Editorial Comment

Atrial Natriuretic Factor
Is It Physiologically Important?

John C. Burnett Jr., MD

The heart as an endocrine gland was unequivocally established with the ingenious experiments of DeBold and coworkers 1981 that demonstrated the existence of atrial natriuretic factor (ANF).1 These and subsequent studies have reported that ANF exists as a prepro-ANF molecule that is stored as a 126-amino-acid pro-ANF within atrial granules.2,3 In response to atrial stretch, pro-ANF is cleaved by a membrane-bound protease and released into the circulation as a 28-amino-acid peptide.4,5 Although hundreds of studies on ANF appear annually, the functional role of ANF in physiological regulation remains unclear. Based on studies that use exogenous administration of synthetic ANF, it is clear that pharmacological concentrations of ANF may decrease cardiac filling pressures and arterial pressure, increase sodium excretion, and inhibit activation of the renin-angiotensin-aldosterone system.6,7 Despite such pharmacological actions, the role of ANF in the physiological regulation of the circulation remains controversial.

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The article by Volpe and colleagues in this issue of Circulation addresses an emerging role for ANF as a modulator of baroreceptor function in humans. The authors elegantly demonstrate that exogenously administered ANF modulates the chronotropic responses to baroreceptor manipulation. Bradycardic responses to phenylephrine are enhanced, and tachycardic responses to nitroglycerin are attenuated. That the observation of the authors may have physiological importance is supported by the recent report of Ebert and Cowley.9 In this latter study, exogenous administration in humans of ANF at lower and more physiological concentrations attenuated baroreflex-mediated cardioacceleration with no effect on baroreceptor-mediated bradycardic responses. Taken together, these two studies in normal human subjects support the conclusion that ANF may be functionally important in the physiological regulation of baroreceptor function. Is this physiological action an isolated action or does it have important and widespread functional significance?

Volpe and coworkers cogently speculate that elevation of endogenous ANF may have functional significance in congestive heart failure (CHF) by counteracting the impairment in the baroreceptor-mediated chronotropic reflex characteristic of heart failure.8 It is this hypothesis that may suggest the key physiological role for ANF. A support of this hypothesis is the observation that CHF is characterized by the highest concentrations of endogenous circulating ANF reported, which are concentrations of ANF with unequivocal physiological actions.10

Lee et al recently proposed an important functional role for endogenous ANF in acute CHF.11 In a canine model of acute CHF produced by rapid ventricular pacing, cardiac output and arterial pressure were decreased in association with elevation of atrial pressures and plasma ANF. Despite the stimulus of arterial hypotension, sodium excretion was maintained and plasma renin and aldosterone were not increased. In contrast, reductions in arterial pressure to similar hyotensive levels in a low-cardiac output model of CHF produced by thoracic inferior vena caval constriction (TIVCC) was not associated with increases in atrial pressures or plasma ANF. In this latter model, plasma renin and aldosterone were markedly increased, and avid sodium retention was observed. When exogenous ANF was infused in dogs with TIVCC to mimic concentrations observed in the high-ANF pacing model of acute CHF, renin and aldosterone concentrations were normalized and sodium was not retained.

Drexler et al have also established an important vasodilatory role for endogenous ANF in CHF by using anti-ANF antibodies in a rat model of chronic CHF.12 In these investigations, exogenous anti-ANF monoclonal antibodies neutralized the action of high endogenous plasma ANF in this rat model of CHF produced by coronary artery ligation. Antibody infusion significantly increased right atrial pressure, left ventricular end-diastolic pressure, and systemic vascular resistance. These studies suggest that elevated endogenous ANF in chronic CHF modulates central hemodynamics by reducing venous pressure as well as by arterial vasodilatation.

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From the Division of Cardiovascular Diseases, Mayo Clinic, Rochester, Minn.

Address for correspondence: John C. Burnett Jr., MD, Division of Cardiovascular Diseases, Mayo Clinic, 200 First Street SW, Rochester, MN 55905.
When all of these recent investigations are taken together, an important role for elevated endogenous ANF emerges. Its functional role as an endogenous hormone may be in acute and chronic CHF; ANF may serve to protect the central circulation from volume and pressure overload. This action is mediated by fundamental actions on cardiovascular, renal, and endocrine systems. Such homeostatic actions appear to include preventing excessive tachycardia via modulation of baroreceptors, limiting activation of the renin-angiotensin-aldosterone system as well as maintaining sodium excretion despite the stimulus of arterial hypotension.

What is the mechanism by which ANF mediates such biological actions? While the cellular action of ANF may be via activation of a cyclic GMP second-messenger system, Volpe et al advances a key role for angiotensin II (Ang II) as a participant in the biological actions of ANF. Chronic administration of the converting enzyme inhibitor enalapril abolished the baroreceptor modulating action of ANF. Is this an important observation by the authors? A growing number of observations involving other actions of ANF support a critical interaction between ANF and Ang II. Showalter et al advanced the concept that Ang II, which is also elevated in chronic CHF, modulates the renal natriuretic action of ANF. In elegant studies by Harris, Thomas, and Morgan, the inhibitory action of ANF on reabsorption of sodium by the renal proximal tubule was mediated by inhibition of Ang II–stimulated sodium and water transport. In the Volpe et al study, ANF may have antagonized the known vagolytic action of Ang II, which is known to enhance the baroreceptor-heart rate reflex. The authors propose that this latter interaction may occur within the central nervous system. The recent study by Floras in humans is also consistent with a central sympathoinhibitory action of ANF.

The emerging important physiological role for endogenous ANF in acute and chronic CHF as a modulator of cardiovascular, renal, and endocrine function has therapeutic relevance. Acute intravenous administration of ANF in the intensive care unit as adjunct therapy in treatment of acute CHF may be indicated. Here, ANF may serve to limit tachycardia by modulating baroreceptor function together with an action to unload the heart, promote sodium excretion, and inhibit activation of the renin-angiotensin-aldosterone system. In chronic CHF, the newly described agents that may promote the action of endogenous ANF by blocking its clearance at silent ANF clearance receptors or attenuating its metabolism by degradative enzymes may emerge as important therapeutic modalities.

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