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Lack of Evidence for Intravenous Vasodilators in Emergency Department Patients with Acute Heart Failure: A Systematic Review

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Abstract

There are nearly 700,000 annual US emergency department (ED) visits for acute heart failure (AHF). While blood pressure is elevated on most of these visits, acute therapy remains focused on preload and not afterload reduction. Data from recent prospective studies suggest AHF patients with concomitant acute hypertension benefit from intravenous (IV) vasodilators. To better understand the use of vasodilators for such patients, we conducted a systematic review of 1) currently available intravenous vasodilators for ED patients with AHF, or 2) intravenous vasodilators which are not yet available, but have completed Phase III clinical trials in AHF, and may be available for ED use in the future. We employed multi-term search queries to retrieve research involving nitroglycerin, nitroprusside, enalaprilat, hydralazine, relaxin and nesiritide. A total of 2001 unique citations were identified from three databases: PubMed, EMBASE, and CINAHL. Of these, 1966 were excluded based on established review criteria, leaving 35 published papers for inclusion. Our primary finding was that IV nitrovasodilators, when used in the treatment of AHF in ED and ED-like settings, do improve short-term symptoms and appear safe to administer. There is no data suggesting they impact mortality. Other commonly used vasodilators such as hydralazine and enalaprilat have very little published data about their safety and efficacy. Of note, few studies enrolled patients early in their course of treatment. Thus, to assess the specific

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Conflicts of Interest

PA, JC, LA: No conflict of Interest

impact of vasodilator therapy on both short- and long-term outcomes, future research efforts should focus on patient recruitment in the ED setting.

Keywords

emergency department; heart failure; treatment

Introduction

Intravenous diuretics are the traditional cornerstone of acute heart failure (AHF) therapy. Typically, patients with AHF receive little other pharmacologic therapy during the initial phase of management.[1] Until recently, evidence regarding their efficacy and safety has been limited.[2, 3] However, data from contemporary prospective studies suggests specific phenotypes of AHF patients, such as those with acute hypertension or renal dysfunction benefit from intravenous (IV) vasodilators.[4-6] Although vasodilators have a Class IIb, level of evidence A indication from recent guidelines, most of the relevant information for this recommendation came from trials involving nesiritide, with data on nitrates limited to a few small studies.[7] While not a strong recommendation, physiologically, vasodilators may play a critical role in specific AHF patient sub-groups, suggesting a therapeutic approach beyond diuretics in isolation may be necessary.

Emergency departments (EDs) see over 800,000 visits for AHF annually, accounting for more than 80% of related hospital admissions.[8, 9] A thorough understanding of the safety and efficacy of existing vasodilators is essential, particularly for emergency physicians, who will initially manage the vast majority of patients with AHF. This will help inform both current and future use based on the available safety and efficacy data. To facilitate this we performed a systematic review with a goal of describing the efficacy and safety of: 1) currently available intravenous vasodilators for ED patients with AHF, or 2) intravenous vasodilators which are not yet available, but have completed Phase III clinical trials in AHF, and may be available for ED use in the future.

Methods

Study Design

Included papers met the following criteria: 1) patients had to be actively treated and enrolled within 24 hours of ED presentation, either in the ED or other similar acute care setting; 2) the treatment had to involve at least one of eight vasodilators of interest: Nitroglycerin (NTG), nitroprusside, enalaprilat, hydralazine, nesiritide, isosorbide dinitrate, clevidipine and relaxin; 3) the study had to address at least one of two categories of endpoints: efficacy (blood pressure or symptom improvement) or safety (hypotension, death, renal dysfunction or hospital readmission). Papers were excluded if they met any of the following criteria: 1) non-English articles; 2) animal or experimental studies; 3) not original research; 4) study size less than ten; 5) vasodilator not currently used in clinical practice; or 6) did not answer the clinical question of interest.

Data Collection and Processing

Databases—A professional librarian (PA) and study author (SC) developed a systematic search strategy that was applied to each of the electronic databases. We employed multi-term search queries to retrieve research exploring use of IV vasodilator therapy for treatment of AHF in the ED, specifically for: NTG, nitroprusside, enalaprilat, hydralazine, nesiritide, isosorbide dinitrate, clevidipine and relaxin. The search included examination of results from three databases: PubMed, EMBASE, and CINAHL.

