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Atrial Natriuretic Peptide, Heart Failure and the Heart as an Endocrine Organ

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Featured Article: Burnett JC Jr, Kao PC, Hu DC, Heser DW, Heublein D, Granger JP, et al. Atrial natriuretic peptide elevation in congestive heart failure in the human. Science 1986;231:1145–7.[3]

Thirty-three years ago, we reported the increase of circulating atrial natriuretic peptide (ANP)[4] in human heart failure (HF). This report, which is featured here, was published 5 years after the landmark work of de Bold that established the heart as an endocrine organ with the discovery of ANP, which he originally named atrial natriuretic factor *(1)*. Indeed, what followed has been a transformational journey that has changed our thinking of the heart as more than a pump and has contributed to the clinical development of a second cardiac natriuretic peptide, b-type natriuretic peptide (BNP), as the gold standard in HF diagnosis. The work of Waldman and Murad importantly established that ANP activated the particulate guanylyl cyclase A receptor resulting in the production of the second messenger, 3′,5′ cyclic guanosine monophosphate (cGMP), which provided momentum for ANP/cGMP drug development *(2)*.

Our 1981 article addressed a major unknown at the time early in the history of the natriuretic peptide system story. By 1986, the human gene for ANP was known and chemical synthesis had been performed with in vitro and in vivo studies, establishing the key role of ANP in body fluid and blood pressure regulation together with aldosterone-suppressing properties. HF was of prime interest to our team and represented a syndrome that connected the heart and kidney, which was a fascinating pathophysiological phenomenon. There existed a controversy of ANP in HF because studies in animal models of HF by crude bioassays or immunohistochemical staining of the cardiac atrial for ANP detection suggested an ANP deficiency state. These early studies speculated that such a deficiency was a mechanism for salt and water retention and activation of the renin–angiotensin–aldosterone system in HF.

We thus were motivated to develop a highly sensitive and specific RIA (radioimmunoassay) for ANP and then to perform careful invasive hemodynamic studies in humans with HF in which we measured atrial pressures, which serve as the stimulus through atrial stretch for ANP release. Plasma ANP values in patients with HF were compared with those in subjects undergoing cardiac catheterization for chest pain with no evidence of HF. Our principal finding was that circulating ANP increased in human HF in our small number of patients and paralleled increases in atrial pressure. What followed was the development of ANP and then BNP as biomarkers for HF, the latter of which, together with its nonbiologically active molecular form NT-proBNP (N-terminal prohormone BNP), is the gold standard biomarker for HF.

Today the field of ANP is alive and well based upon highly original and probing basic and clinical research in diverse areas of biology and medicine. This vibrant area of research and clinical practice was accelerated by the recent Food and Drug Administration approval of a highly effective drug for HF, sacubitril/valsartan, which has reduced HF mortality. Importantly, the inhibition of neprilysin by sacubitril/valsartan reduces degradation of NPs, principally ANP, underscoring the importance of ANP in HF therapeutics *(3)*. Coming full circle, in a more extensive study of humans with HF including establishing normal contemporary values in the general population, we recently discovered that there is indeed a subpopulation of humans with HF that lacks ANP activation *(4)*.

The work of many researchers in the area of ANP and NP research has provided investigators and physicians a new and exciting road ahead. Most importantly, the power of ANP to help the diagnosis of HF, and those who are ANP deficient, lays the foundation for novel ANP/cGMP therapeutics to reduce the burden of HF *(3, 5)*.

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[3] This article has been cited more than 900 times since publication.
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[4] Nonstandard abbreviations: ANP, atrial natriuretic peptide; HF, heart failure; BNP, b-type natriuretic peptide; cGMP, cyclic guanosine monophosphate.

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References

1. de Bold AJ, Borenstein HB, Veress AT, Sonnenberg H. A rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats. Life Sci 1981; 28:89–94.
2. Waldman SA, Rapoport RM, Murad F. Atrial natriuretic factor selectively activates particulate guanylate cyclase and elevates cyclic GMP in rat tissues. J Biol Chem 1984;265: 14332–4.
3. Ibrahim NE, McCarthy CP, Shrestha S, Gaggin H, Mukai R, Szymonifka J, et al. Effect of neprilysin inhibition on various natriuretic peptide assays. J Am Coll Card 2019;73: 1273–84.
4. Reginauld SH, Cannone V, Iyer S, Scott C, Baily K, Schaefer J, et al. Differential regulation of ANP and BNP in acute decompensated heart failure: deficiency of ANP. JACC Heart Fail 2019;7:891–8.
5. Meems LMG, Burnett JC Jr. Innovative therapeutics: designer natriuretic peptides. JACC Basic Transl Sci 2016;1:557–67.