Published in final edited form as:

Curr Heart Fail Rep. 2014 September ; 11(3): 260–265. doi:10.1007/s11897-014-0208-6.

ROSE-AHF and Lessons Learned

Amit K. Jain, M.D.¹ and Horng H. Chen, MB, BCh. FACC²

¹Department of Internal Medicine, Mayo Clinic and Foundation, Rochester, MN

²Division of Cardiovascular Diseases, Mayo Clinic and Foundation, Rochester, MN

Abstract

Nesiritide and dopamine have been recognized as potential renal adjunct therapies in the management of patients with acute heart failure (AHF) for some time. Several studies have yielded conflicting evidence of the efficacy of both medications in enhancing the renal function of patients with AHF. The renal optimization strategies evaluation (ROSE) study was a multicenter double-blind, placebo controlled trial designed to assess the potential renoprotective effects of low-dose nesiritide and dopamine in AHF patients with renal dysfunction. This article will focus on previous research, summary and lessons learned from the ROSE-AHF trial and future directions for clinical research and applications.

Keywords

ROSE-AHF; nesiritide; dopamine; heart failure therapy; natriuretic peptides; renal dysfunction; natriuretic peptides; acute heart failure

INTRODUCTION

Acute Heart Failure (AHF) has become a widely recognized cause of hospital admission in patients aged 65 and over. Presently, approximately 5.1 million Americans over the age of 18 have heart failure. By 2030, this figure is expected to increase to >8 million in people >18 years of age with projected costs increasing from \$30.7 billion to \$69.7 billion [1]. Studies have suggested a definitive link between renal dysfunction and the prognosis of heart failure with a recent meta-analysis demonstrating worsening renal function associated with increased mortality and hospitalization in patients with heart failure[2], including those with heart failure with preserved ejection fraction[3, 4]. Given the increasing prevalence and financial burden of heart failure in the United States, it has become increasingly important to

Corresponding Author: Horng H. Chen MB, BCh, Division of Cardiovascular Diseases, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, chen.horng@mayo.edu, Tel: 507-284-1644, Fax: 507-266-4710.

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest

Amit K. Jain declares that he has no conflict of interest.

Horng H. Chen has received financial support through grants from the National Institutes of Health (NIH) and Scios, Inc.; has received royalties from Nile Therapeutics, Anexon, and UpToDate; holds the patent issued for chimeric natriuretic peptides; and is the co-founder of Zumbro Discovery.

identify strategies to achieve decongestion while preserving renal function in cases of AHF with associated renal dysfunction [5].

Over the past decade, there have been several trials studying the effects of either dopamine or nesiritide in conjunction with traditional diuretics for patients with AHF (Table 1). These trials have not provided enough evidence to justify the routine use of either drug in conjunction with standard therapies for patients with AHF. The 2013 ACCF/AHA guideline for the management of heart failure concluded that low-dose dopamine infusion may be considered in addition to loop diuretic therapy to improve diuresis and better preserve renal function and renal blood flow, but acknowledged the lack of data supporting the efficacy of this intervention. Similarly, the guidelines recommended the use of vasodilators such as nitroglycerin, nitroprusside or nesiritide for the relief of dyspnea in conjunction with intravenous diuretics in patients with AHF with no evidence of symptomatic hypotension as a Class IIb recommendation [6].

DOPAMINE AND RENAL FUNCTION IN AHF

Given the need for preserving renal function in patients with AHF, dopamine has been evaluated for its clinical utility in the hospital setting. Varying doses of dopamine have been studied with regards to their effect on renal function and cardiac output. Dopamine has been observed to exert a graded pharmacological response with dose dependent effects on dopaminergic, beta (β) receptors and alpha (α) receptors. It is recognized that at low-doses of 3 $\mu\text{g}/\text{Kg}/\text{min}$, dopamine tends to activate A1 dopaminergic receptors causing vasodilation of renal arteries and other vascular beds such as mesenteric, coronary and cerebral regions. Additionally, A2 dopaminergic receptor activation causes reduced norepinephrine release from sympathetic terminals leading to increased vasodilation and renal blood flow (RBF). At an infusion rate of 3 to 5 $\mu\text{g}/\text{Kg}/\text{min}$, the activation of β 1- and β 2- adrenergic confers an inotropic effect of dopamine, leading to increased myocardial contractility and cardiac output [7]. When infused at $>5 \mu\text{g}/\text{kg}/\text{min}$, dopamine exerts its effects on alpha 1 and 2 receptors leading to systemic vasoconstriction, theoretically reducing renal blood flow [7].

