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Natriuretic peptides and atrial fibrillation

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Abstract. – *Background and Objective:* **Atrial fibrillation (AF) is the most common arrhythmia in the medical practice, it is associated with an increased total and cardiovascular mortality, as well as cardiovascular morbidity, including stroke and heart failure.**

AF is encountered in different medical specialties including cardiology, family medicine and emergency medicine as well.

Treatment goal is to minimize stroke risk but also taking into account the quality of life. Therefore rate or a rhythm control strategies must be carefully selected.

This review focuses on natriuretic polypeptides (NPs) as potential useful markers in AF patients management.

Evidence and Information Sources: **Pubmed® was searched for natriuretic peptides and atrial fibrillation. Pertinent abstracts were reviewed by the Authors and the articles fully evaluated when considered pertinent.**

State of the Art: **NP biology and physiology is described and general application in heart failure outlined. With regard to AF, the role of NP as predictor of cardioversion is reviewed and discussed. Patients eligible for rhythm control not always respond to treatment. Classic markers for a suitable cardioversion, such an echocardiography, are not immediately available in most settings. NP might be a resource predicting cardioversion (or not) upon patient's presentation.**

Prospectives: **Biomarkers, such NPs, might be used to predict treatment response other than in heart failure.**

Conclusions: **In AF management, NT-ProBNP is a promising tool helping physicians to choose rhythm or rate control strategy.**

Key Words:

NT-proBNP, BNP, Natriuretic peptides, Atrial fibrillation, Cardioversion.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in medical practice, with a prevalence of 5% over 65 year old and up to 8% in elderly population (over 80 year old)[1]. AF is associated with an increased total and cardiovascular mortality, as well as cardiovascular morbidity, including stroke and hearth failure[2].

Particularly, the incidence of ischemic stroke patients with permanent, non-valvular AF, averages 5% per year, 2 to 7 times more than population without AF[3].

The most studied and accepted risk factors for AF are age, male sex, diabetes, hypertension, history of myocardial infarction, congestive heart failure, valvular heart disease and all causes of left atrium enlargement[4].

A mechanism involved in the multifactorial genesis of AF is the stretch and remodelling of the atrium that could be caused from a lot of different heart alteration like hypertension, diastolic dysfunction[5], mild left ventricular dysfunction[6], coronary heart disease[7], or chronic heart failure[8].

Recently, the presence of an inflammatory state of myocardium, found in atrial biopsies in patients with lone AF, has suggested the possibility of an association between AF and flogosis that could be shown by a determination of C-reactive protein (CRP) in serum[9]. In fact, CRP was established to be a predictor for developing AF in several clinical trials[10,11].

Following the same hypothesis, BNP and NT-proBNP were proposed as biomarker for AF management.

Evidence and Information Source

Pubmed® was searched using following key words: "atrial fibrillation [MeSH]" and "Natriuretic peptides (NPs)" or Brain Natriuretic Peptide ("BNP") or N-terminal pro β-type Natriuretic Peptide ("NTproBNP"). A total of 620 articles were found. Abstracts were reviewed and the articles which focused on NPs in AF treatment were obtained in full version. References were also reviewed for possible missed pertinent articles. No languages other than English were con-

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sidered. We did not contact the Authors of the original papers. Final pool reviewed consisted of 210 abstracts and 45 full articles.

Natriuretic Peptides Physiology

Natriuretic peptides (NP) are a class of structurally similar proteins with diuretic and natriuretic actions.

In the NP class there are 5 different peptides: Atrial Natriuretic Peptide (ANP), Brain Natriuretic Peptide (BNP), C-type Natriuretic Peptide (CNP), Dendroaspis Natriuretic Peptide (DNP) and Urodylatin which is produced only in renal district whit an auto-regulation function[12].

These peptides are produced from a preproprecursor molecule which could be processed in different ways to obtain the different NPs. The different cut processes have the common results to obtain a biologically active C-terminal fragment and a N-terminal inactive fragment secreted in equimolar proportion which, in the case of brain NP, are respectively BNP and NTproBNP. These inactive fragment are more resistance to clearance systems than the active ones so their values are more stable over time how is shown by the half-life of BNP and NTproBNP which are respectively 21 min and 60-120 min[13].

The role of NP is to determinate a both arterial then venal vasodilation in way to cause natriuresis and diuresis.

All the actions of NP are mediated by three different receptors: NPR-A,B,C.

