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Acute Heart Failure

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Foreword

Acute heart failure is a leading cause of morbidity and mortality worldwide, and its incidence is increasing as the population ages. This represents a huge clinical and economic burden for all health care systems. With its high prevalence and associated morbidity and mortality, acute heart failure requires better therapies. Greater awareness of the disease process, better understanding of the underlying mechanisms, and improved management of patients with heart failure are urgently needed to ensure that the outcomes of patients with acute heart failure are optimized.

In recent years, the concept of acute heart failure as a single disease entity has changed, and the definition and classification of acute heart failure have gradually been modified with the increased realization that the term *acute heart failure* incorporates several acute heart failure syndromes, which differ in presentation, etiology, pathophysiology, and outcome. Clinicians and investigators around the world are now collaborating to establish more uniform definitions, collect relevant epidemiologic data, and develop more standardized guidelines and recommendations for the management of patients with acute heart failure. Recent epidemiologic studies have helped delineate key characteristics of patients with acute heart failure, highlight important risk factors, and identify national and international approaches to management.

This new book on acute heart failure is thus very timely, drawing together the most recent data and concepts in this field, and providing a fresh look at the complexities of acute heart failure. The editors, who are indeed authorities in the field, have succeeded in producing a truly complete review of this vast and important subject. The book is divided into two main parts, the first concentrating largely on epidemiology and pathophysiology, and the second focusing on diagnosis and management. In addition to the chapters covering the more traditional features of heart failure, other chapters address the nutritional, psychological, and ethical aspects. The text is supported throughout by ample and appropriate imaging and relevant references.

The 85 chapters are written by a broad cross-section of recognized experts from the different clinical arenas involved in the investigation and treatment of patients with acute heart failure, including cardiologists, cardiac and thoracic surgeons, intensivists, anesthesiologists, pharmacologists, nephrologists, and pulmonologists. The wide range of specialties represented by the

authors highlights the multidisciplinary nature of this disease process, which can affect almost all organ systems, creating a heterogeneous and complex entity. In addition, the international nature of the authors, including contributors from some 15 countries, helps make this text relevant for clinicians worldwide.

This highly comprehensive book is an important contribution to the literature in this field and will serve as a valuable text for all those involved in the care of patients with acute heart failure.

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Preface

One challenge in editing a textbook is that by the time the the book is published, it is outdated. We believe that the present textbook on AHFS stands up to this challenge. AHFS is a new and rapidly evolving field. At present, we are just starting to learn about AHFS and to develop paradigms similar to those created in the early 1980s for chronic heart failure, one of the fastest changing areas in cardiovascular medicine during the last 20 years. Researchers have only started to measure how important a burden AHFS is on health care.

We are beginning to investigate some reasonable pathophysiological hypotheses. Only recently, the ESC and ACC/AHA issued the first set of guidelines. None of these guidelines is truly evidence based, as only a few clinical trials have investigated new treatments for AHFS and even fewer have yielded positive results. Therefore, the editors felt the need to assemble in a single compendium a baseline document that establishes the current knowledge of this syndrome. In so doing, we have also tried to highlight unmet needs and to delineate areas for future research. Finally, the editors addressed the large heterogeneity of this syndrome by inviting a variety of contributors with different backgrounds and from different continents to participate.

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Natriuretic Peptides

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Peptide hormones belonging to the natriuretic peptide (NP) family play an important role in maintaining cardiac and renal function by regulating fluid volume, pressure, and sodium concentration. The principal members of this family are atrial natriuretic peptide (ANP); urodilatin (URO); brain natriuretic peptide (BNP); and C-type natriuretic peptide (CNP). The physiologic effects of these molecules generally lead to vasodilation, natriuresis, and diuresis, and regulate sodium and water homeostasis, rendering them promising candidates for potential therapeutic use in cardiovascular and renal dysfunction. This chapter reviews the biochemistry, physiology, and pharmacologic potential of the major natriuretic peptides, with particular emphasis on their clinical importance in the treatment of acute heart failure syndrome (AHFS).

Biochemistry

Structure and Synthesis

The natriuretic peptides are characterized by a highly conserved 17-amino-acid ring structure that varies little even among different species. Whereas the amino- and carboxy-terminal amino acid sequences vary markedly, the ring structure differs in only five positions between ANP/URO, BNP, and CNP (Fig. 56.1). The biologically active forms of these molecules are processed from precursor proteins encoded by two genes on chromosome 1 (ANP/URO and BNP) and a third gene on chromosome 2 (CNP). Atrial natriuretic peptide and URO share the same amino acid sequence from position 99 to 126 of the ANP-prohormone; however, URO has an additional N-terminal extension of 4 amino acids.

