The Use of Vasoactive Therapy for Acute Decompensated Heart Failure: Hemodynamic and Renal Considerations

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Although diuretics remain the most commonly used intravenous medication for acute decompensated heart failure, vasoactive agents play an important role in select patient populations. Inotropes and pressor agents are critical in order to maintain blood pressure and cardiac output in a small subset of patients, and can preserve and even improve renal function. However, they should not be used in the majority of patients with preserved cardiac output. Vasodilators improve hemodynamics and symptoms in normotensive individuals. Their influence on renal function is less clear cut, although more recent data suggest a neutral effect.

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Despite steady progress in evidence-based outpatient management of left ventricular (LV) systolic dysfunction, the inpatient therapy for the million or more individuals in the United States admitted for acute decompensated heart failure (ADHF) remains much more of an art than a science. Diuretics continue to be the mainstay of therapy, yet many studies show a clear association between diuretic dose and mortality.[1] Such simple questions as the appropriate dose, route, type, and duration of therapy must rely on expert opinion rather than on large randomized trials.[2] Perhaps this is not surprising, as the

patient population admitted with ADHF is far different than those entered into trials for LV systolic dysfunction; they are older, more likely to be female, have significant renal dysfunction, and almost 50% do not have systolic dysfunction at all.[3,4] Moreover, mortality in the subsequent 90 days is very high.[5] Because of the complexity of ADHF and the high mortality associated with the syndrome, inpatient randomized trials have been disappointingly negative.[6-8]

Given this rather stark background, the appropriate use of vasoactive therapy for ADHF remains problematic. Unfortunately, despite the lack of data, vasoactive drugs remain critically important for managing selected patients with ADHF. This is especially true for those admitted with significant renal dysfunction and hemodynamic abnormalities. Such patients have much higher mortality and injudicious use or failure to use vasoactive agents can have dire consequences.[9,10] Questions exist as to when vasoactive agents should be used in ADHF and how the clinician decides between an inotrope and a vasodilator. This article is a brief review of vasoactive agents currently available for therapy of ADHF in the United States and provides recommendations for appropriate use in various patient populations.

Pharmacologic Therapy for Acute Decompensated Heart Failure

Sympathomimetic amines remain an important weapon in the clinical armamentarium for managing ADHF, yet they are literally a double-edged sword: their benefits come at a considerable cost.[11] Thus, their appropriate use is still evolving. Dopamine was developed in the early 1970s as a complex agent with dopaminergic, β_1, and α agonist effects.[12] At doses less than 5 μg/kg/min dopaminergic and β agonist effects predominate with significant increase in cardiac output.[13] At higher doses, arterial or vasoconstriction increases afterload, which causes deterioration in myocardial performance and may induce ventricular arrhythmias.[14] However, dopamine is the initial pressor of choice in patients with severe hypotension, followed by an infusion of norepinephrine if dopamine fails to reverse hypotension.

Small studies have demonstrated an increase in renal blood flow in patients with LV dysfunction treated with dopamine, but the clinical importance of low-dose dopamine to maintain or improve renal function has lately been questioned.[15,16]

Dobutamine, developed in 1975 by modifying isoproterenol, provided a significant clinical advantage over dopamine. Cardiac output increases by 50% to 80% without the increase in afterload seen with dopamine.[17] LV filling pressures also fall with the use of dobutamine but do not fall significantly with the use of dopamine.[18] However, individual patient response may vary; dobutamine may reverse marked hypotension in some patients, but high-dose dopamine is usually more successful. Dobutamine has a very short half-life (10 min); as a result, adverse reactions such as ventricular or atrial arrhythmias can be addressed quickly by reducing the dose of the infusion.[19] In severe low-output heart failure dobutamine has been shown to improve renal function by significantly decreasing blood urea nitrogen (BUN) and creatinine.[20]