Two small single center open label studies done in the late 1990s revealed a potential renoprotective effect of low-dose dopamine in combination with diuretics during aggressive diuresis in patients with AHF [8, 9]. Renal function (measured by BUN, serum creatinine, creatinine clearance and urine output) was improved in a small study of 20 AHF patients receiving dopamine (2 $\mu\text{g}/\text{Kg}/\text{min}$) with bumetanide as compared to bumetanide alone [9]. A similar study done by Cotter *et al* in 20 patients with AHF revealed that the patients who received low-dose dopamine (4 $\mu\text{g}/\text{Kg}/\text{min}$) in conjunction with low-dose (80 mg/day) oral furosemide experienced an improvement in renal function (measured by creatinine clearance), a reduced incidence of hypokalemia and a preservation of mean arterial pressure (MAP) as compared to patients that received either low-dose dopamine + high-dose furosemide or patients that received high-dose furosemide alone [8]. It is important to note that the aforementioned studies used variable doses of dopamine, making the efficacy and side-effects profile of this compound difficult to assess.

More recently, the DAD-HF I and DAD-HF II trials further investigated the use of dopamine in AHF. DAD-HF I compared high-dose furosemide with “low” dose dopamine infusion (5 µg/Kg/min) to high-dose furosemide alone, and found no significant differences in 60 day mortality and rehospitalization rates but did find improved potassium homeostasis and preservation of renal function [10]. DAD-HF II studied both low and high-dose furosemide in relation to low-dose furosemide with “low” dose dopamine (5 µg/Kg/min) [11]. There were no significant differences in 60 day and 1 year all-cause mortality rate, hospitalization for heart failure or overall dyspnea relief between treatment groups. Notably, there was a higher incidence of worsening renal failure in the high-dose furosemide group compared to the other treatment arms. The trial was terminated early due to tachycardia noted in the “low” dose dopamine + furosemide treatment arm. It is important to note that the dose of dopamine used in both DAD-HF trials (5 µg/Kg/min) was at a level at which the inotropic effects of the medication predominate [7, 12].

NESIRITIDE AND RENAL FUNCTION IN AHF

Brain natriuretic peptide (BNP) is a cardiac peptide with vasodilating, renin inhibiting, natriuretic and diuretic properties.[13] Human recombinant BNP (nesiritide) has been approved by the FDA for the management of AHF since 2001 [14]. The standard recommended dose of nesiritide is a bolus of 2 µg/kg followed by infusion of 0.01 µg/kg/min [15].

The BNP-CARDS study explored the renal effects over 48 hours of nesiritide infusion (0.01 µg/Kg/min with or without a 2-µg/Kg bolus) compared to placebo for the treatment of patients with AHF and renal dysfunction along with usual clinical care. The study revealed no significant differences in incidence of creatinine rise (20% or greater), weight change or 30 day death/hospital readmission rates between both treatment groups. There was a non-significant trend for study drug discontinuation in the nesiritide group due to hypotension (13 vs 6%) with lower blood pressures overall in the nesiritide group. Overall, nesiritide conferred no renal protective effect in AHF patients with renal dysfunction [16]. A similar study was done at the Mayo Clinic where 71 patients with AHF and underlying renal dysfunction were randomized to nesiritide at standard infusion (2mcg/kg bolus; 0.01 µg/Kg/min for 48 hours) or placebo in conjunction with standard heart failure therapy. Patients randomized to the nesiritide treatment arm had smaller increases in creatinine ($p=0.048$) and BUN ($P=0.02$), but were noted to have greater reductions in blood pressure at 24 hours but not at 48 or 72 hours[17]. Overall, however, there were no significant changes in diuretic responsiveness as measured by weight change and fluid balance. Additionally, there was no significant reduction in aldosterone or angiotensin II levels, and BNP remained relatively unchanged between treatment arms. The authors concluded that adjuvant nesiritide treatment may confer mild benefit in renal function, but did not increase diuretic responsiveness or help prevent activation of the RAAS system[17]. Lastly, the ASCEND-HF trial studied the use of similar nesiritide infusions in over 7000 patients with AHF. The study revealed no significant changes in death or rehospitalization, and no changes in renal function at various time points. Interestingly, there was a mild improvement in subjective symptoms of dyspnea at 6 hours compared with nesiritide. However, this subjective improvement in dyspnea did not reach a level of statistical significance over the course of