Atrial Natriuretic Peptide

Human ANP is a 28-amino-acid peptide synthesized in the myoendocrine cells of the heart atria, derived from a 151-amino-acid preprohormone through a series of proteolytic processing steps. An N-terminal, 126-amino-acid precursor, pro-ANP (ANP_{1-126}), is first derived from the preprohormone and stored in atrial myocyte granules. Pro-ANP is then cleaved into a 98-amino-acid N-terminal fragment and the biologically active, 28-amino-acid C-terminal atrial natriuretic peptide (ANP_{99-126}); both are released by exocytosis into the circulation.[1,2] Under normal conditions, ANP gene expression in the ventricles is seen only at very low levels (about 7% that in the atria), but increased ANP messenger RNA (mRNA) production may occur in pathologic conditions such as heart failure and left ventricular (LV) hypertrophy.[3] Atrial natriuretic peptide release is induced by elevations in cardiac-wall tension,[4] which may be due to physical exercise, neurohumoral stimuli, and other physiologic factors.[1]

Urodilatin

Urodilatin (URO/ANP_{95-126}) is a 32-amino-acid peptide that is produced by differential processing of the pro-ANP precursor peptide in distal renal tubule cells; therefore, it is identical to ANP except for the presence of four additional N-terminal amino acids. Urodilatin is found in urine

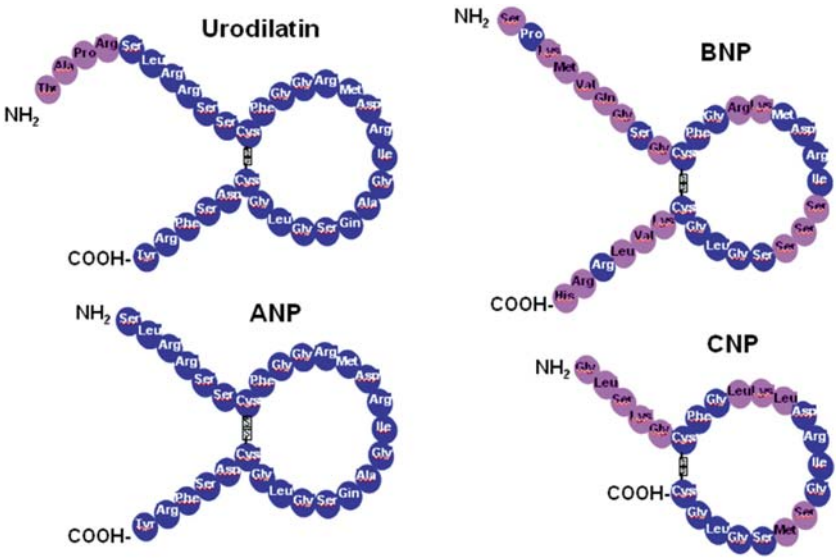

FIGURE 56.1. Structure of the natriuretic peptides ANP_{99-126}, urodilatin/ANP_{95-126}, BNP_{77-108}, and $CNP_{105-126}$ showing the conserved 17-amino-acid ring configuration. Nonconserved residues are indicated in pink.

and has not been detected and isolated from plasma. It is secreted into the tubular lumen and acts as a paracrine hormone, binding further downstream to receptors in the inner medullary collecting duct and inhibiting sodium reabsorption.[5,6] Urodilatin release occurs in response to acute volume load and selective increases in sodium concentration and dietary sodium intake,[7,8] and is closely correlated with the circadian rhythm of urinary sodium excretion.[9] In congestive heart failure (CHF), urinary urodilatin excretion was found to be increased, apparently to counteract antinatriuresis and fluid retention.[10]

Brain Natriuretic Peptide

Brain natriuretic peptide was originally isolated from porcine brain extracts and later identified from human cardiac tissue. It consists of 32 amino acids (BNP_{77-108}) derived from a 108-amino-acid pro-BNP precursor that is found, in humans, predominantly in the ventricles of the heart and in much smaller amounts in the atria, brain, and amniotic tissue.[11,12] N-terminal pro-BNP and mature BNP molecules are released from ventricular myocytes at a 1:1 molar ratio and circulate in plasma. Unlike ANP, which is stored in the form of the 126-amino-acid precursor pro-ANP, BNP is stored mainly as the mature peptide.[4,13] Whereas there is a threefold greater concentration of BNP mRNA in the ventricles than in the atria, the ventricles have only 1% of the amount of mature BNP that is in the atria.[14] Brain natriuretic peptide mRNA is transcribed in response to stretching of ventricle and atrial walls from increased blood pressure or elevated venous volume.[12,15–17]

C-Type Natriuretic Peptide

Processing of CNP starts with the removal of a 23-amino-acid signal peptide from the 126-amino acid preprohormone (prepro-CNP), converting it into pro-CNP (CNP_{24-126}). Pro-CNP is then cleaved to produce a 53-amino-acid intermediate peptide, CNP-53 (CNP_{74-126}); further cleavage of CNP-53 produces biologically active CNP-22 ($CNP_{105-126}$).[18] CNP-22 is produced in brain and endothelial cells and acts primarily as an autocrine or paracrine hormone that regulates vascular tone and blood pressure.[4,19] It is found in much lower concentrations than either ANP or BNP in the heart or in plasma. Like ANP, CNP is stored mainly in the 104-amino-acid propeptide (pro-CNP) form.[18]

