Chronic heart failure (HF) is a leading cause of morbidity and mortality worldwide. One important cause of HF is persistant arterial hypertension. Given the poor clinical prognosis, understanding the mechanisms preventing or driving hypertensive cardiac hypertrophy and the transition to failure is a major focus of research in cardiovascular medicine. In this issue, Perera et al.1 provide new evidence for the existence of a protecting regulatory circuit in the heart, which involves the cardiac hormone atrial natriuretic peptide (ANP), its second messenger cyclic GMP (cGMP), and cGMP/cAMP cross-talk in cardiomyocytes. Förster resonance energy transfer (FRET) was used to monitor cAMP levels in specific submembrane microdomains of living myocytes under real-time conditions. The authors demonstrate that early hypertensive cardiomyocyte hypertrophy is accompanied by favorable spatial redistributions of the cGMP-modulated cAMP-hydrolyzing phosphodiesterase 2 (PDE2) and PDE3A between the microdomains of the β1- and β2-adrenergic receptors (AR). This molecular reorganization leads to ANP-induced augmentation of β1-AR stimulation of cAMP formation, and contractility, a circuit which may help to maintain contractile functions in early stages of heart hypertrophy.1

Endocrine Actions of Cardiac NPs Prevent Arterial Hypertension and Insulin Resistance
Since the original discovery that the hormones ANP and B-type natriuretic peptide (BNP) establish an endocrine axis between the heart and the kidneys,2,3 many additional physiological functions have been characterized. Via these hormones, the heart acts as networker between organs involved in the maintenance of blood pressure and metabolism. Physiologically, both NPs are mainly secreted from atrial granules into the circulation in response to acute or chronic atrial stretch.4 Their shared cGMP-producing guanylyl cyclase A (GC-A) receptor then mediates coordinated effects in the kidney, vasculature, adrenals, and central nervous system, which altogether are critical for the resetting of arterial blood pressure and intravascular volume homeostasis (Figure).5,5 In fact, even common human genetic variants at the ANP–BNP gene locus leading to small decreases in circulating NP concentrations contribute to increased blood pressure and hypertension.6 Moreover, ANP and BNP have emerged as key regulators of energy usage and metabolism, promoting lipolysis, lipid oxidation, and mitochondrial respiration.7 These effects enhance white adipose tissue browning and muscle oxidative capacity, particularly during physical exercise. Again, the pathophysiological relevance is emphasized by large epidemiological studies showing that NP levels are reduced in people with obesity, insulin resistance, and diabetes mellitus, and this deficiency may contribute to enhance their cardiovascular risk.8

Local Cardiac Actions of ANP and BNP Counterregulate Adverse Remodeling and Contractile Dysfunction
Chronic hemodynamic overload provokes a rapid and sustained increase in ANP and BNP expression in the ventricular myocardium. Experimental studies indicated that in this situation, NPs exert not only endocrine but also local actions moderating adverse cardiac remodeling. For instance, mice with selective inactivation of the GC-A receptor in cardiomyocytes exhibit mild cardiac hypertrophy and diminishedlusitropic responses to β1-adrenergic stimulation, despite unaltered arterial blood pressure.9 Furthermore, cardiac hypertrophic and fibrotic responses to pressure-overload or to neurohumoral stressors, such as angiotensin II and aldosterone, are markedly enhanced in these mice.10–11 This adverse remodeling is accompanied by rapid deterioration of cardiac contractile properties.11 Functional and imaging studies reveal that the expression levels of the GC-A receptor even in wild-type cardiomyocytes are low, ANP/GC-A stimulation leading to small cGMP increases in discrete submembrane signaling microdomains.12 However, this is sufficient to activate a local pool of cGMP-dependent protein kinase-I, which in turn phosphorylates specific target proteins at the sarcolemma, such as the regulator of signaling-2 (a GTPase-activating protein for Gqα-coupled receptors) and transient receptor potential canonical-6 Ca2+ channels.10,11 In fact, GC-A and transient receptor potential canonical-6 channels are in close proximity within a stable protein complex.14 Ultimately, ANP and BNP thereby attenuate angiotensin II/AT1-signaling and the activation of Ca2+-dependent prohypertrophic pathways, such as calcineurin–nuclear factor of activated T cells and Ca2+-calmodulin kinase II (Figure).10–15