NPR-A and NPR-B have a 44% homology in amino acid chain between them, are linked to the cGMP-dependent signaling cascade with an intracellular domain whit a guanylyl cyclase activity and are involved in all the renal and vessel activities of the NP, showing different affinities for the different NPs characterising their activities (the A receptor binds both atrial and brain natriuretic peptides, with preference for atrial natriuretic peptide. C-type natriuretic peptide is the natural ligand for the B receptor). Even the localization of the receptors is different. In fact, NPR-A is more abundant in the large blood vessels and in the other hand NPR-B is well represented in brain and together are present in adrenal gland and kidney.

The third receptor is NPR-C which has the role to clearance the NPs from cardiovascular system together with neutral endopeptidases which do clearance by cleavage the NP's chains. However, NPR-C has a different affinity for the NPs (ANP> BNP>CNP).

The different NPs present the same activity although C-type NP is more power than the others and is the one with the less emetic concentration; this thanks his best resistance to clearance systems[14].

The main effects of NPs can be summarized in renal, vascular, cardiac, SNS/RAAS effects. NPs induce renal glomerular filtration rate (GFR) improvement and sodium elimination; on vascular district they reduce arterial and venous tone and have an anti-proliferative effect. NPs have cardiac anti-remodeling effect and lusitropic effect. Finally, NPs reduce sympathetic tone, renine and aldosterone release and up regulation of vagal tone.

The most studied NPs are the ANP and the BNP which have very similar activity but have same differences.

Classically ANP and BNP were considered product respectively from atrium and ventricle. However, this is not completely true. In fact, ANP is more secreted by atrium and BNP by ventricle. Some Authors[15] evidences that this situation is present only in heart diseases and that in a normal hearth the synthesis of the two peptides should be reserved at the atrium alone.

ANP is synthetized at the time of the stimulus and only a little part is storage with minimal parts of BNP in the myocardial cells. On the other hand, BNP secreted from ventricle is exclusively synthesized and stored before stimulus. So the way of secretion of the two NP is very different. ANP is secreted in a pulsatory way and his plasmatic concentration change a lot during the time; BNP is secreted in a more stable way, is less responsive to minimal changes in cardiovascular homeostasis, is less inhibited by clearance systems and has a more stable concentration in time.

(NTproBNP has a best performance in this way, in fact his half-time life is from 60 to 120 minutes versus BNP which has a half-time life near 21 minutes)[16].

For this reason BNP and more recently NT-proBNP are considered the best way to detect the activation of NP system.

ANP and BNP are released in several conditions. The first and most important is the stretching of the cardiac wall, atrium wall for ANP and ventricle's wall for BNP. Others are: tachycardia, trans-parietal pression in heart wall and emetic concentration of thyroid's hormones, glucocorticoids, and vaso-active peptides like endothelin and angiotensin II, independently from their hemodynamics effects.

At the same time the ANP and BNP can inhibit the secretion of vaso-active peptides with a negative feed-back[17].

Physiologically an high pre-load is the cause of an increased stretch wall that is the main stimulus to secrete ANP and BNP activating the regulatory chain showed in Table I.

Currently the more investigated and commercially available NPs are BNP and NTproBNP. Others NPs are under investigation, like middle region (MR) pro-ANP that has been recently introduced in heart failure, but there are still no enough data in AF to be reviewed.

NPs as Biomarkers in Heart Failure

BNP is considered the best marker for acute hearth failure and like prognostic rate because it correlates closely with New York Heart association (NYHA) class and with mortality. Considering overall mortality BNP is more accurated to predict death than NYHA classification and ecocardiogarfic signs[18].

BNP is particularly useful in the dyspnoea differential diagnosis. In fact, it's able to exclude the cardiac origin of this symptom; having exactly the same rule of the D-dimer to exclude the possibility of pulmonary embolism in non hospitalized patients[19].

There is an elevation of BNP blood levels every time that there is cardiac wall stretching so there are a lot of different causes which can explain it. Heart failure, acute coronary syndrome, diastolic dysfunction, AF, amyloidosis, valvular disease, restrictive cardyomiopathy are some of the cardiac diseases which can be cause of elevation of BNP blood levels. There are a lot of extra-cardiac diseases which can influence BNP levels like pulmonary embolism, pulmonary hypertension, chronic obstructive pulmonary disease (COPD) and renal failure[20].

However, there are some limitations in the daily use of BNP and NTproBNP. High BNP levels cannot rule out the presence of comorbidity which are important to treat to improve patient's health condition, especially in elderly. It is necessary to know the patient baseline BNP blood level to understand if the patient is improving or worsening from her/his baseline. The elevation of BNP levels in asymptomatic patients is not specific for a particular cardiomyopathy. BNP and NTproBNP diagnostic thresholds are modified by different conditions other than heart failure per sè, such sex, age, body mass index and, finally, the type of assay used[21].