Atrial natriuretic peptide and BNP secretion is regulated mainly by the degree of atrial and ventricular wall stress that results from volume or pressure overload and by several endogenous

hormones, neurotransmitters, proinflammatory cytokines, and vasoactive factors. Both CNP production and secretion in vitro are stimulated by ANP, 20-fold more potently by BNP, and by several cytokines and growth factors, including transforming growth factor-β (TGF-β), tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and lipopolysaccharide (LPS), although no relation has been established between CNP and any pathologic effects caused by these cytokines.[2]

Natriuretic Peptide Receptors and Metabolism

The three types of natriuretic peptide receptors (NPRs) are NPR-A, NPR-B, and NPR-C. NPR-A and NPR-B are expressed at high levels in the atria, ventricles, aorta, peripheral blood vessels, platelets, lungs, skin, tubules, smooth muscles of the kidney, and presynaptic sympathetic nerve fibers. Both are highly homologous transmembrane proteins composed of an extracellular binding domain (~440 amino acids), a transmembrane domain (37 amino acids), and intracellular domains with kinase (~280 amino acids) and guanylyl cyclase (~250 amino acids) activity. The guanylyl cyclase domain catalyzes the generation of cyclic guanosine monophosphate (cGMP), which mediates most of the physiologic effects of natriuretic peptides.[4] Atrial natriuretic peptide, BNP, and urodilatin all bind predominantly to NPR-A; ANP is the natural ligand for NPR-A and binds to it with a 10-fold higher affinity than BNP. C-type natriuretic peptide binds most strongly to NPR-B.[2,14]

Natriuretic peptide receptor C is expressed in cells of the kidney, adrenal gland, brain, lungs, and blood vessel walls. It is more abundantly expressed than any other NP receptor type, constituting 90% of all NP receptors in target tissues.[4] It has an extracellular binding domain that is approximately 30% homologous to its NPR-A and NPR-B counterparts and a short, noncatalytic 37-amino-acid intracellular domain that shares no homology with the corresponding domains of the other two receptor types. Natriuretic peptide receptor C is considered a "clearance" receptor whose action is geared toward internalization of receptor-ligand complexes and subsequent lysosomal degradation of the ligand.[20,21] One function of NPR-C may be the removal of excess natriuretic peptides in the circulation, although it may achieve other effects through signaling pathways involving other second messengers such as cyclic adenosine monophosphate (cAMP) or by coupling with G proteins. All natriuretic peptides bind avidly to NPR-C, although ANP and CNP bind with a somewhat higher affinity than BNP.[4,22,23]

Natriuretic peptide binding to NP receptors stimulates cGMP production and elevation of intracellular cGMP levels. Cellular responses depend on downstream cGMP signal transduction, mediated by cGMP-dependent protein kinases (PKGs) that catalyze phosphorylation of target proteins (reviewed by D'Souza et al.[4]). Two protein kinases, PKG-I and PKG-II, appear to be involved in this signaling pathway. PKG-I is a soluble cytoplasmic enzyme that modulates intracellular calcium levels and is present in cardiac myocytes, vasculature, lung, cerebellum, kidney, adrenal glands, and uterus. PKG-II regulates fluid homeostasis at the cell membrane and is found in brain, intestine, lung, kidney, and bone but is absent from the heart and vascular tissue. Cyclic GMP may also activate cAMP-dependent protein kinase A (PKA) or cGMP-regulated phosphodiesterases (PDEs) in certain tissues such as the heart, lung, liver, adrenals, brain, platelets, and smooth muscle.

Natriuretic peptides are cleared from the circulation by NPR-C uptake and the enzymatic action of neutral endopeptidase (NEP), a zinc metallopeptidase enzyme present in high concentrations in the brush border of renal proximal tubular cells and also in the vascular endothelium. Neutral endopeptidase digests other vasodilators such as bradykinin, substance P, and adrenomedullin, and vasoconstrictors such as angiotensin II and endothelin 1 (ET-1) (reviewed in Schmitt et al.[14]).

