

Natriuretic Peptides, Heart, Cancer and the Cardio-Oncology

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Abstract

Now-a-days, the heart is considered an endocrine organ of great importance, producing several vasoactive peptides with natriuresis, vasodilation, anti-inflammatory, and anti-cardiac remodeling actions. In the setting of heart failure, a resistance or decrease in the action of the natriuretic peptides occurs, whereas inhibitors of its catabolism have shown a decrease in hospitalization and mortality. Current chemotherapy treatments can decrease or eliminate many of the human cancers, but at the expense of cardiovascular toxicity, which can appear during or after the treatment has completed. From the interrelation between treatment of cancer and the cardiovascular toxicity has emerged the discipline called cardio-oncology. Although the standard test for the diagnosis of cardiac dysfunction is echocardiography, gaps in the diagnosis and surveillance persist, with more investigation being needed. Besides, there are evidences, both in animal experiments and in humans, of the utility of natriuretic peptides in the diagnosis and in treatment of various cancers.

Keywords: Natriuretic peptides; Pathophysiology; Heart; Cancer; Cardio-oncology

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Introduction

The last decades have shaped the heart as a cardinal endocrine organ producing a family of cardiac hormones, i.e., natriuretic peptides (NPs), structurally and functionally related. They are the product of two different genes, natriuretic peptide precursor (NPP) A located in chromosome 1, encoding for natriuretic Peptide A (ANP) and B (BNP), whereas NP C (CNP) is encoded by NPP-C [1,2], located in chromosome 2. These peptides were firstly implicated in the regulation of circulatory homeostasis showing pressure lowering properties, natriuretic, diuretic and kaliuretic effects because of inhibition of renin-angiotensin system (RAAS) and sympathetic outflow [3]. They are produced by cardiovascular, brain and renal tissues [4]. Another peptide included into the family is dendroaspis natriuretic peptide (DNP) isolated from the venom of the green mamba and in patients with heart failure but still with indefinite functions [5].

ANP is produced and stored in atrial granule, whereas in normal conditions ventricle does not[6,7]. Mechanical stretch of cardiomyocytes, hypoxia, cold, or hormonal stimuli (angiotensin, catecholamine, endothelin, vasopressin and glucocorticoid) induce transcription of proteins GATA binding promoters and synthesising Pre-ProANP (151 amino acids [aa]). After removing

a signal peptide of 25 aa, Pro-ANP (126 aa) is produced and stored in the atria. Stimulation caused by a trial and ventricular stretch because of pressure or volume overload, cleavage Pro-ANP by action of corin producing the active C-terminal α -ANP (28 aa), that is spilled into coronary sinus and distributed in systemic circulation, and the inactive N-terminal Pro-ANP (98 aa). Urodilatin is a related natriuretic ANP peptide produced in the kidneys with local functions regulating salt and water excretion [8]. Some investigations meet later fragmentation of NT-ProANP result of several peptides: long acting natriuretic peptide (LAMP), the vessel dilator (VSDL) and the kaliuretic peptide (KP) [9,10]. The half-life of α -ANP is 2 minutes[11] and activates receptor A of NP, highly expressed in kidney, adrenal, lung, terminal ileum, aorta and adipose tissue[12] where catalyze conversion of GTP to GMPc activating protein kinase and phosphodiesterase regulating ion channels, nuclear translocation, gene expression and protein phosphorylation[13,14] resulting in reduction of blood pressure[15], counteracting of sympathetic activity[16] and inhibiting cardiac hypertrophy and fibrosis [17].

BNP is stored and secreted by normal atrium as Pre-ProBNP (132 aa) Only when left ventricular function is insufficient is secreted in ventricles [18]. After a 26aa peptide is removed a 108 ProBNP is produced and subsequently cleaved by the actions of furin (or

corin) into the active BNP32 with a half-life of 2-28 minutes and the inactive form N-Terminal ProBNP [19]. Factors implicated in the production of ProBNP are hypoxia, pressure or volume overload, interleukine-1 β , interleukine-6 and tumor necrosis factor- α . BNP, in addition to natriuresis, diuresis and vasodilation, shows protective cardiac effects by inhibiting necrosis and apoptosis of cardiomyocytes and reducing fibrosis and cardiac hypertrophy [20]. Current immunoassays do not differentiate among the several circulating peptides of BNP, measuring in some extension ProBNP, O-glycosilated BNP, BNP and NT-ProBNP [21] and they do not reflect the bioactivity. In the setting of heart failure BNP-32 is nearly absent in plasma. BNP acts by joining receptor A of NP in a similar way to ANP.