BNP and NTproBNP can be used like markers of a good treatment too. In fact, it is possible to follow the drop down of theirs levels during therapy confirming good response to treatment.

It is important to remember that ACE-inhibitors, ARB, spironolactone are the capability to decrease partially the BNP blood levels immediately. For B-blockers there is a more complex situation. In fact an high sympathetic tone inhibits the secretion of NP so using B-blockers there is a rebound effect in NP secretion with an initially increase followed by a reduction caused by an improved circulation condition given by this drug[22].

A lot of different studies have demonstrate how treatment following BNP and NTproBNP levels improves patient's outcome and resources utilization.

NPs in Atrial Fibrillation

The correlation between AF and high levels of BNP[23,24], and NTproBNP[25] is well known. AF is

Table I. Events induced by an increased cardiac trans-mural pressure promoting NPs release.

Nervous central system	• Reduction in: TSH secretion, vasopressin secretion, thirst sensation, need of salt = reduction of plasmatic volume • Reduction in: sympathetic tone and neuroendocrine function (drop down the baroceptor threshold) = blood pression reduction
Adrenal gland	• Reduction in aldosterone secretion = reduction of plasmatic volume
Kidney (urodylatin effects)	• Reduction in renin secretion = blood pression reduction • Increase of: GFR, natriuresis, urinary volume = reduction of plasmatic volume
Blood vessels	• Peripheral vasculature vasodilation and permeability increase = reduction of plasmatic volume and blood pression

considered an independent predictor of BNP and NTproBNP elevation in dyspnoeic[26], midly symptomatic[27], or asymptomatic patients[28,29]. In several studies the mean level of NTproBNP in AF ranged between 800 and 1100 pg/ml and did not correlate either whit duration of AF or with left atrial dimension[25]. In AF, NTproBNP is secreted mainly from atrium[16]. Furthermore, studies analysed the relationship between NTproBNP levels and recurrence of AF showing that NTproBNP level was able to predict the recurrence of AF in mild hearth failure[30] and post-operative AF in patients undergoing cardiac surgery[31].

Asselbergs et al[32] showed that plasmatic levels of NTproBNP were able to predict the future onset of AF in a population-based cohort, independently from other cardiac comorbidity and diseases.

Finally, another important characteristic of NTproBNP is its characteristics to drop quickly after restoration of sinus rhythm[25,33].

Several studies have analyzed the relationship between NTproBNP plasmatic levels and cardioversion with different conclusions. Danicek et al[34] have shown this drop down in a clear way even if they don't explain if the difference in NTproBNP levels before to after the sinus rhythm restoration are statistically significant.(the mean drop down from 970 pg/ml to 471 pg/ml).

Research also investigated if NTproBNP was able to predict maintenance of sinus rhythm after elective cardioversion.

Few studies witch enrolling small populations found correlation between baseline NTproBNP and AF's recurrence at 1 months[35] 6 months[36] although some others did not found a statistical significance in this correlation[34,37].

Unfortunately these studies are heterogeneous and make difficult to draw definitive conclusion. In fact, the enrolment criteria, the follow-up and the end points were different. There was differences also between cut-off used for NTproBNP. Sanna et al[36] used 1707 pg/ml with a specificity of 92% and a sensitivity of 36% in predicting recurrence at 6 month; while Mollmann et al[35] 900 pg/ml having a specificity of 73.5% and a sensitivity of 84.2% in predicting recurrence at 1 month. These differences make difficult to compare these studies.

NTproBNP has role in monitoring rhythm stability after restoration of sinus rhythm. In fact, in outpatient setting, levels of NTproBNP are significantly lower in patients maintaining sinus rhythm[35,34]. Also, after a successful cardioversion, patients experiencing other episodes of paroxysmal AF have a higher (but not significant) level of NT-ProBNP compared to patients that do not experience AF anymore during study follow-up[35].

In summary, NTproBNP decreases in AF after sinus rhythm (SR) restoration. The degree of this gap (before and after cardioversion) is bigger in patients who subsequently did not experience other AF episodes during the follow-up.

Conclusions

The role and importance of BNP and NTproBNP in heart failure is well none. Biomarkers help to manage such patients but their role in atrial fibrillation is still not clear. We focused on NT-ProBNP, the biomarkers most studied in AF. We reviewed present literature which highlights its possible role in predicting sinus rhythm stability after a successful cardioversion.

In fact, NTproBNP has a direct correlation with presence of AF and its levels decrease with restoration of sinus rhythm. Further research is needed to clarify clinical value in term of sensitivity and specificity of NT-ProBNP, especially in acute setting.

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