

Review

Natriuretic peptides in heart failure: Current achievements and future perspectives

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ABSTRACT

The last two centuries have witnessed countless discoveries in the field of medicine that found their roots in the up growing development of technology as well as in the visionary ideas of brilliant scientists and research groups. One of the most important discoveries in the field of cardiovascular medicine allowed to break the paradigm identifying the heart with mere mechanical pump and to characterize its intriguing endocrine properties. Indeed, the discovery of hormones produced by the cardiac chambers, the natriuretic peptides, represents one of the milestones of the current conception of complexity of integrated human physiology. In the last four decades, the role of these hormones in the regulation of the cardiovascular system, in physiology and diseases, has been defined piece after piece. From diagnostic and prognostic markers, natriuretic peptides have become one of the most relevant clinical biomarker and a reliable target for establishing the efficacy of therapies. Recently and successfully, natriuretic peptide-based strategies are proposed as therapeutic weapons to improve outcome in heart failure.

The future will witness potential further therapeutic application of natriuretic peptides that are currently being actively investigated.

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1. The evolving role of natriuretic peptides in cardiovascular medicine

The discovery of natriuretic peptides (NPs) and of the hormonal function of the heart is a cornerstone of modern cardiovascular (CV) medicine and represents one of the future frontiers in this field. The existence of endogenous natriuretic substances has been early postulated from an observation by Harthshorne in 1847. Then, a seminal experiment by De Wardener and Knock in 1961 showed that a small amount of plasma from a volume-expanded animal when injected into another animal caused prolonged natriuresis. The role of a “third factor”, of hormonal nature, beside glomerular filtration rate and aldosterone to determine sodium filtration rate, was hypothesized [1]. Only in 1979, de Bold made the astute observation that microscopy of granule found in cardiac atrial resembled the ones seen in secretory tissue and that their number varied according to the animal's sodium and water balance [2]. He subsequently showed a considerable increase in diuresis, natriuresis, hemoconcentration and blood pressure (BP) reduction in rats given an intravenous injection of atrial extracts [3]. At last, the

complete amino acidic sequence of the atrial natriuretic peptide (ANP) was identified [4]. Later, a second polypeptide, the brain natriuretic peptide (BNP), was described by Sudoh et al. [5]

This discovery has greatly influenced research and clinical practice over the last two decades mostly in heart failure (HF).

2. Organization of the NP system

The NPs family includes three well characterized hormones: ANP, BNP, and C-type natriuretic peptide (CNP) that play a key role in the maintenance of cardio-renal and body fluid homeostasis. ANP is largely produced from cardiac atria, whereas BNP is predominantly secreted from heart ventricles in response to volume overload and myocytes stress [6,7,8,9]. The neuroendocrine regulation of cardiac NPs involves angiotensin II, endothelin-1 and catecholamines. NPs are synthesized as pre-prohormones and are subsequently cleaved to obtain a biological active α -carboxy-terminal peptide along with the amino-terminal end [5,6]. ANP and BNP produce their biological effects through the interaction with GC-coupled receptors (NPR-A, NPR-B) (Fig. 1) [10]. Natriuresis is mainly achieved through an increase of GFR and filtration fraction, and by a decrease in sodium reabsorption at the level of collecting ducts, distal and proximal tubules. NPs modulate systemic vascular resistance mainly by inhibiting the contraction of vascular smooth muscle cells [11]. At the heart level, ANP inhibits the sympathetic activity

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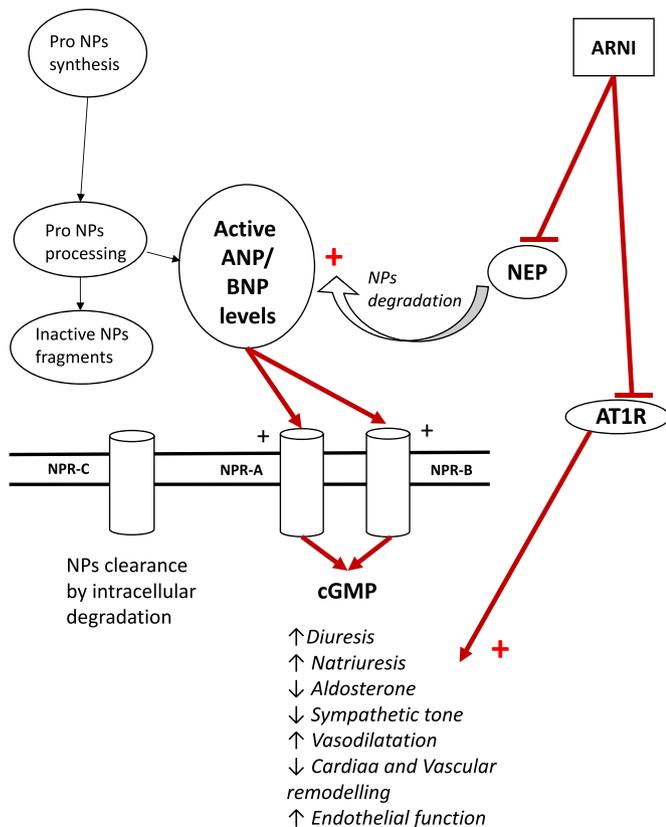


