Nesirtide, Safety and Efficacy: A Review

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Citation

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Abstract

Nesiritide, a recombinant form of human B-type natriuretic peptide is the first new parenteral agent to gain approval from FDA for acute decompensated heart failure in more than a decade. Although Nesiritide has been well studied in many trials and has been shown to be safe and effective, a recent meta-analysis report of increased 30 day mortality and worsening of renal function has created controversies with the use of nesiritide. The problems intrinsic to these meta-analyses were a heterogeneous patient population, enrolled in randomized controlled fashion and none of these trials were designed or powered to assess mortality risk. Until additional therapeutic trials are conducted, use of nesiritide should be based on clinical and hemodynamic improvement but at the same time it is imperative to use nesiritide only at approved doses and for approved duration which might minimize the risk of increased mortality and renal impairment.

INTRODUCTION

Congestive Heart Failure (CHF) is a health care problem of enormous proportions with a dramatic economic impact costing about $10 billion annually with $5,501 spent for every hospital-discharge diagnosis of heart failure [1]. CHF is one of the most expensive conditions covered by medicare. Although there has been a remarkable improvement in our understanding and treatment of chronic heart failure in the past few years with availability of new drugs coupled with progress in cardiac transplantation, little if any advance has been made in the management of acute decompensated heart failure (ADHF). Admissions to the hospital for decompensation are a frequent occurrence and inpatient management of these patients is a major health burden. This is exemplified by the fact that in 1999, heart failure was the primary discharge diagnosis in 962,000 hospitalized patients, representing a 150% increase since 1979 [2]. About 5 million people in the United States have heart failure and each year 550,000 new patients are diagnosed with heart failure, the incidence of the disease being approximately 10 per 1000 Americans over the age of 65. In the foreseeable future, admissions to hospital for acute decompensated heart failure is likely to continue to increase [3,4].

Symptomatic decompensation is the most common reason for hospitalization of patients with CHF. About 21% of patients who come to the emergency room (ER) with ADHF are experiencing their first episode and 79% have had prior hospital visits for the same condition. The management of ADHF in the emergency medical setting poses a major clinical challenge with in-hospital mortality rate for ADHF being 5-8%. Therefore, rapid application of effective intervention is desirable to achieve clinical stability. Hospital management of ADHF has changed little over the last several years with standard therapy directed toward rapid relief of symptoms utilizing parenteral medications to mobilize fluid and improve hemodynamic function. Initial regimen usually includes intravenous diuretics, vasodilators (nitroglycerine, nitroprusside), and /or positive inotropes (dobutamine, milrinone) to decrease cardiac filling pressures and increase cardiac output [4,5,6,7,8].

NESIRITIDE, NATRIURETIC PEPTIDES AND HEART FAILURE

Nesiritide is recombinant human B-type natriuretic peptide (BNP), derived from E.coli using recombinant DNA technology. BNP is a 32 amino acid peptide with vasodilating, natriuretic, and diuretic properties, originally isolated from porcine brain and subsequently found to be produced in humans in the heart, primarily by the left ventricle. Plasma concentrations of BNP are increased in patients with chronic CHF and correlate well with several clinical and hemodynamic parameters of disease severity [3,4,5,6]. BNP belongs to the family of natriuretic peptides, which play a role in cardiorenal homeostasis. There are at least four members in this family (Table 1) viz; hANP (human atrial natriuretic peptide), hBNP (human brain natriuretic peptide), CNP (C-type natriuretic peptide), and