The phosphodiesterase inhibitors, by increasing intracellular cyclic AMP, provide further refinements for modifying hemodynamics in severe heart failure. Often called *inodilators*, they provide improved contractility with peripheral and central vasodilation.[21] Filling pressures decline more significantly with the administration of milrinone than with dobutamine, but arterial blood pressure tends to decline as well.[22] This is especially true when a bolus of milrinone is given prior to infusion, although many clinicians now omit the bolus to mitigate this decline in systolic blood pressure. Myocardial oxygen consumption increases with use of dobutamine and especially with high-dose dopamine but is not increased with milrinone administration.[23] Milrinone has supplanted an earlier phosphodiesterase inhibitor, amrinone, because it causes fewer adverse side effects. Thus far, few data exist regarding the effects of phosphodiesterase inhibitors on renal function, but their improvement of cardiac output, which could improve renal blood flow, must be carefully balanced against their potential to lower blood pressure and hence renal perfusion.

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Despite their rapid and alluring effects on hemodynamics, long-term outcomes of inotropic vasoactive agents suggest an increased mortality with their use.[8,24] This is perhaps not surprising because β antagonists are perhaps the most important tool we possess in heart failure management. In the Prospective Randomized Oral Milrinone Study Evaluation (PROMISE), oral milrinone

increased mortality and vesnarinone, another oral inotrope, met with a similar fate.[25,26] The trial most germane to ADHF, the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) trial,[8] found that randomization with milrinone for the typical patient admitted with heart failure did not shorten length of stay and increased the frequency of atrial fibrillation and hypotension. Abraham and colleagues evaluated inotropes versus vasodilator therapy (nesiritide and nitroglycerin) in patients in the Acute Decompensated Heart Failure National Registry (ADHERE) database using classification and regression tree (CART) analysis and propensity matching to minimize confounding variables.[27] In this analysis inotrope use significantly increased mortality compared with vasodilators. Despite their significant problems, for appropriate patients the inotropes can be lifesaving. The key is to use them in selected patients who require their hemodynamic benefits while avoiding their use in those that do not.

Nitrates

Nitroglycerin undergoes metabolic biotransformation leading to the formation of nitric oxide (NO) or S-nitrosothiol, which increases cyclic GMP and results in arteriolar vasodilatation.[28] Therapeutic effects include substantial reduction in right ventricular and LV filling pressures, systemic and pulmonary vascular resistance, and systemic blood pressure.[29,30] There is no change in heart rate but cardiac output does increase. Putative mechanisms responsible for this increase in cardiac output included afterload reduction, improvement in myocardial ischemia, or reduction in mitral regurgitation.[31,32] Neurohormonal effects evaluated in small studies for ADHF showed reduction in plasma atrial natriuretic peptide levels. In addition, nitrates produced an increase in plasma aldosterone, renin, epinephrine, norepinephrine, and cortisol levels.[33,34] Loh and colleagues compared nitroglycerin with milrinone with a positive response defined as an increase of 20% or more in the cardiac index and a decrease of 25% or more in pulmonary capillary wedge pressure. A significantly greater proportion of milrinone-treated patients reached and maintained these hemodynamic goals compared with nitroglycerin-treated patients and also fewer side effects were observed.[35] Nitrates have little effect on renal function.[20]

In the large Vasodilatation in the Management of acute CHF (VMAC) trial,[36] nitroglycerin or nesiritide was infused in a blinded fashion. The pulmonary artery wedge pressure decreased more with nesiritide than nitroglycerin and there was a greater reduction in symptoms at 3 hours with nesiritide when compared with placebo. In contrast, the onset of the nitroglycerin-mediated hemodynamic effect was delayed, and despite aggressive up-titration, the decrease in pulmonary capillary wedge pressure was gradually attenuated because of early development of tolerance.[37]

The precise mechanism by which tolerance develops is not known; however, several theories have been proposed, including 1) plasma volume expansion, 2) neurohormonal activation, 3) free radical generation, and 4) abnormalities in NO signal transduction.[38-40] Prevention strategies have included sulfhydryl group repletion, intermittent dosing, antioxidants, and concomitant administration of hydralazine.[41-45]

Nesiritide

Nesiritide is the genetically engineered replica drug of B-type natriuretic peptide (BNP), a 32-amino acid product of pro-BNP peptide secreted by human ventricular myocardium.[46] When infused as a drug it is a potent vasodilator that reduces right atrial, pulmonary artery, and pulmonary artery wedge pressure.[47] Systemic vascular resistance and systemic blood pressure may decline as well.[48] It does not possess significant inotropic effects.