As BNP, CNP was originally found in the brain, being subsequently shown in other tissues (atrium, ventricle, kidney, endothelium, blood cells and chondrocyte) [22]. ProCNP is a 103 aa protein cleaved by furin producing two peptides, one of 53 aa (CNP-53) and other of 22 aa (CNP-22), showing both similar activity and functions. CNP-53 predominates in heart endothelium and brain, whereas CNP-22 predominates in plasma and cerebral spinal fluid. CNP lacks natriuretic action and serves as regulator of vascular tone joining the receptor B of NP [23].

The main mechanisms of clearance of NPs are the C receptor which metabolizes ANP, BNP y CNP [24], the exoenzyme system of Neprilysin [25] and the Insulin degrading enzyme [26].

Literature Review

Role of NP in heart failure

The clinical interest of Increased levels of NP were firstly focused in patients with heart failure, with plasma levels proportionally elevated to the severity of ventricular failure [27], particularly BNP and NT-ProBNP. Different NPs have been related to distinct cardiac dysfunction. NT-ProBNP and BNP have been associated to systolic left ventricular dysfunction and NT-ProANP has been reported in patients with asymptomatic left ventricular dysfunction [28]. NPs have also been reported, with a sensitivity and specificity nearly to 100%, in order to differentiate normal from subtle heart failure. NT-ProANP is an independent factor predictor of heart failure and death [29]. BNP and NT-ProBNP are also useful markers for the prognosis of patients with heart failure, stable coronary artery disease or acute coronary syndrome and they can guide the treatment [30].

However, several factors influence the plasma levels, mainly age, sex, heart rate, anaemia, renal function and obesity, making that these factors, frequently found in daily clinic be confounding factors hindering the interpretation [31]. On the other hand, other factors to take into account are the genetic variants of NPs. For instance, Rs5063 variant has been related to lower blood pressure in Chinese and American populations, less arterial hypertension and more myocardial infarctions. Variants in coring gene have been related to arterial hypertension and left ventricular hypertrophy in African-American population [32].

A paradoxical aspect of NPs is that the beneficial effects described counteracting the RAAS, inducing vasodilation and preventing cardiac remodeling in the setting of heart failure with increased

levels of NPs, they are not effective. Indeed, heart failure induces an attenuated response to elevated BNP levels representing a deficiency of active BNP caused by abnormal processing of NPs [33]. Therefore, therapeutic approaches to increase the affectivity of NPs have been carried out. Nesiritide, a recombinant BNP has been used in heart failure with controversial results related to mortality rate and worsening renal function [34]. Carperitide, a recombinant form of ANP and CNP have short half-life that limits clinical application. Ularitide, a synthetic urodilatin, showed hemodynamic and clinical improvement without worsening renal function though without effect in cardiovascular mortality or decreasing troponins. Novel NPs are currently under clinical developing.

Other approaches addressed to reduced NPs degradation inhibiting neprilysin have been proposed. Candoxatril, the first pure inhibitor of neprilysin had not benefit for patients with hypertension or heart failure due to RAAS activation. Ecadotril and Omapatrilat, both dual inhibitors of neprilysin and angiotensin-converting enzyme showed no superior benefit in patients with heart failure or hypertension. Triple inhibition of angiotensin-converting enzyme, endothelin-converting enzyme and neprilysin inhibitor is under investigation.

Dual inhibition with the pro-drug sacubitril, an inhibitor of neprilysin, and valsartan, an angiotensin receptor blocker, have shown to be effective and safe when administrated to patients with heart failure with reduced ejection fraction, reducing all-cause, cardiovascular and sudden death, preventing heart failure progression and hospitalization and improving life quality and renal function [35]. Studies in patients with preserved ejection fraction are ongoing. The inhibitors of neprilysin, by modifying the degradation of NPs, invalidate BNP in the diagnosis and follow-up of patients with heart failure, whereas NT-ProBNP is not modified. Therefore, the use of NT-ProBNP is preferred over BNP in this setting [36].

Although NPs are very sensitive in detection of cardiac volume or pressure overload, often pulmonary or cardiac causes of dyspnoea are hard to differentiate each other with physical signs, laboratory tests, electrocardiograms and chest X-ray not clearly signaling the origin of the symptom. Some types of pulmonary disease are associated with increased levels of NPs such as cor pulmonale, acute respiratory distress syndrome, lung cancer and pulmonary embolism [37]. Plasma level of NT-ProBNP reflects the burden of thrombi in pulmonary embolism [38] and like in heart failure, NT-ProBNP is a consistent risk factor of all-causes delayed mortality rate [39]. NPs have been also shown to be elevated in liver cirrhosis, hyperthyroidism, subarachnoid hemorrhage, carbon monoxide poisoning and renal failure. NT-ProBNP in pleural fluid indicates that its cause is related to heart failure.