DNP (Dendroaspis natriuretic peptide). Hemodynamic overload induces the expression of natriuretic peptides in the ventricular myocardium at the transcriptional level. These genes are expressed in ventricular myocardium only during fetal development and their expression in the adult myocardium is indicative of reversion to a fetal phenotype, likely representing an unsuccessful attempt to re-enter cell cycle [8,9,10] . At least 3 receptor types are identified for these peptides: A type, B type and C type. The stimulation of either A/B type receptor (present in vascular smooth muscle) by ANP/BNP leads to increased synthesis of potent vasodilator molecule cGMP (cyclic guanyl monophosphate) which also mediates vasodilator actions of nitric oxide and the nitro vasodilators and thus a major action of nesiritide is vasodilation (balanced vasodilation). The C type receptor molecule is a clearance receptor (ANP/BNP/CNP all bind it), which along with neutral endopeptidase (NEP) regulates the available levels of these peptides. Further cleavage of the peptides is accomplished by cleavage via NEP. Increase in ANP/BNP should be beneficial in CHF through the systemic vasodilation and antagonism of sympathetic nervous system and possibly endothelin system. These peptides also have natriuretic action and so the natriuretic peptide system is uniquely capable of opposing actions of several neurohormonal pathways believed to be central in the pathophysiology of CHF [11,12] . However despite increased circulating and tissue levels of ANP/BNP in heart failure, the physiological effects of the natriuretic peptides are decreased in patients with CHF with a decrease in vasodilatory and natriuretic response. The mechanism for this apparent resistance is likely a combination of factors including a downregulation of natriuretic peptide receptors [9,10,11,12] , post receptor uncoupling in effector tissues, activation of counter-regulatory vasoconstrictor and anti-natriuretic hormones, an increase in neutral endopeptidase activity resulting in enhanced degradation and a decrease in delivery of sodium to the distal tubule due to hemodynamic and hormonal effects in kidney. However, exogenous administration of hBNP (nesiritide) may potentially overcome this barrier and result in improved hemodynamics and symptom control in the setting of acute decompensation [13] .

VASODILATATION, NESIRITIDE AND DECOMPENSATED HEART FAILURE

Acute decompensated heart failure (Table 2) is characterized by hemodynamic abnormalities and neuroendocrine activation that contribute to heart failure symptoms, end organ dysfunction, arrhythmias and progressive ventricular dysfunction. The therapeutic goals in patients presenting with acute decompensation are to stabilize the patient, reverse acute hemodynamic abnormalities, rapidly reverse dyspnea and/or hypoxemia caused by pulmonary edema and initiate treatments that will decrease progression of disease and improve survival. It has been shown that ADHF is hemodynamically characterized by high right and left ventricular filling pressures, increased systemic vascular resistance, and decreased cardiac output [14,15] . The initial response to decreased systolic performance is an increase in myocardial preload (ventricular filling pressures) and afterload (systemic vascular resistance), which help to maintain blood pressure. However, the systolic function is not enhanced but actually is compromised by the persistent increase in loading conditions because atrioventricular valve regurgitation may increase out of proportion to any net increase in stroke volume e.g. mitral regurgitation may take upto 50% of total stoke volume in patients symptomatic at rest [16] . The sustained increases in cardiac volume and pressure lead to increased wall stress and myocardial oxygen demands, which can adversely affect left ventricular performance and result in acute decompensation [17,18,19,20] . The interaction between vascular resistance and myocardial systolic and diastolic reserve as a mechanism of pulmonary edema studied by Gandhi and colleagues [17] found that echocardiographic ejection fraction in patients with pulmonary edema presenting to the ER was almost within the normal range (50% 15%) and the most significant finding was diastolic dysfunction and elevated systemic vascular resistance showing that peripheral vasoconstriction plays a major role in decompensation in systolic and isolated diastolic heart failure. ADHF is caused by a combination of events in which inappropriate increase in peripheral resistance is met with inadequate systolic and diastolic functional reserve causing acute afterload mismatch leading to a vicious cycle in which inadequate function is met with inappropriately high resistance causing further atrioventricular valve regurgitation and decreased stroke volume. The increase in vascular resistance leads to increase in left ventricular (LV) diastolic pressure, which is transmitted backwards to the pulmonary veins causing pulmonary edema [19] . There is increasing evidence that in ADHF increased LV filling pressure is the hemodynamic abnormality that most directly impacts symptoms and is highly predictive of increased risk of fatal decompensation and sudden death and that measures of systemic perfusion, arterial pressure and vascular resistance are not predictive of symptoms or clinical outcomes. Persistent increase in left ventricular filling pressures (LVFP) is now seen to be

associated with increased disease progression and deterioration of ventricular function and subsequent overall mortality (including sudden death) in patients hospitalized with ADHF (Table 3). In fact, levels of BNP (increased in CHF), which closely correlate to pulmonary capillary wedge pressure (PcWP), have also been shown to be independent predictor of re-hospitalisation or death in patients admitted for ADHF [20,21,22,23] .