the study. The ASCEND study did not demonstrate significant renal protective effects. However, there was a significant increase in the incidence of symptomatic and asymptomatic hypotension in the nesiritide group as compared to placebo [18, 19].

Preclinical studies have demonstrated the renal enhancing effects of systemic nesiritide infusion, but these results have not been replicated in formal clinical studies. The discrepancy in findings between preclinical and clinical data could be due to the fact that clinical studies used a higher dose of nesiritide, predisposing to systemic hypotension which could then negate the renal enhancing effects of the drug [20].

ROSE AHF STUDY

The ROSE AHF trial used a novel design to evaluate two renal optimization strategies in patients with AHF and renal dysfunction, testing the effects of either low-dose nesiritide or dopamine on enhancing decongestion while preserving renal function. The primary endpoints were 72-hour cumulative urine volume and change in serum cystatin C from enrollment to 72 hours as a measurement of renal function preservation. [5, 21].

The ROSE study included subjects aged 18 and over, hospitalized for the treatment of AHF with renal dysfunction (glomerular filtration rate [GFR] of 15 to 60 mL/min/1.73m² as estimated by the Modification of Diet in Renal Disease equation) and enrolled within 24 hours of admission. In order to minimize the number of patients requiring central line placement for dopamine administration, participants were initially randomized 1:1 in an open label fashion to the nesiritide or dopamine strategies. Patients who were in the dopamine strategy were randomly assigned in a 2:1 ratio to low-dose dopamine infused at 2µg/kg/min for 72 hours versus placebo. Patients in the nesiritide strategy were randomized in a 2:1 ratio to low-dose nesiritide (0.005 µg/kg/min) over 72 hours or placebo. All patients received IV furosemide treatment at 2.5 times the equivalent of oral outpatient dosing for the first 24 hours.

Results

A total of 360 patients across 26 sites in North America were enrolled. The median age of the study population was 70 years, median ejection fraction was 33% and the patients had moderate to severe renal dysfunction with a median estimated GFR of 42 mL/min/1.73m². Overall, there were no significant differences in either the co-primary endpoints of 72-hour cumulative urine volume or the change in cystatin-C from baseline to 72 hours when comparing low-dose dopamine or low-dose nesiritide to placebo. Furthermore, there were no significant differences between the groups in other secondary endpoints assessing for decongestion or renal function, such as change in plasma creatinine, weight, NT-pro BNP from baseline to 72 hours and dyspnea visual analog scale area under the curve from randomization to 72 hrs. At 60 days, there were also no significant differences between both treatment groups compared to placebo in terms of death, serious adverse events and heart failure related visits or hospitalization. There were also no significant differences in mortality between both groups and placebo at 180 days.

Safety and Tolerability

In the nesiritide arm, there was a greater incidence of treatment failure primarily due to drug discontinuation secondary to hypotension. This is similar to previous studies, namely ASCEND-HF, which noted greater prevalence of asymptomatic or symptomatic hypotension with this study drug [19]. Compared with the placebo group, dopamine treated patients were more likely to have the study drug discontinued due to tachycardia. Overall, the study demonstrated that in patients with AHF and moderate to severe renal dysfunction, neither low-dose nesiritide nor low-dose dopamine enhanced decongestion or improved renal function in conjunction with a standard diuretic.

Subgroup Analysis

Subgroup analyses suggest that there was a trend for differential treatment effects according to the ejection fraction. The 72 hour cumulative urine volume tended to be higher and there was a trend for less increase in cystatin C from baseline to 72 hours as compared to placebo in subgroup of patients with lower ejection fraction.