Fig. 1. Legend: Natriuretic peptides metabolism and ARNI mechanism of action (in red). NP: natriuretic peptide; ANP: atrial natriuretic peptide; BNP: brain natriuretic peptide; cGMP: cyclic guanosine monophosphate; NPR A: natriuretic peptide receptor type A; NPR B: natriuretic peptide receptor type B; NPR C: natriuretic peptide receptor type C; ARNI: angiotensin receptor neprilysin inhibitors; AT1R: angiotensin II receptor 1 type. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

associated with an increase of vagal afferent activity, leading to reduction of heart rate and cardiac output [12]. The degradation of NPs is achieved through the type C natriuretic peptide receptor (NPR-C) and the NEP, also known as neprilysin [13,14].

3. NPs as biomarker in heart failure

ANP and BNP plasma levels increase in parallel with the degree of left ventricular dysfunction and haemodynamic stress. Due to their longer half-lives, the N-terminal pro-hormones NT-proBNP and NT-proANP (particularly, the mid regional NT-proANP, MR-proANP) are considered suitable biomarkers in cardiovascular diseases (CVD) [15].

Current ESC guidelines recommend measurements of levels of BNP, NT-proBNP or MR-proANP for the diagnosis of HF [16].

A predictive role of NPs-based screening to predict HF development has been documented in different populations [17–23]. Interestingly, in 2014 Canadian Cardiovascular Guidelines recommended the use of NPs in at-risk individuals to implement strategies to prevent HF [24].

With the progression of HF, the rise of NPs presumably attempts to balance the overwhelming activation of the RAAS and the SNS [25]. However, the highest NPs levels are detected in patients with more severe HF who have a worse prognosis and thus NPs have insightful prognostic value [26–30]. Different reasons may explain the NP paradox. First, commonly used BNP assays are unable to distinguish between different BNP peptide fragments, so that even if BNP levels are high, a relatively greater abundance of immature less active BNP forms are present in HF [31]. Additional explanations of the NP paradox in HF may be a reduced processing of proANP or proBNP into ANP and BNP, respectively, due to reduced corin levels [32,33], the glycosylation status

of proBNP_(1–108) [34], an increased degradation of cGMP [35] and an increased local degradation of NPs [36,37].

The value of NPs as reliable markers for the long-term prognostic stratification, both in acute and CHF, is well established, both in HFpEF and HFrEF [28]. Higher baseline NP level at hospital admission and a failure of NPs to decrease with hospitalization are associated with increased event rates [38]. In CHF, subsequent measurements of either BNP or NT-proBNP levels provide independent information regarding the risk for disease progression across a wide spectrum of adverse outcomes [29].

NPs level may also represent a useful marker to monitor benefits derived from therapies [39,40], although, a low level of recommendation for NP-guided therapy in chronic HF has been assigned by AHA-ACC-HF guidelines [41].

3.1. NP-based therapeutic strategies in HF

In view of the biological properties of NPs, therapeutic strategies aiming to manipulate their levels have been attractive. The design of synthetic NPs was first attempted. Anaritide and carperitide are synthetic forms of ANP. Nesiritide is a synthetic form of BNP. These synthetic peptides have shown some positive effects in the treatment of HF, particularly in AHF [42], but there is not enough evidence to support their clinical use.

Inhibition of endogenous NPs degradation has been also proposed. Since NPR-C plays pleiotropic functions, its inhibition to increase NP levels does not appear suitable. The initial development of neprilysin inhibitors (NEPi) focused on the use of an inhibitor, Candoxatril, and a dual NEP/Angiotensin Converting Enzyme inhibitor (ACEi), omapatrilat, though they were both dismissed due to insufficient efficacy and side effects [43–45]. The first compound formed by the NEP inhibitor sacubitril and the ARB valsartan (LCZ696) in a 1:1 M ratio led to an approximately 20% relative reduction in the risk of CV death or HF hospitalization versus enalapril in patients with stable HFrEF receiving optimal therapy [46]. Therefore, the regulatory agencies in Europe and United States approved sacubitril/valsartan and both North American and European guidelines were updated [15,47]. This is extensively discussed in other contributions to this issue.