In contrast, despite low cardiac output being a central feature in ADHF, it has not been shown to be predictive of subsequent outcome [24,25] . This is translated into the observation that inotropic treatment targeted at increasing cardiac index has not resulted in improved patient outcomes. Infact studies with acute or chronic intravenous/oral inotropes have shown these agents to be associated with increased risk of adverse events and in many trials to actually increase mortality for e.g. outpatient use of dobutamine , milrinone, vesnarinone, enoximone, xamoterol have been shown to increase mortality compared to placebo [26,27] . Intravenous milrinone has been shown to be associated with increased adverse events compared to placebo (12.6% v/s 21% P<.001) and trend toward increased mortality (3.8% v/s 2.3%) OPTIME-CHF [28] and i.v dobutamine has been associated with substantial proarrythmic and chronotropic effects in ADHF patients [28,29] . Use of inotropic agents, therefore, carries with it the risk of aggravating ischemia and arrhythmias and weaning from inotropes is also usually slow which further contributes to prolonged hospitalization. Thus, focusing on vasodilation to reverse the decompensated state in CHF is physiologically more appealing and rational as this primarily targets the increased filling pressures and at the same time allows a rapid transition to oral ACE inhibitors (ACEI) and beta blockers.Intravenous vasodilation can rapidly reverse symptoms with normalization or near normalization of resting hemodynamics which can then be maintained with oral medications. An ideal agent for ADHF would be one that rapidly decreases PCWP, causes balanced vasodilation (arterial/venous), promotes natriuresis, lacks direct positive inotropic effect and does not result in reflex neuroendocrine activation [25] . Such an agent might be nesiritide (Table 4).

Nesiritide mimics the actions of the endogenous natriuretic peptides and pharmacologic effect is mediated by a guanyl cyclase-coupled natriuretic peptide receptor-A on the smooth muscle and endothelial cells causing increase in cGMP which leads to relaxation of vascular smooth muscle (veins and arteries). This is hemodynamically manifested as balanced vasodilation, decreasing both systemic vascular resistance and central venous pressure with no evidence of tolerance and facilitating cardiac output at reduced filling pressures. Reduction of systemic venous pressure may also improve left ventricular function in some advanced heart failure patients through ventricular interdependence [29,30] . In addition, decrease in left ventricular filling pressure may improve myocardial perfusion resulting in an improvement in both systolic and diastolic function, particularly with coronary artery disease [30,31] . Nesiritide also has favorable renal excretory effects manifested as diuresis and natriuresis (Table 5). Nesiritide has been evaluated in patients with ADHF and clinical trials have confirmed that nesiritide produces prompt hemodynamic and clinical improvement in ADHF patients (Table 6). When administered to heart failure patients i.v nesiritide has been shown to result in significant dose related reductions in capillary wedge pressure (PcWP), mean right atrial pressure (MRAP), systemic vascular resistance (SVR), mean arterial pressure (MAP) and increase in cardiac index (CI), urinary volume and urinary sodium excretion [12,13,14] . This suggests a unique combination of desirable hemodynamic, neurohormonal and renal effects in CHF patients. As early as 1hour after the start of treatment as well as after 24 hours of infusion, hemodynamic effects of nesiritide include a marked reduction in preload coupled with a decrease in afterload, facilitating an increase in stroke volume (SV) and cardiac output [10] . Pulmonary capillary wedge pressure, right atrial pressure, systemic vascular resistance decrease and cardiac index increase may occur as early as within 15 mins of starting an infusion. Balanced vasodilation (both arterial and venous) causes reduction in SVR and central venous pressure leading to a decrease in filling pressure and increasing cardiac output and index. This is evidenced by decreasing MAP, PCWP, MRAP and pulmonary artery pressure (PAP). A linear trend is seen for all variables affected by nesiritide, meaning that larger doses produce greater changes from the baseline.