The renal effects of nesiritide infusions have been studied as well. In normal subjects, BNP infusions produce a natriuresis with increased urine output and improvement in glomerular filtration rate (GFR).[49] Natriuresis and increase in urine volume has been demonstrated in some studies in heart failure as well, but in others no increase has been found.[50-53] No study of intravenous nesiritide has shown an improvement in GFR in patients with heart failure, although direct infusion on the drug into the renal artery does increase GFR and renal blood flow.[54] It is possible that when nesiritide is infused intravenously, the demonstrated dilation of the renal artery and renal blood flow is counterbalanced by a proportional decline in systemic blood pressure, resulting in no significant change in GFR.[55,56]

A meta-analysis for nesiritide trials by Sackner-Bernstein and colleagues[57] reported a 0.5 mg/dL rise in serum creatinine within 30 days in 21% of patients receiving nesiritide infusions versus 14% of placebo-treated patients. There is no significant difference between groups for the endpoint of severe renal dysfunction requiring dialysis. Although worsening renal function is a poor prognostic indicator there are several drawbacks to this study: 1) this is a meta-analysis rather than a large randomized trial; and 2) significant differences between the groups, with more patients in the nesiritide group who had significant hypotension,

prior inotrope use, and low systolic blood pressure. In a review of the VMAC trial, there is a dose-related increase in renal dysfunction with nesiritide. At the 0.01 μg/kg/min dose there was no significant increase in renal dysfunction compared with the 0.02 and 0.03 μg/kg/min doses.[58] On this basis the 0.01 μg/kg/min dose is the only currently recommended dose. Of note, a small trial by Chen and colleagues using one-half to one-quarter the standard dose of nesiritide found an improvement in BUN and creatinine when compared with the standard dose of nesiritide.[59]

Two recently published large trials have provided further information about the effects and safety of nesiritide in patients with LV dysfunction. In the Nesiritide Administered Peri-Anesthesia (NAPA) trial[60] nesiritide was given as a defined 24-hour infusion versus placebo to high-risk patients with LV dysfunction who were undergoing bypass and/or mitral valve repair. In this trial the infusion was not preceded by a bolus. Creatinine increased slightly in both groups but significantly less so with nesiritide; Length of stay was reduced as well with nesiritide. The second trial, Follow-Up Serial Infusions of Nesiritide for the Management of Patients With Heart Failure (FUSION II),[61] enrolled 900 patients randomized to biweekly infusions of nesiritide versus placebo (2 μg/kg bolus followed by continuous infusions of 0.01 μg/kg/min). There was a small but statistically significant decrease in the endpoint of worsening renal function during this trial. These last 2 trials were not specifically targeted at patients with ADHF but at high-risk groups with LV dysfunction with clinically stable heart failure.

The safety of nesiritide in terms of 30-day mortality has been questioned as well. A meta-analysis of 3 nesiritide trials demonstrated a risk ratio for mortality of 1.74 ($P = .059$). With a Kaplan-Meier survival analysis the harms ratio was 1.86 ($P = .04$); no difference in mortality was seen at 6 months, however.[62] Abraham and colleagues have evaluated all 7 nesiritide trials and risk-adjusted the patients to improve comparability between the nesiritide- and placebo-treated groups.[63] The adjusted harms ratio was 1.12 at 30 days in favor of placebo without a significant P value ($P = .63$). Again, no difference was seen at 6 months. The NAPA trial found a survival advantage of 6 months with nesiritide and FUSION II found no difference with nesiritide infusions versus placebo.[60,61] The effect of nesiritide on survival will be a primary endpoint for the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial, which is planned to be the largest trial (N = 7000) in ADHF.