Although the actions of NPs on pathological myocyte growth have been extensively studied, their role in the regulation of cardiac contractile functions is much less explored. In healthy murine cardiomyocytes or intact murine hearts,
synthetic ANP has no direct effect on electromechanical coupling. Also, ANP does not modulate β-AR responses under baseline conditions. Importantly, the work by Perera et al. now shows that this picture significantly changes in early stages of experimentally induced hypertensive heart hypertrophy. Intriguingly, ANP enhances the inotropic/chronotropic effects of β-AR stimulation in hypertrophied myocytes and in intact hearts from mice with surgically induced cardiac pressure overload. The authors reasoned that ANP-induced cGMP increases at the sarcolemma inhibit the activity of cAMP-degrading PDEs and thereby stabilize the cAMP pool formed in response to β-AR stimulation. To follow subcellular cAMP/cAMP cross-talk in real-time by Förster resonance energy transfer imaging, Perera et al. generated a novel, elegant transgenic mouse model expressing a CAMP sensor pmEpac1 exclusively in caveolin-rich sarcolemmal microdomains, close to T-tubular membranes and at the surface sarcolemma. Indeed, ANP augmented cAMP responses to β-AR stimulation in hypertrophied cardiomyocytes but not in unaltered cells. Combination of specific β/β-AR agonists with inhibitors of specific types of PDEs unraveled that myocyte hypertrophy is accompanied by a reduction of PDE2 and PDE3A favoring PDE2 increase, whereas PDE3A (the cGMP-inhibited PDE) decreases. This PDE switch results in reinforcement of β-AR–stimulated cardiac contraction/re-laxation, why do they not prevent HF? As always in nature, these circuits are dynamic and vulnerable. Patients with HF have high ANP and BNP plasma levels, correlating with disease severity. Therefore, in clinical practice, BNP is better known as a diagnostic marker than as a hormone. In fact, HF is a state of functional NP hormone deficiency. The cardiomyocytes secrete large but unprocessed amounts of the poorly active prohormones pro-ANP and pro-BNP. Their shared GC-A receptor dephosphorylates, which leads to receptor desensitization. ANP, via a desensitized GC-A receptor, can provoke paradoxical activation of transient receptor potential canonical-6 calcium channels and pathological Ca2+ entry. Even more, a recent study by Lee et al. reveals that diseased human and mouse cardiomyocytes have higher levels of another type function in early heart hypertrophy. Fluorescence ratio imaging of cAMP in single living cells is a powerful technique that was established many years ago. Perera et al. now made an elegant step forward by creating a new sensor allowing to follow in real-time cAMP dynamics in discrete subcellular sarcolemmal microdomains of the highly compartmentализed cardiomyocytes. Thereby, they uncovered a local cGMP/cAMP cross-talk that would have been unappreciated by conventional Förster resonance energy transfer techniques. Although their studies harbor the limitations of isolated cells subjected to pharmacological concentrations of synthetic ANP, the relevance in vivo is supported by observations in mice with cardiomyocyte-restricted deletion of the GC-A receptor. As mentioned above, the lusitropic effects of β-AR stimulation are diminished in these mice and they are prone to hypertensive cardiac failure. Together, these experimental observations emphasize that ANP and BNP are not only important endocrine hormones but also exert local, protective actions on myocyte growth and contractile functions.

**Pathophysiological and Therapeutical Implications**

If ANP and BNP, via cGMP, drive antihypertrophic regulatory circuits and improve β-AR–stimulated cardiac contraction/re-laxation, why do they not prevent HF? As always in nature, these circuits are dynamic and vulnerable. Patients with HF have high ANP and BNP plasma levels, correlating with disease severity. Therefore, in clinical practice, BNP is better known as a diagnostic marker than as a hormone. In fact, HF is a state of functional NP hormone deficiency. The cardiomyocytes secrete large but unprocessed amounts of the poorly active prohormones pro-ANP and pro-BNP. Their shared GC-A receptor dephosphorylates, which leads to receptor desensitization. ANP, via a desensitized GC-A receptor, can provoke paradoxical activation of transient receptor potential canonical-6 calcium channels and pathological Ca2+ entry. Even more, a recent study by Lee et al. reveals that diseased human and mouse cardiomyocytes have higher levels of another type.
of phosphodiesterase, PDE9, that degrades the NP-derived cGMP pool near to the T-tubules. If cGMP is equally important in human when compared with rodent hearts, reduced local NP/cGMP signaling may contribute to the transition of cardiac hypertrophy to failure. Indeed, the view that augmentation of ANP/BNP signaling in general benefits patients with HF is supported by the recent clinical observation that a drug combining blockade of the angiotensin II/AT1-receptor with inhibition of neprilysin, a peptidase which degrades NPs, diminished the risks of hospitalization and death in patients with HF. Another approach presently studied in preclinical and first small clinical studies is the application of synthetic modified natriuretic peptides. Finally, considering the aforementioned molecular changes accounting for NP deficiency in patients with HF, inhibition of the cGMP-degrading PDE9 or stimulation of corin, the cardiac convertase that locally activates the natriuretic peptide prohormones, may also represent targets for the development of novel heart therapies saving the protective actions of these old friends.

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Disclosures

None.

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Michaela Kuhn

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