Despite the vasodilation, no reflex increase in heart rate is seen which compares favorably with other vasodilator agents that usually increase heart rate (Table7). Thus compared to other agents, the increase in cardiac performance seen with nesiritide may occur at a lower metabolic cost to the heart. The absence of reflex tachycardia during nesiritide-induced peripheral vasodilation supports the proposed anti-adrenergic effect of the natriuretic peptides. Decrease in adrenergic activity may be due to nesiritide induced improvement in hemodynamics with subsequent decrease in central sympathetic outflow, improved norepinephrine

clearance and presynaptic inhibition of NE (norepinephrine) release or a combination of these. Favorable systemic hemodynamic actions are also accompanied by direct effects on renal hemodynamics and function. The effects in the kidney are attributable to its direct actions on the guanyl cyclase coupled receptors in the kidney. Despite a fall in the MAP, nesiritide has little effect on the glomerular filtration rate (GFR) or renal blood flow (RBF). The relative preservation of renal hemodynamics during administration of nesiritide is probably caused by the known vasodilating effects of the natriuretic peptides. There also appears to be a direct tubular effect on sodium and water handling, with nesiritide increasing the distal tubular delivery of sodium resulting in natriuresis and diuresis and this effect of sodium delivery is also expected to improve diuretic responsiveness in patients with ADHF. Nesiritide also has salutary effects on the neurohormonal pathways that are activated in heart failure. It can act at multiple levels like the natriuretic peptides. Thus acting centrally it can attenuate the sympathetic outflow [19] . It can inhibit the production of several potent molecules including endothelin, renin, aldosterone and it can also oppose neurohumoral pathways at the cellular level including endothelin, norepinephrine and angiotensin in various cells, like cardiac myocytes, cardiac fibroblasts, and vascular smooth muscles and can also promote cardiac relaxation or lusitropy The suppression of aldosterone production is through activation of the natriuretic peptide receptor type A in adrenal glands. Nesiritide thus has venous, arterial and coronary vessel dilatory properties that reduce preload and afterload, increase cardiac output without direct inotropic effects, improve echocardiographic indices of diastolic function and improve symptoms in patients with ADHF without increasing the heart rate or being proarrythmic. In addition, nesiritide increases filtration fraction, urinary output, sodium output, and suppresses renin- angiotensin aldosterone axis in patients with ADHF. The most frequently reported side effect with the use of nesiritide has been hypotension, usually asymptomatic and not requiring intervention. Overdiuresis may be the primary factor promoting hypotension with nesiritide and thus the caution that diuretic doses may be adjusted downward when nesiritide infusion is used. Hypotension has traditionally occurred more frequently with nesiritide in clinical trials where higher than the currently recommended dose (bolus of 0.02 micrograms/kilogram followed by infusion of 0.01mcg/kg/min) was used. Only in rare cases has hypotension been prolonged or required intravascular volume expansion. Nesiritide does not exacerbate arrhythmias, does not generate toxic metabolites and does not lead to ischemia. Again no hypersensitivity or tolerance has been observed.

EFFICACY OF NESIRITIDE AS A THERAPEUTIC AGENT IN ADHF

One of the most important advances in heart failure has been the growing interest in neurohormones and the natriuretic peptide system. The offshoot of this has been the emergence of BNP as a marker for diagnosis, prognosis and treatment of heart failure and the birth of nesiritide. Nesiritide's novel activity at the cellular level sets it apart from the more traditional drugs currently utilized for the treatment of ADHF. Nesiritide infusion in patients admitted to the hospital for the treatment of ADHF, results in improvements in hemodynamic function and rapid and sustained improvements in clinical status. Nesiritide is indicated for patients with ADHF, which may be defined as a sustained deterioration in function of at least one NYHA (New York Heart Association) class associated with evidence of total body salt and water overload (jugular venous distension, rales, hepatojugular reflux, edema, etc.). Elimination half life of nesiritide is 18-20 minutes and its hemodynamic effects dissipate entirely within 2 hours of stopping of the infusion. Although eliminated, in part, through renal clearance, clinical data suggest dose adjustment is not required in patients with renal insufficiency. Nesiritide has been administered concomitantly with other medications including digoxin, diuretics, ACEI's, angiotensin receptor blockers (ARBs), beta-blockers, statins, class III anti-arrythmics and dopamine with no evidence of any adverse interaction.