Selection of Appropriate Therapy for Patients With ADHF

Unlike therapy for chronic stable LV systolic dysfunction, management of the patient with ADHF must be much more individualized. Those presenting with hypotension and shock cannot receive the same drugs as those who are hypertensive and markedly dyspneic. In an ideal world, measurement of hemodynamics and cardiac output would allow immediate tailoring of therapy but this is currently not practical. In the future, however, wider use of echocardiography in the may provide rapid noninvasive hemodynamic characterization.[64]

While the diagnosis of ADHF is being made the cause of decompensation should be sought. Dietary or medical noncompliance may be addressed in the emergency department, whereas more serious complications such as acute coronary syndromes, pneumonia, and acute valvular problems will require hospital admission, as will more severely ill patients.

As to therapy the most important determinates of prognosis are the severity of symptoms, the systemic blood pressure, renal function, and minimal symptoms.[9] Severe dyspnea that requires intubation is associated with a 12% to 15% mortality rate.[65] Data from the ADHERE database show that as renal function worsens and systolic blood pressure declines hospital mortality increases from approximately 2% to almost 20%.[9] Even relatively small increases in serum creatinine during hospitalization also lead to a poor outcome.[66] Therefore, absent data from large randomized trials, therapy to improve hypotension, improve or at least maintain renal function and alleviate severe symptoms in order to avoid intubation should be of benefit to the patient. On the other hand, potentially expensive or detrimental vasoactive therapy in the absence of data should be avoided in patients who have normal blood pressure and renal function.

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The Hypotensive Patient With Renal Dysfunction

Patients presenting with ADHF and volume overload in addition to new-onset hypotension represent a true medical emergency. Evidence of end-organ hypoperfusion (worsening

renal insufficiency, elevated hepatic enzymes, lactic acidosis, or mental confusion) underscores this precarious and unstable situation. Inotropes, usually dobutamine and/or dopamine, should be used first and may be quite effective in restoring cardiac index and renal perfusion pressure. Epinephrine or phenylephrine may be needed in rare cases. If these fail, mechanical support with an intraaortic balloon pump or an LV assist device should be considered early in those who may be transplant candidates.[67,68] Cardiology consultation is usually indicated and should be obtained expeditiously to assist with management, as prolonged hypotension may lead to irreversible renal damage.

Poor renal perfusion secondary to low cardiac output should be suspected in a patient with sudden deterioration of renal function.

The Patient With Renal Insufficiency and Without Systemic Hypotension

ADHF presenting with renal insufficiency even with normal systolic blood pressure significantly complicates management. Unfortunately, renal insufficiency is common; 64% of those in the ADHERE database had an estimated GFR consistent with moderate or severe renal insufficiency.[10] In addition, as the degree of renal insufficiency worsened, mortality and length of stay increased.[10] In the normotensive patient renal insufficiency results from inadequate renal perfusion secondary to poor cardiac output or more commonly secondary to intrinsic renal disease.[69] The kidney is able to maintain GFR with a cardiac index of 1.5 L/min/m^2 or greater; however, once cardiac index falls below this level, GFR falls.[70] In animal models, very high venous pressures may impair renal function as well.[71] Unfortunately, clinicians are very poor at estimating adequacy of cardiac output; therefore, the cause of renal insufficiency may be in doubt in a particular patient. Moreover, even when cardiac index is severely reduced, it may be secondary to either reduced contractility or markedly increased afterload. Poor renal perfusion secondary to low cardiac output should be suspected in a patient with sudden deterioration of renal function. An inodilator such as milrinone is preferred if the systolic blood pressure is greater than 80 to 90 mm Hg, especially for those on β-blockers, which may blunt the effects of dobutamine.[72] If intense vasoconstriction is suspected (cold extremities) a vasodilator (nesiritide or nitroprusside) with or without an inotrope should be considered.[69]

Renal insufficiency secondary to intrinsic renal disease is much more common than poor renal perfusion due to low output. Clues to the diagnosis are history of longstanding renal insufficiency, especially in conjunction with diabetes and hypertension. Proteinuria is another marker for intrinsic renal disease.[73] Because the cardiac output is usually preserved with an adequate blood pressure in these patients, inotropes have little role in this common scenario. Diuretic resistance is frequently seen in these patients. Nesiritide and/or nitrates may provide faster symptom relief because diuresis may be slow or incomplete.[36] Efforts to improve diuresis in this setting may include continuous diuretic infusions, adding a second diuretic such as metolazone or hydrochlorothiazide.[69] Ultrafiltration is another mechanical means of fluid removal.[74]