Physiology and Pharmacology

Atrial Natriuretic Peptide and Brain Natriuretic Peptide

Atrial natriuretic peptide and lower levels of BNP are produced in the atria and ventricles in response to changes in transmural atrial pressure or stretch

as a consequence of pressure or volume expansion. Neurohumoral stimuli such as vasopressin, angiotensin II, endothelin (ET), enkephalin, morphine, and TNF-α also induce ANP release.[24–28]

The effects of ANP and BNP on the cardiovascular and renal systems are well documented.[17,29–36] Under physiologic conditions, ANP and BNP have similar physiologic effects, including vasodilation; suppression of the renin-angiotensin-aldosterone system (RAAS), endothelin, and sympathicoadrenergic systems; reduced blood pressure and peripheral vascular resistance; and enhanced diuresis, natriuresis, and kaliuresis.[29,30,36] In canine models and isolated arterial strips, ANP relaxes coronary arteries[37] and appears to be more selective for the renal arteries when compared to others (vertebral, femoral, and common carotid).[38] In humans, however, results of studies on the effects of BNP on coronary arteries and coronary flow rate have been equivocal.[39,40]

As natural antagonists of the RAAS, ANP and BNP inhibit Na^+ reabsorption in the inner medullary collecting duct and also modify the renal hemodynamics by increasing preglomerular vasodilation and postglomerular vasoconstriction, thereby increasing the glomerular filtration rate (GFR). All these actions have the end effect of enhancing natriuresis and diuresis. The pro-ANP fragment ANP_{31-67} also stimulates the release of prostaglandins, which induce natriuresis indirectly by blocking adenosine triphosphatase (ATPase)-dependent sodium exchange in the inner medullary collecting duct of the kidney.

Atrial natriuretic peptide or BNP infusions in healthy subjects increase urinary flow rate and Na^+ excretion in a dose-dependent manner and inhibit plasma renin secretion.[34,41] Brain natriuretic peptide also has predominantly central hemodynamic effects, such as decreased stroke volume and mean arterial pressure and increased heart rate, but it does not seem to affect the peripheral microcirculation in the skin and conjunctiva, capillary density, or skin oxygen capacity.[36]

Atrial natriuretic peptide also appears to play an important role in organogenesis and embryogenesis by regulating the differentiation and regulation of multiple organ systems, including the skeletal system, immune response, natural killer cell activation, histamine release, reproductive system, and central nervous system (reviewed in Schmitt et al.[14]). Additionally, other studies emphasize the potential role of ANP and BNP as important factors in cardiovascular remodeling as a result of their antiproliferative activity.[4] The mechanism by which these NPs modulate proliferation, cell growth, and apoptosis in cardiac myocytes, smooth muscle cells, and fibroblasts, as well as extracellular matrix production, is currently the subject of intensive research.

The biological half-life of ANP is approximately 3.5 minutes, whereas that of BNP is nearly seven times longer at 22.6 minutes as a result of its slower degradation by NEP and lower affinity for the NPR-C.[2]

Urodilatin

Because they are highly homologous to each other and are derived from the same precursor, the biologic actions of urodilatin and ANP are similar; however, the effects of urodilatin on renal sodium excretion are more critical than those of ANP. Urodilatin infusion in animal models results in a much stronger natriuretic and diuretic effect than that produced by an equimolar ANP infusion.[42,43] This is most likely due to the lesser susceptibility of urodilatin to degradation by the neutral endopeptidase as it passes the proximal tubules in the kidney.[44]

Urodilatin causes dilation of preglomerular and constriction of postglomerular vessels[45] and also increases GFR in animal models of acute renal failure.[46] In healthy human volunteers, urinary excretion of urodilatin is directly correlated to increased sodium intake and renal sodium excretion.[7] After prolonged diets with varying sodium doses, infused urodilatin at 20 ng/kg/min for 60 minutes increased diuresis and natriuresis in proportion to the amount of sodium in the diet, further suggesting an important role for endogenous urodilatin in sodium homeostasis.[35] The renal response to urodilatin appears to be exerted at the collecting duct where sodium reabsorption is inhibited. Even lower doses (5 and 10 ng/kg/min) of intravenously administered urodilatin to healthy subjects with normal LV function have significant systemic effects on the cardiovascular, endocrine, and renal systems. In contrast to the response in heart failure patients, in healthy volunteers these low doses led to a reduction in the

cardiac output by 7% and 16%; in stroke volume by 10% and 20%, respectively, most likely due to venodilation; and in renal blood flow (hippurate clearance) by 13% to 37%, with no changes in arterial pressure or GFR.[47]

In addition to its effects on the kidney, in healthy volunteers, urodilatin at ≤20 ng/kg/min inhibits the neurohumoral axis, resulting in decreased secretion of renin, angiotensin II, aldosterone, vasopressin, and BNP into the plasma. At higher dosages, plasma renin, angiotensin II, aldosterone, and vasopressin levels actually increase in a compensatory fashion because of the decrease in blood pressure.[5,47,48]

In a randomized, placebo-controlled phase II study of subjects with bronchial asthma, urodilatin at various doses, alone or in combination with albuterol, improved bronchodilation parameters, including forced expiratory volume (FEV), maximum expiratory flow (MEF), and peak expiratory flow (PEF), and showed potential as an adjunct to β_2-adrenergic agonists for asthma management.[49]

Unlike ANP, urodilatin is more resistant to NEP degradation, probably because of the four additional amino acids at its N-terminal tail, and it seems to be cleared from circulation also by binding to NPR-C.[50] Infused urodilatin has a plasma half-life of approximately 5 to 24 minutes; with bolus injections, however, the half-life is shortened to 2 to 3 minutes.[48]