The effectiveness and efficacy of nesiritide as a therapeutic modality for ADHF has been well investigated in several trials covering more than 2000 patients and has rapidly emerged as an adjunct to the standard drugs that have been used for decades e.g. diuretics. Though the latter still continue to be the mainstay for the treatment of ADHF, it is a timely reminder that their use is associated with pronounced neurohumoral activation secondary to concomitant decrease in stroke volume and increased vascular resistance. This would translate into limitation in the relief of symptoms, incomplete treatment and setup for early rehospitalisations. Similarly the use of inotropic drugs, though effective in the early stabilization of ADHF is limited by side effects that can be egregious and associated with increased risk of adverse events like substantive ventricular

arrhythmias. In comparative studies with the available vasoactive agents, nesiritide has been proven to be comparable in efficacy to inotropic therapies like dobutamine [2,4] and milrinone [18], but with a superior safety profile and recently has been shown to be more effective and better tolerated than nitroglycerine [6], the traditional vasodilator used for ADHF. Nesiritide use is more physiologic and is associated with rapid symptom relief and reduction in patient morbidity and thus has the potential to help control rising health care costs by decreasing admissions, length of stay and rehospitalisations. A comparison between the parenteral agents (besides diuretics) used in decompensated heart failure is shown in Table 7 [23,24,25,26,27,28]. As can be seen, the advantages of nesiritide besides its nontoxicity and comparatively minimal side effects also include the fact that its use does not require invasive hemodynamic monitoring and neither a right heart catheterization nor an arterial line is required to monitor therapy. Patients can thus receive nesiritide on a telemetry unit with frequent vital sign monitoring. The PRECEDENT [2] and the VMAC [31] trials are benchmark studies which compared nesiritide with dobutamine and nitroglycerine respectively, and furthered the evidence in support for the use of nesiritide in ADHF. The PRECEDENT [2] study revealed that dobutamine use compared to nesiritide was associated with significant increase in ventricular ectopy, heart rate and more likely than nesiritide to cause new onset ventricular tachycardia during treatment whereas nesiritide actually reduces ventricular ectopy or has a neutral effect. A post hoc analysis combining the long term mortality results from the comparative trial [31] and the PRECEDENT [2] trial showed that patients who had received nesiritide had a lower mortality rate at 6 months after therapy than patients who had received dobutamine. The VMAC [31] trial which compared nesiritide with nitroglycerine found nesiritide to be more effective than nitroglycerine, based on more rapid improvement in pulmonary capillary wedge pressure and a more sustained benefit over 24 hours and also fewer adverse effects [33,34,35,36,37,38].

The recently published data on nesiritide however created controversies [39,40,41,42,43,44,45]. Two meta-analyses of the data submitted to the FDA at the time when nesiritide was approved, were performed by Sackner- Bernstein et al. In the first analysis [42], which involved the data from five trials worsening renal failure occurred more frequently in patients randomized to the nesiritide arm. Worsening renal failure, defined as > 0.5mg/dl rise in serum creatinine within thirty days after randomization, in nesiritide group was statistically significant compared to non-inotrope based control therapies (relative risk [RR], 1.52; 95% CI, 1.16- 2.00). In the second meta-analysis [43], 30 days risk of death occurred more frequently in patients randomized to nesiritide versus non-inotrope based control therapy (hazard ratio [HR], 1.80; 95% CI, 0.98-3.31). The investigators concluded that nesiritide use should be limited to patients of ADHF in whom conventional therapy with vasodilators and diuretics fail, until adequately powered, large scale randomized control trial specifically addressing the mortality risk is conducted. However till date there has been no large scale, randomized controlled trial evaluating the safety, efficacy and mortality risk associate with the use of diuretics and vasodilators in patients with ADHF either.

