Levels of NT-proBNP and Troponin T in Cancer Patients – Mini-Review

Hladiny NT-proBNP a troponínu T u onkologických pacientov – stručný prehľad

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Summary

Background: Natriuretic factors are peptidic substances produced by atrial and ventricular myocardium. Primary stimulus to the synthesis of these factors is intramural pressure of atriums by the increase of venous return during intravascular hypervolemia. They may serve as useful cardiac markers in clinical practice. The elevation of N-terminal fragment of atrial natriuretic peptide is characteristic for cardiac failure. Troponin T is a basic component of muscle and is specific for myocardial cell. It is a marker of myocardial damage, specifically of myocardial infarction. ***Purpose:*** This paper aims to summarize the current knowledge on levels of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and their associations with cancer. At present, it is well known that natriuretic peptides may be produced by cancer cells without cardiac failure. While small cell lung cancer is a known producer of natriuretic factor, all oncologic diseases may have a potential to produce these substances. ProBNP synthesis may be stimulated by several pro-inflammatory cytokines, including tumour necrosis factor alpha and some interleukins. The production of pro-inflammatory cytokines has been proven in cancer. The influence of natriuretic factors to proto-oncogenes and cancer cells is considered and cross-reacting antibodies increasing NT-proBNP in paraproteinemias were described. Works discussing extreme elevations of NT-proBNP in terminal cancer patients without symptoms of cardiac failure were previously published. NT-proBNP and troponin T are also markers of myocardial damage during cardiotoxic chemotherapy with anthracyclines. ***Conclusion:*** NT-proBNP and troponin T can be valuable markers of the prognosis of oncologic diseases regarding not only cardiac damage during chemotherapy but also prognosis and extension of cancer patient lives.

Key words
natriuretic factors – troponin T –malignancy

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Súhrn

Východiská: Nátriuretické faktory sú peptidické substancie produkované atriálnym a ventrikulárnym myokardom. Primárnym stimulom ich syntézy je zvýšený intramurálny tlak predsiení spôsobený zvýšením venózneho návratu počas intravaskulárnej hypervolémie. Sú užitočným kardiálnym markerom používaným v klinickej praxi. Elevácia N-terminálneho fragmentu atriálneho nátriuretického peptidu je charakteristická pre kardiálne zlyhávanie. Troponín T je základným komponentom svalov a je špecifický pre myokardiálne bunky. Je to marker kardiálneho poškodenia, špecificky infarktu myokardu. ***Cieľ:*** Tento článok sumarizuje súčasné znalosti o súvise N-terminálneho prohormónu mozgového natriuretického faktoru (N-terminal prohormone of brain natriuretic peptide – NT-proBNP) a troponínu T s onkolgickými ochoreniami. V súčasnosti je známe, že nátriuretické peptidy môžu byť produkované nádorovou bunkou bez prítomnosti kardiálneho zlyhávania. Je známe, že malobunkový karcinóm pľúc priamo produkuje nátriuretické faktory. Tento potenciál majú však všetky onkologické ochorenia. Syntéza proBNP môže byť stimulovaná zápalovými cytokínmi, ako je faktor nádorovej nekrózy (tumor necrosis factor), a niektorými interleukínmi produkovanými nádorom. Pri paraproteinémiach je popísaný vplyv nátriuretických faktorov na protoonkogény a výskyt skrížene reagujúcich protilátok produkovaných nádorom, zvyšujúcich hladinu nátriuretických peptidov. Boli publikované práce, kde boli namerané extrémne zvýšené hladiny nátriuretických peptidov u terminálne chorých onkologických pacientov. NT-pro BNP a troponín T sú taktiež markermi myokardiálneho poškodenia počas kardiotoxickej liečby antracyklínmi. ***Záver:*** NT-proBNP a troponín T môžu byť cenné markery nielen kardiálneho poškodenia počas chemoterapie a prognózy onkologických chorôb, ale taktiež aj pre prognózu ochorenia a dĺžku prežívania onkologického pacienta.