NPs in detection of cardiotoxicity

The last 20 years have been of great importance since we have observed a significant reduction of cancer mortality. Chemotherapy can effectively eradicate or suppress most cancer; however, drugs used in treatment have a wide range of secondary deleterious effects which limit their clinical use, conducting often to reassessing of therapy and sometimes changed to a

less aggressive regimen that could be less effective. Of these effects cardiotoxicity is one of the most severe secondary effects, decreasing the quality of life and survival of cancer patients. Therefore, cardiotoxicity can be defined as the occurrence of adverse effects affecting the cardiovascular system during or after cancer treatment and an integrative medicine between oncologist and cardiologist is needed.

Most of the cardiac complications associated with chemotherapy occur during or shortly after completion of therapy; nevertheless, some of these problems can persist and become chronic, or in certain cases the cardiac damage can be so subtle that it becomes apparent only months to years later after the completion of cancer treatment. The relationship between cardiac damage and chemotherapy of cancer needs often a narrow collaboration between oncologist and cardiologist, since cancer and cardiovascular disease may often coexist in the same patient, so a new discipline called cardio-oncology has emerged [40].

Many chemotherapy agents and targeted therapies can induce cardiotoxicity. About the half of adult survivors of child cancer have been treated with an anthracycline at some point of the treatment and anthracycline cardiotoxicity is a well-known of cardiac dysfunction. They can produce acute heart failure, myocarditis, pericarditis and acute coronary syndrome and late-onset of cardiomyopathy and chronic heart failure, being its effects cumulative and dose-dependent.

Other many agents can cause cardiotoxicity: Fluorouracil, Methotrexate, alkylating agents, anti-microtubule agents (Docetaxel, Paclitaxel), small molecule tyrosine kinase inhibitors (Dasatinib, Imatinib, Lapatinib, Sunitinib), proteasoma inhibitor (bortezomib) monoclonal antibodies Bevacizumab (blocker of the vascular endothelial growth factor) and Trastuzumab (human epidermal growth factor receptor 2 blocker acting as an angiogenesis inhibitor). All of them have been related with dysfunction manifested by heart failure, arrhythmia, myopericarditis or hypertension. Arterial or venous thromboembolism has occurred with Bortezomib and Bevacizumab. Radiotherapy is also able to damage cardiac structures (pericardium, cardiac muscle and vessels) when is included into the field of radiation [41].

A system to identify drugs that have the potential to cause cardiac damage has been proposed. Type I refers to drugs that potentially cause irreversible damage whereas type II drugs would be those that cause predominantly reversible dysfunction. However, this classification has problems, for instance trastuzumab, a type II drug can trigger irreversible cardiac damage in patients with pre-existent cardiac disease or potentiate anthracycline type I cardiotoxicity [42].

The pathophysiology of type I damage consists in cell loss. Anthracyclines have been demonstrated to cause disruption of the cell membrane, loss of filaments, swelling of sarcoplasmic reticulum and vacuolization of cytoplasm [43]. The reversible damage of type II drugs consists on cellular dysfunction, mitochondrial and protein dysfunctions. While non-reversible damage can induce progressive cardiovascular disease, mainly heart failure, a reversible dysfunction is usually temporary.

The diagnosis of chemotherapy induced cardiotoxicity is

currently evaluated by echocardiography. The American Society of Echocardiography [44] and the European Association of Cardiovascular Imaging [45] define cardiotoxicity as a reduction of left ventricular ejection fraction higher 10% with a cut-off value of less 53%. According to the European Society of Cardiology echocardiography is the method of choice for the diagnosis of myocardial dysfunction before, during and after cancer therapy. However, echocardiography has several limitations, is observer-dependent, the measured parameters are influenced by the structure of the thorax and it is a relatively insensitive tool unless a considerable change in ejection fraction occurs, and besides a normal ejection fraction does not exclude a later deterioration. Strain rate echocardiography could be a more sensitive tool to demonstrate cardiac damage.

Cardiac MRI provides detailed information about the heart morphology along the cardiac cycle and the global and regional function of the heart. However, is an expensive test and it being not feasible in patients with metallic implants. Regarding radionuclide imaging, they have not shown utility in detecting early cardiotoxicity.