In patients who begin with significant renal insufficiency, great care must be made to avoid worsening an already tenuous situation. At least twice daily monitoring of BUN, creatinine, and potassium, as well as careful observation of urine output, is necessary. This is especially important in those with new-onset renal insufficiency. Lack of diuresis or worsening of renal function should trigger a careful re-evaluation of therapy in consideration for invasive monitoring. Vasoactive therapy may need to be modified based on hemodynamic profiling of the patient or even mechanical support may be necessary.[68]

The Patient With Relatively Normal Renal Function and Normal to High Systolic Blood Pressure

Most patients admitted with ADHF have adequate systolic blood pressure without marked renal dysfunction. This statement needs great qualification because the average creatinine level at admission for the ADHERE population was 1.9; 64% had at least moderate renal dysfunction or worse when GFR was calculated.[10] The average systolic blood pressure in ADHERE patients was 144 mm Hg and only 3% were hypotensive.[3] Dyspnea was a very common presenting symptom and most had evidence of fluid overload. Therefore, diuretics would be appropriate first-line therapy to improve filling pressures and reduce symptoms. Indeed, the degree of dyspnea may help guide therapeutic options; with mild dyspnea diuretics are certainly adequate by themselves. However, with severe dyspnea (especially with impending respiratory failure) the addition of vasoactive therapy may more rapidly improve symptoms and

perhaps avoid intubation. Pulmonary artery wedge pressure falls significantly within 15 minutes following the addition of nesiritide and dyspnea improves to a greater extent at 3 hours compared with standard therapy alone.[36] Nitroglycerin also can improve filling pressures but tolerance may rapidly develop unless doses are up-titrated. For marked hypertension, nitroprusside or nesiritide will lower systolic blood pressure. Other options for patients with severe dyspnea include bilevel positive airway pressure and ultrafiltration.[75]

Conclusions

Despite (or perhaps because of) the many pharmacologic, and now mechanical, modalities available to the clinician for the management of ADHF, this field remains more art than science. For many patients diuretics combined with angiotensin converting enzyme inhibitors and β-blockers are perfectly adequate. However, there are clearly subsets of patients for whom vasoactive therapy can certainly improve symptoms and may prolong life. There is no argument that the severely hypotensive patient requires a pressor, but more subtle hemodynamic derangements, especially coupled with renal insufficiency, may require inotropes or vasodilators to reverse significant cardiac and vascular dysfunction. Because invasive hemodynamic monitoring is impractical and unnecessary for many of these patients, the clinician often selects therapy on an empiric basis. The key here is to reevaluate the patient frequently to determine if the therapy is working or not. When the patient fails to improve or further deteriorates, this requires careful and rapid reconsideration of the therapeutic options to try to reverse this unstable situation. To paraphrase the opening line from Tolstoy's *Anna Karenina*, "All healthy hearts are all alike, all unhealthy hearts are unhealthy in their own way." ■

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Main Points

- At doses less than 5 μg/kg/min the dopaminergic and β agonist effects of dopamine predominate with significant increase in cardiac output; at higher doses, arterial or vasoconstriction increases afterload, which causes deterioration in myocardial performance and may induce ventricular arrhythmias.
- Therapeutic effects of nitroglycerin include substantial reduction in right and left ventricular filling pressures, systemic and pulmonary vascular resistance, and systemic blood pressure.
- When infused as a drug, nesiritide is a potent vasodilator that reduces right atrial, pulmonary artery, and pulmonary artery wedge pressure. Systemic vascular resistance and systemic blood pressure may decline as well; it does not possess significant inotropic effects.
- Renal insufficiency secondary to intrinsic renal disease is much more common than poor renal perfusion due to low output. Diuretic resistance is frequently seen in these patients; nesiritide and/or nitrates may provide faster symptom relief because diuresis may be slow or incomplete.

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