Kľúčové slová

nátriuretické faktory – troponín T – malignita

NT-proBNP and natriuretic factors

The family of natriuretic peptides plays an important role in regulation of cardiovascular homeostasis and extracellular fluid volume [1]. Natriuretic factors are peptic substances produced by atrial and ventricular myocardium. Primary stimulus to the synthesis of these factors is intramural pressure of atriums by increasing of venous return during intravascular hypervolemia [2]. Cardiac natriuretic peptides like atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP) and C-type natriuretic peptide (CNP) are known because of their compensation effects – systemic arterial vasodilatation, natriuresis, diuresis, inhibition of system renin-angiotensin-aldosterone and neuromodulation [1]. They protect organism against volume overload, hypertension and excessive vasoconstriction acting as a dual system; ANP as a hormone of quick reaction and BNP as a hormone of reserve, which is active during long term ventricular overload [3].

ANP is secerned by cardiomyocytes of atrium as pro-hormone pro-ANP which is divided into two fragments; ANP and N-ANP. The biological half-time shorter than 5 minutes makes these biomarkers meaningful for diagnostic purposes [4].

BNP was discovered in 1988. As it was first isolated from the brain of a sow and it was named the brain natriuretic peptide. Subsequently it was ascertained that main producers of BNP are myocardial cells of ventricles, the atrial cells produce BNP to a lesser extent [5]. The release of BNP into circulation is secured by increased pressure of the ventricles by volume and pressure overload. BNP is secreted in a form of pro-hormone (pre-pro-BNP) [2]. After the stimulation of myocardial cells, it is split into two fragments – BNP (a biologically active peptide) and an inactive N-terminal fragment (NT-proBNP). Both are released into circulation; thus, there is a possibility to measure effectively the serum levels. The levels of BNP and NT-proBNP are equal in the healthy population [3]. The 2–10-fold elevation of NT-proBNP versus BNP is pathognomic for patients with cardiac failure. The measurement of NT-proBNP is considered advantageous compared to BNP due to longer biological half-life and higher biochemical stability. The blood sample is not required to be processed by quick fixation or freezing. This is the reason why NT-proBNP is examined in normal conditions, such as room temperature [6]. On the other hand, BNP levels are less affected by renal failure compared to the levels of NT-proBNP [5].

NT-proBNP is mainly used for the diagnosis of heart failure. In addition, it may predict the development of heart failure and death in patients with cardiovascular disease. However, NT-pro BNP could have predictive power beyond cardiovascular risk [5]. In fact, this biomarker is associated with a higher risk of death in patients with cardiovascular diseases and in elderly subjects [7]. It is very helpful in the differential diagnosis of dyspnoea. The cut-off value to exclude the cardiac failure is defined by the European Society of Cardiology (ESC) guidelines for the diagnostic and treatment of acute and chronic heart failure in 2016 [8] as the levels < 300 ng/L in case the symptoms originated quickly and the levels < 125 ng/L when symptoms are not of acute character. Levels of NT-proBNP are age-dependent. The cut-off value for cardiac failure exclusion is < 450 ng/L when patients are under the age of 50, < 900 ng/L for people 50–75 years old and < 1800 ng/L for people older than 75 years [8]. However, the interpretation of elevated NT-proBNP levels remains difficult because of several confounding factors, such as coronary disease, advanced age, renal insufficiency, respiratory diseases such as pulmonary hypertension leading to right ventricular dysfunction, thromboembolic disease, atrial fibrillation, cirrhosis, sepsis or dysthyroid could be responsible for the elevation of NT-pro BNP [9].

Troponin T

The basic component of muscle is a muscle cell. Inside these cells reside muscle filaments (myofilaments). Two types of myofilaments are generally distinguished. The thin filaments consist of actin and the heavy ones consist of myosin. Actin filaments entail three com-

ponents: actin, tropomyosin and troponin [10]. Troponin complex, as well, entails three known components: troponin I with the affinity to actin, troponin T with the affinity to tropomyosin and troponin C with the affinity to calcium (Ca^{2+}). Troponins are used as markers of cardiac injury in medical practice [6]. Troponin T and troponin I are found in skeletal muscle and myocardium. The cardiac isoforms troponin T and troponin I are specific for the myocardium. Troponin T and I are not present in blood in normal conditions. Their level increases after the injury of myocardium [10]. They are widely used for the diagnosis of acute myocardial infarction, unstable angina, postsurgical myocardial trauma and other diseases related with cardiac muscle injury [11]. Both markers can be detected in patient blood within 3–6 hours after the onset of the chest pain, reaching the peak level within 16–30 hours. Elevated levels of troponin I and troponin T in blood samples can be detected even 5–8 days after the onset of symptoms, making both proteins useful also for the late diagnosis of acute myocardial infarction. The process of liberation of troponin T is biphasic. It starts after 3 hours after the infarction followed by 2nd peak on 3rd day. The excess of troponin I is monophasic and is starts 3 hours after the cardiac injury [6].