Natriuretic peptides, including ANP, BNP and NT-ProBNP are the most widely used biomarkers for early identification of chemotherapy induced cardiotoxicity [46]. They have shown increases as soon as 24 hours after the initiation of chemotherapy but without clinical or image correlation. More valuable could be the persistence of elevated levels of NT-ProBNP months after the end of treatment [47].

Overall, regarding NP in the detection of chemotherapy induced cardiac damage there are controversial results with some studies demonstrating elevated NP signaling cardiac damage in patients treated both with conventional and newer therapies; however other studies did not find correlations between NP and the development of cardiac dysfunction in patients receiving chemotherapy. Most studies enrolled a limited number of patients, with different types of cancer and with different schedules of treatment. Therefore, valid conclusions cannot be drawn, needing well-standardized studies to better define the role of NP in the cardio-oncology setting. However, a cautious approach to management would be the utilization of NPs combined with echocardiography for the early detection of cardiotoxicity.

The case of trastuzumab could illustrate the elusive terrain of cardio-oncology. In the 90 years, in the pivotal phase III trial of trastuzumab in HER2 positive breast cancer with concurrent anthracycline-trastuzumab treatment, 27% of patients developed symptomatic or asymptomatic left ventricular dysfunction. Of them, 16% had NYHA class III or IV heart failure [48]. These results conditioned that therapy schedules were modified with trastuzumab administrated sequentially after the completion of anthracyclin chemotherapy, the monitoring of ejection fraction with echocardiography at baseline and at 3 months intervals during trastuzumab treatment, exclusion of the patients with significant previous heart disease and stopping trastuzumab on the basis of ventricular function. In four subsequent large assays the incidence of ejection fraction decline ranged from 7.1% to 18.6% and the rate of NYHA class III or IV heart failure ranged

from 0.4% to 4.1%. With this disagreement in the figures and after a decade of follow-up of patients treated in the adjuvant setting with trastuzumab regimes, the available evidence does not support a specific schedule of screening nor does it demonstrate improved outcomes for the screened patients [49].

However, despite the fact that the incidence of adverse cardiac events is not well established and the gaps in the sensitivity of the diagnostic methods for the diagnosis of cardiac dysfunction, active research is necessary for obtaining progress in the early detection of cardiotoxicity. Thus, since heart failure, presenting during or after cancer treatment, is a condition that affects survival and life quality of the patients, recommendations of guidelines must be followed. The American College of Cardiology and the American Heart Association describes the heart failure as a progressive disorder, beginning with the risk factors known to be associated with the heart failure, including the toxicity of chemotherapy and/or radiation (stage A). The stage B is reached after structural changes have occurred, either asymptomatic or symptomatic preceding the development of overt signs and symptoms (stages C and D) [50]. Cardiac dysfunction can present as systolic impairment with reduction in ejection fraction of left ventricle or diastolic impairment, i.e., with preserved ejection fraction. There is a paucity of information on the incidence and risk factors for diastolic dysfunction in survivors of adult cancer. Therefore, the focus of the guidelines are put on the prevention and monitoring of systolic dysfunction in patients adults with cancer for whom cardiotoxic anticancer therapies are considered: high dose anthracycline, high dose radiotherapy, or lower dose of anthracycline in combination with lower dose radiotherapy or lower dose of anthracycline or trastuzumab alone in the presence of risk factors [51,52]. The guidelines recommend before the initiation of therapy to avoid or minimize the use of potentially cardiotoxic therapies if established alternatives would not compromise cancer specific outcomes and to take a complete clinical history regarding risk factors of cardiovascular disease, and an echocardiogram before the initiation of potentially cardiotoxic therapies.

During the phase of treatment guidelines recommend that patients be actively screened and managed the modifiable cardiovascular risk factors, the use of cardioprotective drug dexrazoxane or infusion of liposomal formulations of anthracycline (moderate recommendation) and modifications of radiotherapy when the heart is included in the radiation field (strong recommendation).

The recommended monitoring approaches during treatment in patients at risk of cardiac dysfunction are the realization of echocardiogram (strong recommendation), cardiac MRI or radionuclide scan if echocardiogram is not available or technically feasible (moderate recommendation). Plasma cardiac biomarkers (NP and troponins) and strain echocardiography are of moderate recommendation.

During the surveillance imaging can be obtained in asymptomatic patients at increased risk preferring echocardiography (moderate recommendation). The option of discontinuation of cancer therapy in patients with evidence of cardiac dysfunction must be taken in collaboration with cardiologist (insufficient information to make a recommendation). In patients with metastatic breast

cancer whom continues receiving trastuzumab, surveillance with echocardiography must be done (moderate recommendation).