C-Type Natriuretic Peptide

C-type natriuretic peptide is produced in endothelial cells, acts in a paracrine/autocrine manner, and is rapidly inactivated so that plasma measurements do not always reflect changes in CNP levels. C-type natriuretic peptide has been shown to regulate vascular tone and induce arterial vasodilation and relaxation. Its potency varies with the size of the blood vessel and the type of NP receptor expressed on the vessel. It is more potent than ANP in relaxing smooth muscle and likely plays a more important role in dilating blood vessel walls than in inducing diuresis or natriuresis.[19]

Infused CNP has been shown to lower blood pressure in animal models as well as in healthy human volunteers.[18] C-type natriuretic peptide knockout mice, however, appear to compensate with increased ANP production so that they are not hypertensive as expected; rather, they are mildly hypotensive. C-type natriuretic peptide also suppresses adrenocorticotropic hormone (ACTH), vasopressin, and aldosterone synthesis.

C-type natriuretic peptide plays an important role in modulating vascular inflammation and in other vascular protective mechanisms (reviewed in Scotland et al.[18]). C-type natriuretic peptide production is stimulated by inflammatory cytokines such as IL-1 and TNF and by LPS; septic shock patients actually have significantly higher levels of circulating CNP. The antiinflammatory effect of CNP includes suppression of proinflammatory prostaglandin E_2 (PGE_2) production in isolated cells, reduced expression of vascular adhesion molecules, and inhibition of leukocyte migration, or "rolling." Vascular protection by CNP may also involve its beneficial effects on the vascular endothelium and smooth muscle and inhibition of coagulation and thrombus formation.

Clinical Significance

Studies of NPs have significantly expanded our understanding of homeostatic mechanisms underlying fluid volume and pressure regulation. Alterations in circulating levels of the cardiac NPs have been used as diagnostic and prognostic markers in various cardiovascular conditions, such as CHF, hypertension, LV dysfunction, acute coronary syndromes, and aortic valve diseases[2,51–53] (reviewed in D'Souza et al.[4]).

Natriuretic Peptides as Disease Indicators

Congestive Heart Failure

Increased mechanical strain in the atria and ventricles is a major stimulus for the synthesis and release of both ANP and BNP, resulting in a marked increase in ANP and BNP levels in circulation during the development of heart failure. Plasma ANP and BNP are negatively correlated with left ventricular ejection fraction (LVEF). Several studies have shown that plasma BNP, as well as the N-terminal pro-BNP fragment (NT-pro-BNP), may be a more powerful prognostic

indicator of development of LV systolic or diastolic dysfunction and LV hypertrophy than is ANP.[2,17,51,52,54]

Rapid (15-minute) BNP immunofluorescence assays (Biosite Diagnostics, San Diego, CA, and Bayer Diagnostics, Tarrytown, NY) are currently approved as a tool for the diagnosis and prognosis of patients with acute coronary syndromes, including acute decompensated heart failure. There is also an 18-minute electrochemiluminescence assay for NT-pro-BNP (Roche Diagnostics, GmbH, Basel, Switzerland). Although BNP testing does not replace echocardiography and a full cardiologic assessment and should be used only within the clinical context, heart failure appears more likely with plasma BNP concentrations above 100 pg/mL.[51,52] At or above this level (100 pg/mL), BNP was more accurate than the National Health and Nutrition Examination Survey (NHANES) and Framingham criteria in diagnosing heart failure.[54] The ratio of plasma ANP to plasma BNP is significantly higher in patients with obstructive airway disease than in those who have heart failure, perhaps because of increased right atrial pressures secondary to severe primary lung disease.[4,55]

Serum BNP levels are useful guides for risk stratification for predicting mortality and for designing heart failure treatment regimens by titrating doses of standard medications to a desired BNP level.[56] The BNP levels rise in direct proportion to the severity of symptoms and cardiac damage, and BNP is an independent predictor of mortality in CHF patients. A pilot study of patients with decompensated heart failure has suggested that BNP concentration measured before discharge may help determine the risk of readmission within the month following discharge.[57]

Because BNP concentration is a good indicator of elevated end-diastolic pressure and LV wall tension, which in turn closely correlates with dyspnea, it also correlates well with the New York Heart Association (NYHA) classification scheme. However, tests are currently in progress to evaluate the prognostic and diagnostic value of NT-pro-BNP, which may be a better indicator of abnormal cardiac function than BNP itself in NYHA class I and II patients. In NYHA class III and IV patients, sensitivity and specificity are comparable. The NT-pro-BNP levels may also be more tightly linked to renal function, and negative predictive values for NT-pro-BNP are >95%.[54] The diagnostic value of NT-pro-BNP, however, depends on the patient's age, because NT-pro-BNP levels change with age and declining GFR (the cutoff for detecting CHF rises sharply from 125 pg/mL to 450 pg/mL after age 75), and there is a gray period coinciding with the peak incidence of CHF between 65 and 85 years of age when NT-pro-BNP is of little use to the clinician. Clearly, further research is required to determine how NT-pro-BNP measurements can be best applied in cardiovascular and cardiorenal management.