Recently, nesiritide was found to significantly reduce postoperative renal dysfunction (defined as > 0.5 mg /dl rise in serum creatinine) and improve both glomerular filtration rate and urine output in NAPA [46,47] (Nesiritide Administered Post Anesthesia in Patients Undergoing Cardiac Surgery) study. The trial randomized 303 patients with LV dysfunction and NYHA class 2-4 HF at 54 centers who were undergoing cardiopulmonary bypass-supported CABG (coronary artery bypass graft) with or without a mitral-valve procedure to receive nesiritide, initiated during anesthesia, at 0.01 mcg/kg per minute for 24 to 96 hours. The safety analysis ultimately consisted of 279 patients. Patients in the two arms were treated with diuretics to about the same degree. Results of this study showed statistically significant benefits in postoperative renal function, a statistically significant decrease in mortality at 180 days (6.7% of patients treated with nesiritide vs. 14.7% of those treated with placebo; P = .046) and a reduced length of hospital stay (P= .043). Compared with placebo, nesiritide was associated with a significantly attenuated peak increase in serum creatinine (0.15 ± 0.29 mg/dl vs. 0.34 ± 0.48 mg/dl; $p < 0.001$) and a smaller fall in glomerular filtration rate (?10.8 ± 19.3 ml/min/1.73 m^2 vs. ?17.2 ± 21.9 ml/min/1.73 m^2 ; $p = 0.001$) during hospital stay or by study day 14, and a greater urine output (2,926 ± 1,179 ml vs. 2,350 ± 1,066 ml; $p < 0.001$) during the initial 24 h after surge. The overall frequency of adverse events was similar between nesiritide and placebo. Details of a second NAPA trial that has started recruitment in the first half of 2007 have been released by Scios. NAPA II, a multicenter, randomized, double-blind study, aims to enroll a total of 1500 patients aged ? 18 years with NYHA class II-IV heart failure and ejection fraction < 40% who are scheduled for CABG surgery utilizing cardiopulmonary bypass. Patients will be randomized to

treatment with an infusion of nesiritide or placebo beginning at the time frame of induction of anesthesia in addition to usual care for 24 to 96 hours. Mortality and morbidity will be assessed by evaluating multiple clinical endpoints.

Nesiritide is also being investigated for use following cardiac surgery in infants in a pilot study being carried out at Children's Hospital Boston. A total of 20 infants aged < 1 year with congenital heart disease who have undergone cardiac surgery with cardiopulmonary bypass will be recruited into the study. Patients will be eligible if they have received 2 conventional diuretics (furosemide and chlorothiazide) for ?12 hours but have not achieved a negative fluid balance, prohibiting sternal closure or tracheal extubation. Twenty patients will be randomized to receive either of 2 study protocols: a 10-hour continuous infusion of nesiritide, a 2-hour washout period followed by a 10-hour infusion of placebo or the study drug sequence in reverse order. The primary outcome of the study is urine output, with secondary outcomes of cardiac index and safety. The study was scheduled to be completed in January 2007 but as of the writing of this article, results are not available. The Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) is another nesiritide based trial that is supposed to be led by the Duke Clinical Research Institute in collaboration with the Cleveland Clinic Cardiovascular Coordinating Center. The study will evaluate nesiritide administered at the currently recommended dose of an intravenous bolus of 2 mcg/kg followed by a continuous infusion of 0.01 mcg/kg/min. Clinical endpoints will include symptom relief, quality of life, rehospitalization for heart failure, and mortality. The randomized, double-blind, placebo-controlled trial is supposed to enroll approximately 7000 patients with ADHF at approximately 600 medical centers in the United States, Canada, and Europe. Patient enrollment for ASCEND-HF was expected to begin in the first half of 2007.

Also, a recently published analysis of data from ADHERE [48] (Acute Decompensated Heart Failure National Registry) registry, compared the risk factor adjusted and propensity adjusted mortality for nitroglycerine, dobutamine, and milrinone. This was a retrospective analysis of observational patient data from a multicenter registry designed to prospectively collect data on each episode of hospitalization for ADHF and its clinical outcomes. Data from the first 65,180 patient episodes (October 2001 to July 2003) were included in this analysis. Cases in which patients received nitroglycerin, nesiritide, milrinone, or dobutamine were identified and reviewed (n = 15,230). Risk factor and propensity score-adjusted odds ratios (ORs) for in-hospital mortality were calculated. Nesiritide did not increase mortality risk compared with nitroglycerine (OR [odds ratio], 0.94; 95% CI, 0.77-1.16) and significantly reduced it compared with dobutamine (OR, 0.47; 95% CI, 0.39 – 0.56) or milrinone (OR, 0.59; 95% CI, 0.48-0.73).