Tab. 1. Conditions which influence natriuretic peptides from noncardiac reasons [6].

Increased natriuretic peptides	Cut down natriuretic peptides
Higher age	Obesity
Woman	Diuretic therapy
Lung diseases	ACE-inhibitors
Arterial hypertension	Spironolactone
Hyperthyroidism	Beta blockers
Cushing syndrome	Hypothyroidism
Renal failure (acute, chronic)	
Conn syndrome	
Cirhosis hepatis with ascites	
Subarachnoidal bleeding	
Paraneoplastic syndromes	

NT-proBNP, troponin T and troponin I in cancer

In oncologic patients, there are many mechanisms of the damage of cardiovascular system: breakdown of coagulation (most commonly hypercoagulation), anaemia (chronic diseases, bleeding), exhaustion of organism (malnutrition, associated illnesses), realizing of cardiodepressive factors (cytokines), malignant pericarditis, direct influence of tumour to the heart or vascular system and the therapy of malignant illnesses (chemotherapy, radiotherapy) [12].

At present, it is well known that natriuretic peptides may be produced by cancer cells [13]. In this regard, small cell lung cancer may secrete both pro-atrial natriuretic peptide and BNP. Also, BNP is expressed both in normal adrenal glands and in adrenal tumours, suggesting that natriuretic peptides may have other roles unrelated to the cardiovascular system [14]. A special situation is carcinoid heart disease, a well-known complication of long-lasting exposure to high levels of serotonin. NT-proBNP is a reliable marker to make rapid differentiation between patients with and without carcinoid heart disease. The survival of patients with normal levels of NT-proBNP is better compared to those with elevated levels [15].

ProBNP synthesis may be stimulated by several pro-inflammatory cytokines, including tumour necrosis factor alpha and several interleukins [16]. Tumour necrosis factor alpha and interleukin-6 are expressed in the Reed-Sternberg cells in patients with Hodgkin lymphoma. Moreover, they may predict the outcome in diffuse large B-cell lymphomas and, as explained, are increased in malignancies at advanced stages [7]. However, the specific cause of the elevation of natriuretic peptide plasma levels seen in cancer has not been elucidated. In recent years, it has been demonstrated that natriuretic peptides, or compounds with similar activity, decrease the number of several cancer cells *in vitro* through the reduction of DNA synthesis and inhibition of *C-Fos* and *c-Jun* proto-oncogenes, inhibit lung metastases and skin carcinogenesis in animal models, and diminish the expression of vascular endothelial growth factor and that of its receptor VEGFR2, thus having the potential to control vasculogenesis [17]. A study by Tuñón et al has shown the opposite effects of natriuretic peptides on carcinogenesis depending on their levels [7]. In this paper, atrial natriuretic peptide enhanced proliferation of human gastric cells *in vitro* at low levels, but inhibited their proliferation through cyclic guanosine 3-5-monophosphate-dependent pathways when it was present at high levels [18]. Then, given that most data suggest an anticancer effect of natriuretic peptides, the possibility exists that their production by cancer cells represents a negative feedback mechanism to control the tumor growth [5]. In this case, NT-proBNP elevation would only be a response to the existence of malignancies. Nevertheless, the fact that natriuretic peptides are related to the mechanism of cancer, which are common to multiple malignancies, would be in agreement with these findings, since the authors did not observe significant differences in NT-proBNP levels among patients with different types of cancer [7].