Acute Myocardial Infarction

Acute myocardial infarction is associated with compensatory activation of the RAAS and sympathetic nervous system, a low to moderate rise in ANP, and a 100-fold increase in plasma BNP via rapid synthesis in infarcted and periinfarcted areas. The ANP and BNP levels correlate with pulmonary capillary wedge pressure (PCWP), but BNP levels at 72 hours correlate inversely with the cardiac index (CI) and LVEF at day 5 and month 3 post-MI.[4] Although BNP gene expression and de novo synthesis occur rapidly in both ventricles, ANP is secreted from storage in the atrium, further indicating distinct pathologic roles for ANP and BNP in AMI.

Myocardial Ischemia and Coronary Artery Disease

In vivo models of experimental ischemia have shown that even brief periods of hypoxia generated by coronary artery occlusion trigger the rapid release of both ANP and BNP without any correlation to myocardial wall stress. In patients undergoing percutaneous transluminal coronary angioplasty (PTCA), inflation of the PTCA balloon induces transient myocardial ischemia, followed immediately by a rapid and transient increase in plasma BNP levels. However, no correlation was found between the magnitude of increase in BNP levels and the duration of myocardial ischemia from this procedure. The ANP levels also increased slightly after balloon inflation. Plasma BNP and pro-BNP levels are also elevated in patients with

chronic coronary artery disease CAD without LV dysfunction.[58]

Natriuretic Peptides as Therapeutic Agents in Acute Heart Failure Syndrome

Acute heart failure syndrome (AHFS) comprises a set of severe, life-threatening symptoms resulting from congestion or fluid retention in the lungs and inadequate perfusion of tissues and organs.[59] Specific signs and symptoms of AHFS include dyspnea or orthopnea, fatigue, pulmonary congestion, rales, coughing, cachexia, peripheral edema, hypoperfusion, and jugular vein distention. Patients with AHFS may not have any previously known cardiac dysfunction but may suffer from symptoms following an acute coronary event such as a myocardial infarction (new-onset AHFS), or they may experience acute decompensation of chronic heart failure.[60]

Current Therapy of Acute Heart Failure Syndrome

The goals of AHFS therapy are (1) to improve clinical symptoms and hemodynamics without increasing the risk of short- and long-term mortality, (2) to preserve or improve renal function, and (3) to minimize myocardial damage. Current treatment strategies focus on rapidly improving hemodynamics and relieving congestion by reducing fluid volume with diuretics; increasing contractility and cardiac output with digoxin and inodilators such as dobutamine, dopamine, and milrinone; and enhancing pulmonary and peripheral circulation with vasodilators such as nitroglycerin and angiotensin-converting enzyme (ACE) inhibitors such as lisinopril and enalapril.

Current therapies have limitations, however. Controlled clinical trials have shown that hemodynamic improvements observed with AHFS interventions do not translate into long-term patient benefit, with most resulting in minimal or no benefit, some deleterious effects, or high mortality rates. For instance, vasodilators generally used when hypoperfusion is accompanied by congestion, normal or high blood pressure, and insufficient response to diuretics alone can also cause hypotension and induce tolerance with prolonged use. High-dose diuretics are associated with increased risk of renal deterioration and neurohormonal activation of the angiotensin-aldosterone and sympathetic nervous systems, perhaps affecting long-term outcomes such as mortality.[61] Some inodilators such as dobutamine and milrinone may increase the risk of ventricular arrhythmias, postdischarge morbidity, and mortality.[61,62] Digoxin increases cardiac contractility and improves symptoms with possible a reduction in the number of hospitalizations, but its long-term clinical outcomes are neutral at best.[63] Therefore, new therapeutic approaches that improve short-term outcomes without negatively affecting renal and cardiac function and long-term survival are desired.

Newer therapies include levosimendan, an inotropic, Ca^{2+}-sensitizing, K^{+} channel opener with antiischemic and anti-stunning effects that increases myocardial contraction without increasing myocardial oxygen consumption, and tolvaptan, a vasopressin V2-receptor antagonist that increases urine volume and serum sodium with little or no sodium loss (reviewed in Gheorghiade et al.[64]). Levosimendan is well tolerated. Most common adverse effects include headache, hypotension, nausea, and dizziness believed to be secondary to its vasodilatory effects and slight reductions in red blood cell count, hemoglobin, and serum potassium, but no proarrhythmic effects.[65,66] However, a multicenter randomized trial (Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support [SURVIVE]) evaluating its efficacy in improving survival in AHFS patients showed no significant reduction in mortality when compared with dobutamine.[67]