After the treatment, echocardiography is recommended if symptoms are present (strong recommendation) with MRI or radionuclide image, if echocardiography is not available and cardiac biomarkers (moderate recommendation) Referral to a cardiologist on the basis of findings (strong recommendation) must be considered. In asymptomatic patients an echocardiogram may be performed between 6 and 12 months after completion of therapy (moderate recommendation) and patients with asymptomatic heart dysfunction should be referred to a cardiologist (strong recommendation). The frequency and duration of surveillance is unsettled but is recommended the management of cardiovascular risk factors in patients previously treated with cardiotoxic cancer therapies (moderate recommendation).

Besides limitation of cumulative dosage of anthracyclines, the administration of anthracyclines by continuous infusion instead of in bolus and the utilization of less cardiotoxic anthracyclines or the liposomal formulations, other strategies have been addressed by using cardioprotective drugs (anti-oxidants, N-acetyl-Cysteine, Q10 coenzyme, carnitine, bosentan, probucol, erythropoietin) although its beneficial effects have not been proved. The best-known cardio-protective agent is dexrazoxane (an antimetabolic agent with immunosuppressive properties), approved by FDA in patients with metastatic breast cancer who have already received more of 300 mg/m² of doxorubicin, whereas current data do not support the routine use of neurohormonal antagonists or statins as cardio-protective agents in patients treated with cardiotoxic chemotherapies [53].

NPs as target in the treatment of cancer

Increased levels of NPs have been demonstrated in the setting of several animal and human cancers, such as invasive squamous cell carcinoma, malignant pericardial effusion, and small cell lung cancer and in several cancer cell lines. NPs have shown to have anticancer effects when they are used at supra-physiological doses [54].

Peptides derived from ANP have shown in cell cultures great reductions of tumour cells of a large variety of cancers: prostate, human pancreatic, colon, breast, renal, small cell lung, squamous cell lung and ovarian carcinomas, angiosarcomas of the heart, melanomas, medullar thyroid carcinoma and glioblastoma of the brain. However, BNP have not shown anticancer effects [55].

Studies *in vitro* have shown that peptides derived of NT-ProANP eliminate up to 86% of human small cell lung carcinoma in mice treated during 28 days with subcutaneous ANP [56,57]. The Vessel Dilator and the Long-acting Natriuretic Peptide were the most beneficial an ANP the least. In mouse models the administration of ANP inhibits the adhesion of cancer cells to microvascular endothelial cells, suppressing E-Selectin expression suggesting that ANP prevents cancer metastasis.

The mechanism implicated in anticancer effects of NPs would be at different levels, including the activation of Ras-MEK/1/2-ERK1/2 kinase cascade, working as a multikinase inhibitor and inhibiting the receptor of the vascular endothelial growth factor,

the effects on Wnt/ β catenin pathway and on the regulation on the pH by cancer cells through a Frizzled related mechanism [58,59].

In humans, the administration of ANP during the perioperative period to patients with lung cancer considered appropriated for surgery, resulted in lower cardiovascular complications and less cancer recurrence [60,61]. The presence of natriuretic peptide receptor in advanced prostate cancer tissues, but not in normal prostate epithelial cell line or in benign prostate hyperplasia epithelial cell line has settled that in androgen-independent prostate cancer they have been signalled as a prognostic marker of the disease and opening paths to new investigations in the treatment of prostate cancer [62,63]. On the other hand, the expression of receptor C of ANP in prostate tumour tissue has enabled the development of a new nanomagnet for prostate cancer PET imaging [64].

Discussion and Conclusion

Major advances in malignant growth restorative consideration

have brought about an unexampled enhancement in patient survival for a few diseases. on account of increased life span, it's turned out to be clear that the circulatory framework is frequently minimized by treatment, radiation, and fundamentally beyond any doubt focused on therapeutic consideration. Ebb and flow treatment medicines will diminish or dispense with a few of the human tumours, anyway to the detriment of vessel lethality, indication peptides (NPs) are hormones which are mainly secreted from heart and have important natriuretic and kaliuretic properties. Nonetheless, next to no advancement has been made in tackling the restorative capability of those inner organ hormones. therefore, our study was focussed on studies which reduce the risk of cardiac Toxicity by implementing alternative methods using cardiac Toxicity levels using NPs. Natriuretic peptides now seen as attractive candidates to fight against cancer, both in the field of diagnosis and treatment.

Therefore, NPs are now seen as attractive candidates to fight against cancer, both in the field of diagnosis and treatment.

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