Malignant cells have been shown to manipulate the endocrine system, controlling hormonal secretion while expressing the appropriate receptors to promote tumour survival and progres-

sion. Recent publications reported elevated levels of several emerging cardiovascular hormones which mostly derive from the vascular endothelial cells in patients with cancer. Malignant cells were shown to produce vasoactive peptides (adrenomedullin, vasopressin) as well as cardiac hormones ANP and BNP. Elevated levels of troponin T have also been detected in cancer. These have been associated with a worse prognosis in contrast to the natriuretic hormones which primarily represent a functional measure, troponin T is a specific morphological marker for cardiac cell destruction. The association between advanced cancer stages and cancer cachexia potentially accompanied by cardiac wasting is a well-described phenomenon [19].

The study of Oluleye found that higher levels of troponin T, NT-proBNP and CRP are associated with an increased risk of death, not just from cardiovascular diseases, but also from non-cardiovascular causes [20].

The study of Bando showed a significant positive correlation between BNP and CRP levels in cancer patients, which suggested that the plasma BNP levels may have been elevated due to cancer-related inflammation. In addition, the plasma BNP levels are increased in an advanced stage of cancer (stage IV), which might be accompanied by systemic inflammation. Furthermore, the plasma BNP levels significantly decreased after a radical surgery in patients with solid cancers and the plasma BNP levels tended to decrease after chemotherapy in patients with haematological cancers [1]. BNP has been shown to be upregulated at the transcriptional and translational levels by pro-inflammatory cytokines in cardiac myocytes. The pro-inflammatory signals are postulated to stimulate members of the mitogen-activated protein kinase (MAPK) family and c-Jun kinase, as well as other intracellular signalling cascades, which leads to the upregulation of BNP gene expression [1].

In the study of Aceña et al, plasmatic levels of NT-proBNP in patients with stable coronary artery disease predict the development of cancer in a short-middle term. Increased NT-proBNP levels detect subclinical cancers [21].

Findings of Kamai et al in patients with renal cell carcinoma (RCC) suggested that the preoperative serum levels of cardiovascular hormones (BNP and NTproBNP) might be related to the progression of renal cell carcinoma and to a worse prognosis. The author based this interpretation on the fact that the serum levels of NTproBNP declined after the nephrectomy. The expression of BNP was very low in both RCC and normal kidney tissues. Possible reasons for lower BNP after nephrectomy may be the indirect production of these hormones by cancer cells. The suggested secretion from other organs such as heart may be influenced by mechanisms through which RCC had certain effects on the myocardium [13]. The association between hypoxia-inducible factor (HIF) and NTproBNP was also suggested [22]. The expression of HIF is typical for RCC. Increased expression of HIF alpha may stimulate BNP production [23]. A study by Kamai et al has found very low expression of BNP in RCC and normal kidney tissue [13]. In addition to its beneficial cardiac effects, BNP can act as an autocrine factor with anti-proliferative, anti-fibrotic and direct cytoprotective effects. Thus, HIF-mediated induction of BNP production might be a part of the local defense mechanism of the myocardium against the hypoxic damage [24].

Antineoplastic therapy with anthracyclines is often complicated by the development of cardiotoxicity which leads to heart failure [25]. In some cases, it is detected too late at echocardiography when significant myocardial damage has already occurred [26]. The availability of biomarker for the identification of risk in such patients is needed. Serum measurement of NT-proBNP level in patients on chemotherapy with anthracyclines is useful for both acute and late toxicity. The measurement of troponin I and troponin T is useful for acute toxicity during chemotherapy but not for late toxicity after 12 month following chemotherapy when troponin T a troponin I are in normal ranges [27]. Findings of the study of Ky et al suggest that there is an association between troponin I positivity and subsequent dysfunction during chemotherapy with anthracyclines and provide the evidence to support the importance of assessing changes in biomarkers over time [28]. Romano et al made serial measurements of NT-proBNP levels in not-high-dose anthracycline chemotherapy patients. They ascertained that NT-proBNP is useful in the early identification of patients with a high risk of the development of anthracycline-induced cardiotoxicity [29].

The study of Vladimirova et al measured serum NT-proBNP levels in patients with breast cancer during chemotherapy with anthracyclines. The conclusion of this study was that NT-proBNP is bound to be the most sensitive marker of cardiotoxicity and could serve as an earlier marker in patients with breast cancer who undergone chemotherapy with anthracyclines [30].