Natriuretic Peptide Therapy for Acute Heart Failure Syndrome

Three natriuretic peptide agents are currently approved or undergoing development for the management of acute heart failure (Table 56.1). Carperitide and ularitide are synthetic analogues of ANP and urodilatin, respectively, and nesiritide is a recombinant form of human BNP. All three

TABLE 56.1. Characteristics of therapeutic natriuretic peptides

	Carperitide	Nesiritide	Ularitide
Peptide analogue	ANP_{99-126}	BNP_{77-108}	Urodilatin (ANP_{95-126})
Source	Synthetic	Recombinant	Synthetic
Development phase	Approved in Japan for acute heart failure	Approved in the U.S. for ADHF	Phase II–III
Secreted by	Atrial and ventricular myocytes	Ventricular myocytes	Renal tubular cells
Stimulus for secretion	↑ Blood pressure, venous volume; atrial wall stretching	↑ Blood pressure, venous volume; ventricular wall stretching	↑ Plasma Na^+; ↑ blood pressure
Receptor	NPR-A, NPR-C	NPR-A, NPR-C	NPR-A, NPR-C
Plasma half-life	2–5 min	18–23 min	2–24 min
Sensitivity to NEP	Yes	Yes	Yes, but less than ANP
Physiologic targets	Vascular wall endothelium and smooth muscle	Vascular-wall endothelium and smooth muscle	Collecting ducts
Pharmacologic effects: mechanism of action	↓ Na^+ reabsorption, ↓ renal perfusion rate; ↑ GFR; ↓ RAAS; predominantly venous vasodilation; bronchodilation	↓ Na^+ reabsorption, ↓ renal perfusion rate; ↑ GFR; ↓ RAAS; vasodilation; bronchodilation	↓ Na^+ reabsorption, ↓ renal perfusion rate; ↑ GFR; ↓ RAAS; vasodilation; bronchodilation
Clinical effects in ADHF patients	↓ PCWP, LVFP; ↑ CI	↓ PCWP and systemic arterial pressure; relief from dyspnea	↓ PCWP, PAP, and SVR; ↑ CI; ↑ relief from dyspnea
Adverse effects	Hypotension; renal dysfunction	Hypotension; renal dysfunction (azotemia, ↑ serum creatinine); potential ↑ mortality	Sweating; hypotension; nausea; dizziness; bradycardia

ADHF, acute decompensated heart failure; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; LVFP, left ventricular filling pressure; NPR-A and NPR-C, natriuretic peptide receptor-A and -C; CI, cardiac index; RAAS, renin-angiotensin-aldosterone system; GFR, glomerular filtration rate; NEP, neutral endopeptidase; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance.

restore hemodynamic balance and improve cardiac or renal function in patients experiencing AHFS.

Carperitide (Synthetic Atrial Natriuretic Peptide)

Carperitide is a synthetic form of human ANP that was approved for use in Japan in 1995 for the management of acute heart failure (AHF). In a 6-year open-label study of 3777 patients with AHF treated with 0.085 μg/kg/min carperitide for 65 hours, 82% of patients experienced clinical improvement in terms of severity of Killip classification and renal dysfunction.[68] A much smaller, earlier study in patients who had severe heart failure with AMI also demonstrated a decrease in PCWP by almost 50% (21 to 11 mm Hg) and plasma aldosterone from 148 to 56 pg/mL after carperitide infusion (0.05 to 1.0 μg/kg/min) without altering heart rate and systemic blood pressure.[69]

Studies on the effect of ANP infusion in CHF patients vary widely in design, patient population, and type of ANP analogue used, making interpretation difficult.[14] They all show an invariable reduction in cardiac filling pressure, however, that occurs too early to be due to a fluid shift or changes in diuresis and pulmonary or peripheral vascular resistance and has been attributed to ANP-induced venous vasodilation. This reinforces the concept of ANP as a vasodilator on veins rather than arteries in patients with high PCWP and plasma noradrenaline.[70]

Nesiritide (Recombinant Brain Natriuretic Peptide)

Nesiritide (Natrecor®) is a recombinant human B-type natriuretic peptide (hBNP) that was approved in the United States in 2001 for the treatment of AHFS patients with dyspnea at rest or minimal activity. The recommended dose is an intravenous bolus of 2 μg/kg followed by a continuous infusion of 0.01 μg/kg/min. Nesiritide improves short-term dyspnea and produces dose-dependent reductions in PCWP and systemic arterial pressure in patients with heart failure.[71] In clinical trials, the decrease in PCWP was observed within 15 minutes of the start of administration, and most of the effect was achieved at 60 minutes of the infusion.

Unlike dobutamine, nesiritide did not cause ventricular or supraventricular arrhythmias in patients with decompensated heart failure, and it actually reduced ventricular ectopy or had a neutral effect (Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Natrecor Therapy [PRECEDENT] study).[72] Urine output (mean change in volume status) during the first 24 hours of nesiritide infusion did not differ from that obtained with nitroglycerin treatment. Nesiritide may also cause hypotension (Vasodilation in the Management of Acute Congestive Heart Failure [VMAC] study).[73] The VMAC study also showed that relief from dyspnea was indeed reduced by nesiritide treatment but at levels not significantly different from the reduction caused by the relatively low dose of nitroglycerin used for comparison.