LESSONS LEARNED FROM ROSE AHF

Potential differential responses in AHF with Reduced versus Preserved Ejection Fraction

AHF is a heterogeneous entity with multiple underlying causes. AHF can be broadly classified based on either reduced or preserved left ventricular ejection fraction (LVEF). AHF with reduced LVEF is characterized by impaired contractile function leading to an impaired cardiac output and subsequent tissue perfusion. On the other hand, AHF with preserved LVEF is secondary to impaired ventricular relaxation leading to reduced filling, increased filling pressure and impaired cardiac output.[22]. Previous studies have revealed that AHF with preserved LVEF makes up as much as ~50 % of all cases of AHF [23]. Patients with AHF and preserved LVEF tend to be older, more likely female, and have hypertension, but are less likely to have had a history of myocardial infarction when compared to those with reduced LVEF. Importantly, recent data suggest that mortality rates and rates of rehospitalization are not significantly different between those with reduced or preserved LVEF [24]. In an elegant study, Schwartzberg *et al* determined acute hemodynamic responses to vasodilation with intravenous sodium nitroprusside in patients with HF reduced LVEF and those with HF preserved LVEF [25]. As compared to patients with HF with reduced LVEF, those patients with HF with preserved LVEF demonstrated greater blood pressure reduction and increased likelihood of stroke volume reduction in response to vasodilators. These findings suggest fundamental physiological differences in the 2 HF phenotypes in response to vasodilators. Subgroup analyses of the ROSE AHF study suggest a trend that those patients with HF with reduced LVEF had more favorable responses to both low-dose dopamine and nesiritide as compared to those with preserved LVEF. With low-dose dopamine, the 72 hour cumulative urine volume trended higher in patients with reduced LVEF as compared to placebo. Similarly, with low-dose nesiritide, patients with reduced LVEF demonstrated a trend toward greater 72-hour cumulative urine volume with diminished increases in cystatin C from baseline up to 72 hours as compared to placebo. As stated by the authors, one of the limitations of the ROSE AHF study was that it was not powered to detect differences in the subgroups. To date, literature review does not

reveal any significant clinical trials studying the differential effect of AHF therapies on patients with reduced versus preserved LVEF. Future studies in AHF should be designed and powered to target those with reduced LVEF or those with preserved LVEF separately.

Use of low-dose dopamine in AHF

Despite previous studies suggesting that low-dose dopamine may have renal specific actions to enhance renal blood flow with renal protective actions, the ROSE AHF study demonstrated that low-dose dopamine at 2 µg/Kg/min did not enhance decongestion or preserve renal function in patients with AHF and renal dysfunction. Importantly, the study also demonstrated that this low-dose is not renal specific in all patients. This is supported by the fact that patients in the dopamine group were more likely to have the study drug discontinued due to secondary tachycardia and less likely to develop hypotension as compared to placebo. One of the lessons learnt from the ROSE AHF study was that the routine use of low-dose dopamine in addition to diuretics in patients with AHF and renal dysfunction did not enhance decongestion or preserve renal function. Does this mean that there is no role for dopamine in the management of AHF at all? The ROSE AHF study evaluated the routine and up-front use of low-dose dopamine within 24 hours of admission; hence it may still be reasonable to consider the use of low dose dopamine in patients with AHF who develop worsening renal function or diuretic resistance. Furthermore, the ROSE AHF study only enrolled AHF patients with systolic blood pressure greater than 90 mmHg, therefore dopamine may still have a role in AHF patients with systolic blood pressure less than 90 mmHg. The 2013 ACCF/AHA guideline for the management of heart failure provide the following level IIb recommendation: short-term, continuous intravenous inotropic support may be reasonable for hospitalized patients presenting with documented severe systolic dysfunction, low blood pressure and significantly depressed cardiac output to maintain systemic perfusion and to preserve end-organ performance [6]. Therefore, the use of dopamine in AHF should be individualized.

