ± 12.27 pmol/l, $p<0.001$). There was no significant difference in NT-proBNP between males and females, on day one (4.24 ± 2.56 pmol/l vs. 5.10 ± 2.33 pmol/l, $p=0.406$) and on day two (21.08 ± 12.01 pmol/l vs. 28.54 ± 11.88 pmol/l, $p=0.139$).

We found a statistically significant decrease in serum sodium on day two (139.7 ± 2.0 mmol/l on day one vs. 137.6 ± 1.6 mmol/l on day two, $p<0.001$). Values of serum sodium, urinary loss of sodium, creatinine clearance, sodium clearance, sodium fractional excretion, diuresis and intake of fluids and sodium can be seen in Table 1. We found significantly elevated levels of $CNa^+$ (0.033 ± 0.014 ml/s, $p<0.001$), $FENa^+$ (0.018 ± 0.008, $p<0.001$) and $fUNa^+$ (326.9 ± 125.2 mmol, $p<0.01$) above the reference ranges.

There was a significant positive correlation between NT-proBNP immediately after the operation and NT-proBNP on day two (r=0.47, $p=0.014$, Figure 1), but we did not find any correlation between these values of NT-proBNP and further measured parameters.

None of the patients had any defined cardiovascular events from operation until 1 year.

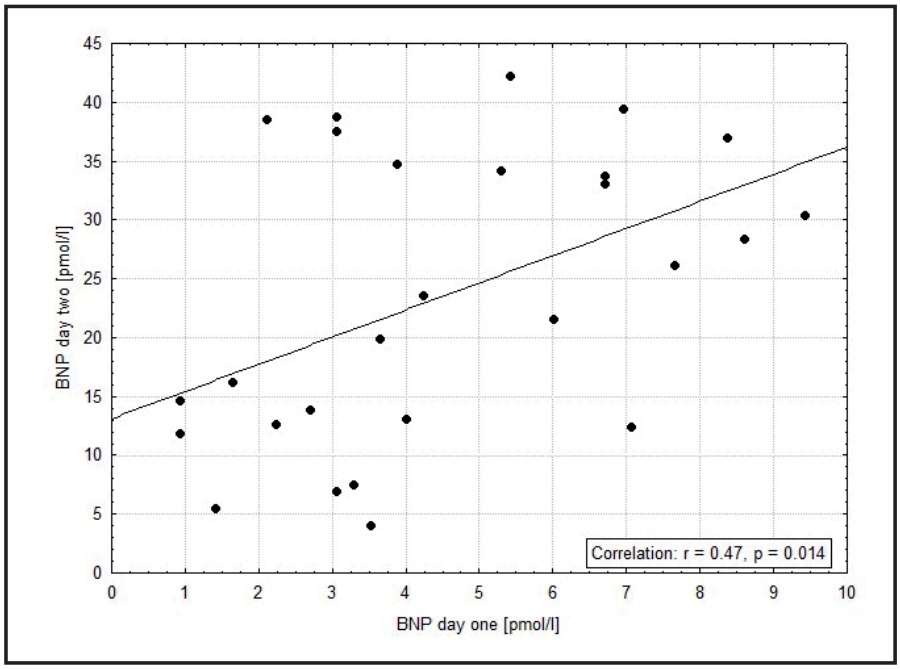


**Fig. 1.** Significant positive correlation between values of NT-proBNP on day 1 and 2 in all patients.

## DISCUSSION

The results of this prospective study demonstrated a postoperative significant elevation of NT-proBNP serum values (mean from 4.53 pmol/l to 23.57 pmol/l) not connected with cardiovascular events either in the short or long term. None of these patients had myocardial infarction, heart failure or cardiac death postoperatively during a period of 1 year. Significantly different values were observed in gender, in accordance with literature, higher concentrations of BNP were found among women (Clerico *et al.* 2002; Knudsen *et al.* 2004).

Increased diuresis and natriuresis cause elevation of $FENa^+$ and of $CNa^+$. Both these parameters in our study were found to be significantly increased above the reference range, nevertheless no significant relation was found between these raised values and NT-proBNP. The advantage of $FENa^+$ for clinical practice is that the collection of urine is not necessary for its calculation. This contrasts with the obligatory urine collection for the calculation of $CNa^+$.

We focused on both mentioned parameters in relationship to NT-proBNP, because they had not been investigated in previous studies (Cuthbertson *et al.* 2009; Oscarsson *et al.* 2009; Ryding *et al.* 2009; Schutt *et al.* 2009; Choi *et al.* 2010).

Elective cervical spine surgery for degenerative disc disease is a model noncardiac surgery. All patients participating in the study suffered from radiculopathy and nobody had clinical or radilogical signs of myelopathy. Surgical procedure involved a standard anterolateral approach, cervical discectomy and foraminal decompression with the use of a microscope and a high-speed drill. The authors consider this procedure to be a suitable model as it utilizes the anatomical intermuscular approach and has minimum blood loss and a very low rate of complications of any kind.

The reason for elevations of NT-proBNP was not accurately identified. All patients included in this study were otherwise healthy, classified as NYHA I and none of them had any defined postoperative cardiovascular events. They received a relatively high amount of fluids in the perioperative period. During increased volume of circulating fluids, BNP acts as an endogenic diuretic. It denotes a protective effect together with vasodilation in vessels against volume and pressure overloading of the heart (Pemberton *et al.* 2000). The mean fluid intake was 4 430.7 ml from the start of operation to the second day and we did not find a correlation between this amount and values of NT-proBNP.

NT-propBNP is a parameter routinely used as a diagnostic and prognostic cardiac biomarker (Choy *et al.* 1994; Davis *et al.* 1994; Cowie *et al.* 1997; McDonagh *et al.* 1997; 2004; Richards *et al.* 1998, Maisel *et al.* 2002, Morrison *et al.* 2002; Lainchbury *et al.* 2003; Hobbs *et al.* 2005). Its negative predictive value is especially appreciated. However, it is not a specific biomarker of heart disease in the sense that it does not enable differentiation of the causes of heart failure. Further possibilities are being sought for its prognostic and negative predictive significance. It is also used increasingly as a time marker of cardiovascular complications not only in cardiac surgery but also during surgical treatment for other diagnoses. Studies show that preoperatively raised values of NT-proBNP are connected with higher cardiac risk postoperatively (Cuthbertson *et al.* 2009; Oscarsson *et al.* 2009; Ryding *et al.* 2009; Schutt *et al.* 2009; Choi *et al.* 2010). However, the cut-off connected with increased cardiac risk is still being sought (Ryding *et al.* 2009). For our investigation we used the cut-off 14.75 pmol/l.

In conclusion, the significant postoperative elevation of NT-proBNP in patients after elective cervical spine surgery had no relationship with the rise in fractional extraction of sodium or with sodium clearance and was not connected with any occurrence of cardiac events either in the short or long term.

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