Thereafter, many trials have been proposed to further investigate possible clinical application of LCZ696. The ongoing *HFN-LIFE* study ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02816736) NCT02816736) is investigating the effects of a lower dose of sacubitril/valsartan (i.e. 24/26 mg) in patients with HFrEF in NYHA class IV. This will help assessing its safety and tolerability and the specific role of NEP inhibition in the most symptomatic patients.

A *PIONEER-HF* study ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02554890) NCT02554890) will address the role of ARNI in in-patients with AHF, with a glance to the “real world” outcomes, such as urgent care and emergency department visits.

Ongoing trials are investigating the benefits of ARNI on different endpoints in HF: biomarker changes and ventricular remodelling among patients with NYHA Class II–IV HFrEF (*PROVE-HF*, [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02887183) NCT02887183), changes in aortic impedance among patients with NYHA Class I–III HF and hypertension (*EVALUATE-HF*, [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02874794) NCT02874794), changes in functional mitral regurgitation (*PRIME*, [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02687932) NCT02687932) in patients with HFrEF, and changes in mean pulmonary artery pressure in patients with LVEF <35% (*PARENT*, [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02788656) NCT02788656). Finally, the potential for sacubitril/valsartan to attenuate atrial remodelling in patients with risk for future HF will be addressed by the *PARABLE* study.

As an alternative to NEP inhibition, a novel synthetic peptide, M-ANP, with a 12-amino acid terminal extension, highly resistant to NEP degradation, may represent a new candidate for the treatment of HF [48,49]. The evidence that a significant improvement of cardiac function was observed in a mouse model of dilated cardiomyopathy by increasing corin expression highlights this approach as a promising one to develop treatments of HF as well [50].

3.2. New perspectives for the clinical applications of NP-based therapies

Based on the known effects of NPs on the infarcted myocardium, ARNI might also represent a plausible therapy in post-MI [51,52]. Animal data show that LCZ696 attenuates LV remodelling and preserves LV systolic function [53]. The PARADISE-MI trial will test the benefits of ARNI in MI patients (ClinicalTrials.gov NCT02924727).

There is also evidence that ARNI therapy, when compared to conventional RAS inhibitors as an anti-hypertensive agent, confers significantly advantages [54,55]. A recent study from our group has underscored the superiority of sacubitril/valsartan vs valsartan in lowering BP and preventing stroke and renal injury development in the stroke-prone spontaneously hypertensive rat [56]. Therefore, sacubitril/valsartan may be an attractive therapeutic agent to treat hypertension and prevent HFpEF.

Moreover, since NPs inhibit RAAS, reduce SNS and promote natriuresis and diuresis, ARNI may be useful in patients with renal impairment. The UK Heart and Renal Protection (HARP)-III (ISRCTN 11958993), will compare the effectiveness of sacubitril/valsartan vs. irbesartan in preserving GFR among diabetic and nondiabetic patients with an initial GFR between 20 and 60 ml/m²/1.73 m². Preliminary data suggest that sacubitril/valsartan might also enhance glycaemic control in patients with diabetes and HFpEF [57,58]. Finally, the role of ARNI in disorders of sleep is an emerging area of interest [59]. (ENTRESTO-SAS, Clinicaltrials.gov identifier: NCT02916160) (AWAKE-HF, Clinicaltrials.gov NCT02970669).

4. Conclusions

Following the discovery of a family of natriuretic hormones, of their predictive, diagnostic and prognostic implications, the last piece of the puzzle is the therapeutic relevance of NPs. Testing the clinical benefits of NEP inhibition has evolved from single agents to ARNI. The area of pertinence of NEP inhibition is identified with HF, but other clinical areas are explored.

Current knowledge on the NP cascade underscores the concept that NP concentrations depend on myocardial wall stretch (i.e., NP production), the capacity to increase the biologically active NPs (i.e., NP processing) and on NPs metabolism (Fig. 1). The patient's capacity to increase and maintain active "the active NP availability", is important for determining the effects of medications targeting the NP cascade. Therefore, a more holistic approach when looking at NP in clinical setting should be now adopted, starting from the HF clinical setting.

Declarations of interests

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2018.04.045>.

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