The study of Mladosievicova et al documented that higher levels of NT-proBNP detected in childhood leukaemia survivors after low anthracycline cumulative doses might reflect an initial stage of anthracycline cardiotoxicity before the development of echocardiographic abnormalities. NT-proBNP is one of the best available biochemical markers of late anthracycline cardiotoxicity [31].

The study published by Aujollet et al documented elevated NT-proBNP levels among patients (75%) with lung cancer. In this study, 50% of patients with elevated NT-proBNP had also elevation of C-reactive protein (CRP). The relationship between NT-proBNP levels and presence of inflammation in patients with no previous history of cardio-pulmonary disease has also been shown [14].

The exact mechanism of what is causing these elevated natriuretic peptides is unclear. There are several hypotheses about the aetiology of increased NT-proBNP levels in cancer patients. First, it was suggested that the fluid overload often may be a contributing mechanism in hematologic malignancies [32]. Some studies have suggested that natriuretic peptides themselves may be released from certain cancer cells. The study of Popat et al documented increased NT-proBNP levels in patients with paraproteinemias. A possible explanation is that cross-reacting antibodies are produced during the chemical immunoassay used to detect the natriuretic pep-

tides [16]. The study by Burjonroppa et al suggested that elevated BNP values in cancer patients are not associated with clinical evidence of volume overload or left ventricular dysfunction and occur predominantly with solid tumor malignancies [33].

The coherence between NT-proBNP and a malignant disease was confirmed in the study by Papazisis et al who assessed a group of patients with metastatic renal cell carcinoma treated with sunitinib (a tyrosine kinase inhibitor). The patients that obtained a clinical benefit 15 days after the treatment had significantly lower NT-proBMP compared to those without any clinical benefit (a 3-fold increase in patients with progressive disease compared to stable NT-proBNP levels in patients with clinical benefit; $P < 0.0001$). The median progression free survival was 12.0 months in patients with less than 1.5-fold increase ($N = 22$) and 3.9 months in patients with more than 1.5-fold increases in plasma NT-proBNP ($N = 13$) (long-rank test; $P = 0.001$) [22].

The elevation of NT-pro-BNP and CA 125 were markers of shorter surviving of patients with breast cancer treated with trastuzumab. The study of Rossner et al divided 28 patients with HER-2 positive breast cancer to two groups: group A with NT-proBNP levels < 155 pg/mL ($N = 16$, age 57 ± 13 years) and group B with NT-proBNP > 155 pg/mL ($N = 12$, age 62 ± 9 years). The levels of NT-proBNP before vs. after trastuzumab therapy were 65 ± 36 pg/mL vs. 66 ± 33 pg/mL in group A and 520 ± 443 pg/mL vs. 498 ± 411 pg/mL in group B. Elevated levels of NT-proBNP, CA125 and CA 15-3 indicate a higher median 3-month mortality in trastuzumab-treated patients on long-term immunotherapy [34].

Elevated levels of cardiovascular peptides including BNP/NT-proBNP and troponin T were reported in patients with renal cell cancer in the study by Kamai et al. The authors reported that higher preoperative serum levels of BNP, NT-proBNP and vascular endothelial growth factor (VEGF) as well as elevated HIF-2 alpha expression in the primary tumor were associated with a worse performance status, local invasion, distant metastasis and shorter overall survival. However, BNP expression was very low in RCC tissues and normal kidney tissues and there was no relationship between the serum levels of BNP/NT-proBNP and serum VEGF or tumor expression of HIF-2 alpha. Moreover, the serum levels of BNP and NT-proBNP decreased significantly after tumor resection. These observations suggested that RCC itself might have some influence on such damage. If so, the decrease of serum BNP and NT-proBNP after tumour resection in patients with RCC might be associated with alleviation of stress on the heart [13].