Use of low-dose Nesiritide in AHF

The ASCEND trial demonstrated that while the use of nesiritide in AHF at the approved recommended dose was safe, it did not enhance renal function despite preclinical studies that have established favorable renal effects. The ROSE AHF trial studied nesiritide at a lower dose with the rationale that there would be less hypotension and more renal-specific therapeutic effects. However, even at the reduced dose, systemic effects were still noted as evidenced by the increased risk of hypotension in the nesiritide treatment arm. The results of ROSE AHF provided no significant support for the routine and upfront use of low-dose nesiritide infusion in the treatment of AHF patients with renal dysfunction with regards to its renal sparing effects. However, the role of low dose nesiritide in patients with AHF who develop worsening renal function or diuretic resistance remains undefined.

CONCLUSION

There is a definite need for renal-targeted therapies in AHF patients with associated renal dysfunction. While the ROSE-AHF trial did not yield answers regarding definitive treatment for these patients, it did shed light on the heterogeneous nature of AHF by showing how

therapies for AHF cannot be broadly applied to a syndrome with such a multifaceted pathology. Both compounds may warrant further investigation in dedicated clinical trials involving AHF patients with reduced LVEF. In the meantime, clinicians still have some latitude in choosing medical therapies for patients with diuretic resistant AHF or AHF with hypotension, with options still including either dopamine or nesiritide.

Acknowledgments

Dr. Chen received Research Grants from NIH; Scios Inc; Mayo Clinic and has filed patents for chimeric natriuretic peptides; Mayo Clinic has licensed patents to Nile Therapeutics and Anexon with other patents pending at the U.S. patent office; Dr. Chen received royalties from Nile Therapeutics, Anexon Inc and UpToDate; and is the Co-founder of Zumbro Discovery Inc.

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Table 1
Summary of clinical studies using dopamine or nesiritide in acute heart failure [8–11, 15–17, 19]

Trial	Study Arms	Primary Endpoint	Patient population
Dopamine Studies			
Cotter et al: Refractory congestive heart failure	low-dose dopamine combined with low-dose furosemide, low-dose dopamine with medium-dose furosemide or high-dose furosemide alone	Change in AHA functional class, urinary output, weight loss, changes in renal function.	20 patients with CHF without severe renal failure with EF<40%
Varriale et al: --Vigorous Diuresis	Low-dose dopamine with IV bumetanide vs. IV bumetanide alone	Blood measurements of BUN, creatinine, creatinine clearance and electrolytes during treatment along with 24 hour urinary volume for each day at treatment + baseline	20 patients with severe chronic CHF with renal impairment.
DAD-HF 1	Low-dose dopamine + low-dose furosemide vs. high-dose furosemide	Worsening renal function	60 class 4 CHF patients with ECHO confirmed systolic or diastolic dysfunction
DAD-HF 2	Low-dose dopamine + low-dose furosemide vs. high-dose furosemide vs. low-dose furosemide alone	1-year mortality or rehospitalization all cause	161 class 4 HF patients with ECHO confirmed systolic or diastolic dysfunction, on ACE inhibitor
Nesiritide Studies			
ASCEND HF	Standard dose nesiritide vs. placebo in conjunction with standard diuretic therapy	Change in dyspnea at 6 + 24 hours, rate of hospitalization and death up to 30 days	7141 HF patients hospitalized within elevated BNP, PCWP or LVEF <40% in past 12 months
Mayo Clinic Study	Standard dose nesiritide vs. placebo in addition to usual CHF care	Renal function as measured by creatinine, cystatin C, BUN and diuretic responsiveness as measured by cumulative weight and fluid loss	72 HF patients with class III/IV HF with renal impairment
BNP-CARDS Study	Standard dose nesiritide (with or without bolus) vs. placebo in addition to usual CHF care	Rise in serum creatinine $\geq 20\%$, change in serum creatinine. Secondary endpoints included changes in weight and 30-day death + hospital readmission rates	75 ADHF patients with renal impairment
VMAC	Intravenous nesiritide vs intravenous nitroglycerin vs placebo	Change from 0 to 3 hours in PCWP and changes in subjective complaints of dyspnea 3 hours after drug initiation.	489 patients with cardiac dyspnea, elevated cardiac filling pressures, elevated PCWP>+ 20 mm hg, requiring hospitalization