The only double blinded randomized controlled comparision of Nesiritide versus placebo in

patients admitted to the Emergency department has been published recently by Miller etal [49] . In his study 101 patients were randomized during a 16-month enrollment period. Sixty-six percent of the patients were men and 34% were women. Fifty-six percent were black; all patients had New York Heart Association class II to IV heart failure and most had dyspnea at rest or with minimal exertion. Complete follow-up data were available in 97 of 101 patients. After the 8-hour treatment period, acute symptom relief was experienced in 95.7% of the nesiritide group (95% confidence interval [CI] 88.9% to 100%) versus 86.8% of the placebo group (95% CI 72% to 98.9%), with an absolute difference between the 2 groups of 8.9% (95% CI -3.3% to 24.2%). Diuresis was similar between the 2 groups, but hypotension occurred more frequently in the nesiritide-treated group. The primary outcome measure of return visit to the ED or hospitalization at 30 days was higher for nesiritide (41.5%) than placebo (39.6%; absolute difference 1.9%; 95% CI -17.2% to 21.1%). There was only 1 death. No measurable change in renal function was observed. They concluded administration of nesiritide for acutely decompensated congestive heart failure in a county ED was no better than standard therapy alone for return to the ED or hospitalization at 30 days.

Figure 1

Table 1: Natriuretic Peptides

ANP	• Mainly secreted by atrial myocytes • Synthesis and release stimulated by atrial distension • Lower concentration in ventricle and kidney in the form of urodilantin(5,7) • Not expressed in normal ventricular myocardium. • Secreted by ventricular myocardium in response to hemodynamic overload and increased in myocardium in a wide range of situations associated with myocardial hypertrophy including systemic hypertension, after MI, obstructive or regurgitant valvular disease and most forms of cardiomyopathy regardless of origin
BNP	• Not expressed in atria • Not expressed in normal ventricular myocardium • Secreted by ventricular myocardium in response to hemodynamic overload and increased in myocardium in a wide range of situations associated with myocardial hypertrophy including systemic hypertension, after MI, obstructive or regurgitant valvular disease and most forms of cardiomyopathy regardless of origin
CNP	• Primarily in CNS as well as renal cells and vascular endothelial cells • Very low concentrations in the plasma normal humans
DNP	• Very low levels in the plasma of normal humans (6,7)

hANP = human atrial natriuretic peptide, hBNP = human brain natriuretic peptide, CNP = C-type natriuretic peptide, DNP = Dendroaspis natriuretic peptide.

Figure 2

Table 2: Clinical Classes of Heart Failure

Heart failure type	Congestion at rest (elevated PCWP)	Low perfusion at rest (reduced cardiac index)
Warm and dry	No	No
Warm and wet	Yes	No
Cold and dry	No	Yes
Cold and wet	Yes	Yes

PCWP = pulmonary capillary wedge pressure

About 90% of patients are wet on presentation.

Modified from Fonarow. Treatment targets in ADHF. Rev Cardio Med .2001;vol 2

Figure 3

Table 3: Left Ventricular Filling Pressures and CHF

• Increased sympathetic activation (high NE levels and sympathetic neural activity)- mechanical neurohormonal activation
• Increased Angiotensin II which directly and indirectly induces myocyte apoptosis.
• Progressive structural remodeling.
• Increased wall stress/myocardial oxygen demand with resultant ischemia and complications
• Increased probability of ventricular reentrant arrhythmias and abnormal automaticity and triggered automaticity from partial depolarization of purkinje fibers secondary to stretch.
• Increased intracellular cAmp/calcium and subsequent increased sudden death.
• Desensitization of baroreceotors and prolonged atrial distension leading to exacerbation of secondary baroreceptors dysfunction, predisposing to baroreceptor syncope and bradyarrythmic events.
• Decreased cardiac vagal activity increasing chances of sudden death.
• Progressive atrioventricular valve regurgitation.