Higher NT-proBNP levels were associated with a worse health status and cognitive impairment of brain tumor patients. Two studies in primary and metastatic brain tumor patients reported that greater NT-proBNP level was associated with greater mass effect and extent of perifocal brain oedema. Elevated NT-proBNP levels before surgery were associated with inferior outcomes at the hospital discharge and inferior prognosis of brain tumor patients [35]. Therefore, NT-proBNP assessment can be considered for perioperative risk stratification, prognostication and evaluation of cognitive/mental health status of brain tumor patients. Further studies investigating the clinical significance of NT-proBNP in brain tumor patients are recommended. The study of Bunevicius et al ascertained in 245 patients undergoing craniotomy for brain tumor (mostly meningioma in 36% and high grade glioma in 20%) that higher NT-proBNP levels were associated with greater five-year mortality risk (hazard ratio (HR) = 1.845 (95% CI 1.166 – 2.920; $P = 0.009$) controlled for patient age, gender, history of cardiovascular disease, histological diagnosis and adjuvant therapy. In sum, higher preoperative NT-proBNP levels are associated with a worse health status, unfavourable discharge outcome and shorter survival of brain tumor patients [36].

A study by Pavo et al from 2015 demonstrated that NT-proBNP and troponin are systematically elevated in cancer patients and that they are likewise related to long-term mortality independently of age, gender, tumour entity, tumour stage and manifest cardiac disease at first clinical presentation. This study confirmed a significant correlation between the pro-inflammatory cytokine IL-6 and the inflammatory marker C-reactive protein (CRP) and the hormone NT-proBNP. Whether the effect on mortality is primarily due to a determinant local influence on the tumour microenvironment or it is induced by systemic cardiovascular dysregulation cannot be determined [19].

Chronic suppression of thyroid stimulating hormone (TSH) in patients treated for differentiated thyroid carcinoma may induce a cardiac damage and increase the risk for cardiovascular events. In the study by Klein Hesselink et al, the authors observed elevated NT-proBNP levels in patients with differentiated thyroid

Tab. 2. Events accompanied with elevation of cardiac troponins [6].

Tachyarrhythmias, bradyarrhythmias
Dissection of aorta
Aortal valvular heard disease
Arterial hypertension, hypertonic crisis
Hypotension, haemorrhagic shock
Acute and chronic cardiac failure
Hypertrophic cardiomyopathy
Coronary vasculitis
Cardiac contusion
Cryo-/radiofrequency ablation
Rhabdomyolysis
Myocarditis
Cardiotoxicity of drugs (anthracyclines, trastuzumab)
Combustion
Embolization to the pulmonary artery, pulmonary hypertension
Chronic renal failure
Acute brain cerebrovascular accident
Extreme physical labour
Sepsis
Acute respiratory failure
Defibrillation

carcinoma vs. healthy controls. Median NT-pro BNP was 70 (40–119) ng/L for patients with carcinoma and 49 (25–89) ng/L for controls (P < 0.001). Furthermore, the risk of cardiovascular event and all-cause mortality was higher in patients with higher NT-proBNP, HR = 3.22 (95% CI 2.17–4.79) and HR = 1.61 (95% CI 1.17–2.63), respectively [37].

Therefore, the determination of NT-proBNP may identify patients with differentiated thyroid carcinoma at an increased cardiovascular risk, who could benefit from more stringent cardiovascular risk surveillance [28].

Clinical implication

Using of NT-pro BNP in oncology is open. There are a lot of studies which documented elevation of NT-proBNP in different cancer diagnosis, e. g. the study of lung cancer by Aujollet et al [14], the study of multiple myeloma by Nico Pavo et al [19], the study of renal cancer by Kamai et al [13] or the study of brain tumor patients by A. Bunevicius et al [36]. The elevation of NT-proBNP is different. The NT-pro BNP levels are not very high, compared to the cut-off values in cardiac diseases. Nevertheless, extremely elevated NT-proBNP levels are documented in terminal oncologic patients. It is possible that NT-pro BNP levels depend on the degree of tumor development. In the study of Kamai et al [13], patients after nephrectomy with renal cancer had lower NT-proBNP levels after surgery than before it. This is the reason why this biomarker can be useful in oncology to see the effect of therapy and, of course, extension of the tumor.

Conclusions

Serum NT-proBNP levels are commonly elevated in cancer patients without overt cardiovascular disease. The biological mechanisms underlying the increased production of NT-proBNP in cancer setting remain poorly understood, but it was demonstrated that higher levels of NT-proBNP and other biomarkers of myocardial damage, such as troponin T, are associated with a worse prognosis and shorter survival of cancer patients not receiving cardiotoxic chemotherapy. These findings suggest that subclinical dysfunction of the cardiovascular system is common and has prognostic significance in cancer patients [36].

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