Controversy remains, however, as to whether nesiritide is associated with a significantly increased risk of worsening renal function and death after treatment.[74,75] This finding was based on meta-analyses of all available randomized clinical trials evaluating nesiritide in acute decompensated heart failure. Its use has not translated into long-term improvement in clinical outcome.[73]

Ularitide

Ularitide is a synthetic version of urodilatin that is currently under clinical development for the treatment of AHFS. Ularitide has the same ANP_{95-126} amino acid sequence as urodilatin. Like urodilatin, the synthetic version ularitide also binds to NPR-A receptors. Maximum concentration is reached 1.5 to 2 hours after the start of infusion. Various studies have reported a half-life range of 2 to 24 minutes.[48,76,77]

The primary pharmacodynamic effects of ularitide are preload and afterload reduction due to vasodilation of peripheral veins and arteries and increased diuresis and natriuresis at higher doses, lowering blood pressure. These effects result from its direct action on vascular smooth-muscle cells, causing dilation of renal, pulmonary, and coronary arterial vessels, and from inhibition of sodium reabsorption in the renal tubules. Ularitide activity is largely mediated by binding to NPR-A receptors, leading to increased intracellular cGMP levels. Consistent with this mode of action, dose-dependent ularitide-induced increases in plasma cGMP levels have been observed in both healthy subjects and subjects with AHFS.[78]

Ularitide restores fluid hemostasis by inducing diuresis and natriuresis, and vasodilation. In healthy volunteers, ularitide increased the renal filtration fraction by increasing GFR and reducing the effective renal plasma flow, and it increased the fractional excretion of sodium and the rate of urinary sodium excretion.[48] Additionally, administration of ularitide in healthy subjects at dosages up to 20 ng/kg/min leads to a decrease in plasma concentrations of renin, aldosterone, and angiotensin II, suggesting that ularitide may also have a downregulating effect on the RAAS that inhibits aldosterone secretion from the adrenal cortex.[47,48] Ularitide infusion into healthy volunteers also led to reduced cardiac preload, pulmonary arterial pressure (PAP) and PCWP, increased CI, and reduced systemic vascular resistance (SVR).[79] These mechanisms suggest that ularitide may provide a potential benefit to patients with AHF characterized by elevated left and right ventricular filling pressures and neuroendocrine activation.

The clinical efficacy of ularitide in patients with ADHF was evaluated in SIRIUS II, a parallel-dose, placebo-controlled, double-blinded study in 221 patients randomized to placebo or one of three ularitide dosing arms. Ularitide was administered by 24-hour intravenous infusions at 7.5, 15, or 30 ng/kg/min. Compared with placebo for change from baseline to +6 hours, all three ularitide doses were associated with significantly greater reductions in the co-primary efficacy end point of mean PCWP. Dyspnea at 6 hours (the second of two co-primary end points) was rated moderately or markedly improved by a greater percentage of subjects in each ularitide dose group than in the placebo group.[80]

Adverse effects of ularitide include increased sweating, nausea, dizziness, and hypotension (decreased blood pressure) with infusions of 5 ng/kg/min or greater. In the studies where these were observed, all side effects resolved without vasoconstrictor treatment. No apparent worsening of renal function was observed through 72 hours in the SIRIUS II study.

Conclusion

Natriuretic peptides are a family of peptide hormones with distinct biomolecular properties and clinical effects that have been well studied as a treatment modality for AHFS. Structurally, each has a 17-amino-acid loop differing in up to five positions among the different natriuretic peptides.

The vasodilators nesiritide and carperitide have been approved in the United States and Japan, respectively, for acute heart failure. The natural analogues of carperitide and nesiritide (ANP and BNP) are both produced by the atria and ventricles of the heart in response to increased blood pressure and stretching of the cardiac wall and generally cause vasodilation, RAAS inhibition, and reduction in blood pressure without affecting fluid volume. Plasma BNP has also been used as a diagnostic or prognostic marker for acute and chronic cardiac syndromes.

Ularitide, a synthetic form of the renal NP urodilatin, is currently undergoing clinical development. In contrast to the other peptides, urodilatin (ularitide), is produced in the kidney and acts in a paracrine fashion on collecting ducts, resulting in reduced Na^+ reabsorption and thereby increased natriuresis and diuresis. Intravenously applied ularitide also causes vasodilation, reduction in blood pressure, and bronchodilation.

Because of the capacity of the natriuretic peptides to restore hemodynamic balance and fluid homeostasis, they hold promise in the management of cardiopulmonary and renal symptoms of AHFS, although further studies are required to understand more completely their impacts on short- and long-term morbidity and mortality in AHFS patients.

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