CHF= Congestive heart failure, NE = Norepinephrine.

Figure 4

Table 4: Nesiritide as an ideal vasodilator in ADHF.

• Balanced Vasodilation(arterial/venous)
• Rapid decrease in LV filling pressure (PCWP)
• Rapid decrease in symptoms of congestion.
• No reflex tachycardia.
• No positive inotropic effect
• No proarrythmic effect.
• No tachyphylaxis
• Neurohumoral suppression
• Promotion of diuresis and natriuresis
• Convenient dosing
• No hemodynamic monitoring required.
• Good safety profile with adverse effects limited to dose dependant hypotension.
• Shorter treatment course and few additional agents required
• Long term benefit from reduced hospitalization for CHF
• Continuation of baseline treatment with Beta blockers, ACEI/ARBs

ADHF = Acute decompensated heart failure. LV= Left ventricle, PCWP = Pulmonary capillary wedge pressure, ACEI = Angiotensin converting enzyme inhibitor, ARB = Angiotensin receptor blocker

Figure 5

Table 5: Nesiritide and pharmacologic effects.

Hemodynamic: Balanced vasodilation of veins, arteries and some direct vasodilatory action on the coronaries.
Neurohumoral: Decrease in aldosterone, NE, Decrease in endothelin.
Renal: Increased diuresis, Increased natriuresis.
Cell Growth: Anti-mitogenic effect in heart and other organ systems suggesting a potential role in the modulation of cell growth[7].
Intravenous administration of nesiritide: Decrease in PCWP, SVR, MAP, PVR, PAP Increase in CI, Stroke volume, urinary rate, and urinary sodium.

PCWP = Pulmonary capillary wedge pressure, SVR= Systemic vascular resistance, MAP Mean arterial pressure, PVR = Peripheral vascular resistance, PAP = Pulmonary arterial pressure, CI = Cardiac index.

Figure 6

Table 6: Comparison of Nesiritide with Vasodilators and Inotropes.

Nesiritide and other vasodilators

Variable	Nesiritide	Nitroglycerine	Nitroprusside
Tachyphylaxis	-	+	-
Toxic	-	-	+
Hypotension	+	+	+
Special handling	-	+	+
Invasive monitoring	-	-	+
Headache	+	+	+

Nesiritide and inotropic agents

Variable	Nesiritide	Dobutamine	Milrinone
Inotrope	-	+	+
Chronotrope	-	+	-
Vasodilation	+	-	+
Diuretic	+	-	-
Arrhythmias	-	+	+
02 demand	-	+	±

CONCLUSION

Our understanding of the pathophysiology of heart failure has now shown that it is a syndrome mostly influenced by activation of the sympathetic nervous system and neurohumoral axis (renin-angiotensin-aldosterone) whose consequences are maladaptive. This paradigm shift has primarily been reflected in the management of chronic heart failure with very little if any change having occurred in the domain of acute decompensated heart failure.

Decompensated heart failure is a heterogeneous syndrome in which the patient's clinical condition changes from moment to moment and no single treatment is a panacea [35] . However, there are reports of increased worsening of renal function and an increase in short term mortality associated with nesiritide use [39,40,41,42,43,44,45] . However these trials were never designed to assess death or a worsening renal failure either as a primary or a secondary end point. The worsening renal failure in these meta-analyses although statistically significant was without clinical relevance as no difference was found between treatment groups (nesiritide versus non-inotrope based treatment arm) in the need for dialysis [42] . Today, there has been no single therapy for ADHF considered gold standard when compared with newer emerging therapies. With the limited and imperfect available data, use of Nesiritide in the treatment of ADHF should be primary based on a sound clinical judgment by physicians. When a decision to use Nesiritide is taken, physicians should strictly use it at the FDA recommended doses. Large scale randomized, placebo controlled trials are clearly mandated in future to evaluate safety and efficacy of almost all ADHF related therapies with nesiritide being no exception.

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