Search Strategy—Controlled vocabulary terms served as the foundation for our search strategy in each resource, complimented by combinations of relevant keyword terms and phrases. Specific concepts used for the vasodilator agents included the subject terms Isosorbide Dinitrate, Relaxin, NTG, Nitroprusside, Enalaprilat, Hydralazine, Natriuretic Peptide, Brain, and vasodilator agents and keywords such as NTG, nitroprusside, enalaprilat, hydralazine, nesiritide, relaxin, clevidipine or vasodilator agents. Search terms employed for AHF included subject terms such as Heart Failure and keywords such as, acute heart failure, acute heart failure syndromes, acute systolic heart failure, decompensated heart failure, and acute HF (Appendix 1). MeSH terms in PubMed automatically included isosorbide mononitrate as part of the literature search. This medication has vasodilator properties and was included in this review.

To locate any unpublished manuscripts, we ran supplemental searches in key grey literature resources for the last two years including clinicaltrials.gov and conference proceedings from relevant organizations: the American College of Emergency Physicians (ACEP), the American College of Cardiology (ACC), the American Heart Association (AHA), the Heart Failure Society of America (HFSA), the Society for Academic Emergency Medicine (SAEM), and the European Society of Cardiology (ESC).

Reviewers SC and PA reviewed all abstracts independently. A data collection form was used to extract data from each study that appeared to satisfy the inclusion and exclusion criteria. The 2 reviewers then compared their inclusion and exclusion criteria for reviewed abstracts. Disagreements not resolved by consensus were adjudicated by a third reviewer, AS. We structured our review using relevant criteria from the PRISMA 2009 checklist to ensure a comprehensive and transparent reporting of results.[10] A modified version of the Cochrane Collaboration's Risk of Bias template was used to identify strength and weaknesses within studies selected for inclusion in the review.[11]

Assessment of Study Quality—We used a previously described five-level modified instrument that has been applied to clinical trials, descriptive studies and surveys.[12, 13] Quality level 1 consisted of prospective studies that studied a clearly defined outcome measure with a random or consecutive sample large enough to have narrow confidence intervals as well as heterogeneous enough to have good generalizability. Quality level 2 was similar to level 1, but was more limited with respect to sample sizes or generalizability. Quality level 3 included retrospective studies which would have otherwise qualified as level 1 or 2. Quality level 4 were studies that used convenience sampling or other techniques

prone to bias. Quality level 5 included studies lacking a clearly defined or validated outcome measure (Table 1).

Results

A total of 8328 citations were retrieved from PubMed, 499 from EMBASE and 91 citations from CINAHL. After eliminating duplicate records, there were 2271 unique citations retrieved.

A total of 2227 papers were excluded based on pre-specified criteria established for our review (Figure 1). Grey literature searches of clinicaltrials.gov and conference proceedings revealed one relevant manuscript missed in the prior search strategies; thus leaving 36 published papers for inclusion. Study designs were varied and are highlighted in Table 1.

Our results are summarized in two tables. Table 1 is an article summary table, which provides a synopsis of the study type, number of patients enrolled, study quality, interventions and outcomes. Table 2 summarizes the trends in risk of bias associated with the studies reviewed. This table suggests the majority of reviewed studies addressed incomplete data and were free of selective outcome reporting, but performed poorly in categories such as blinding, allocation concealment and freedom from other remaining sources of bias.

Nitrovasodilators

Widely used for patients with acute hypertensive HF, NTG and isosorbide dinitrate (ISDN) are potent vasodilators that work via nitric oxide (NO) mediated pathways. Despite broad uptake into regular clinical practice, both NTG and ISDN have been subject to surprisingly little prospective study. Moreover, of the existing trials, only a few have involved direct, head-to-head comparison with other vasodilators or similar agents, limiting consideration of relative superiority.

Nitroglycerin—A total of six studies met criteria for inclusion in our review, three of which were prospective (Table 1). The first of these compared morphine plus furosemide vs. NTG plus N-acetylcysteine (NAC) in patients with acute cardiogenic pulmonary edema.[14] Powered to evaluate changes in gas exchange over the first hour rather than clinical outcomes, this small study (n = 69; 32 in the furosemide/morphine group and 37 NTG/NAC) found only minor differences between treatment groups, with no evidence of advantage for one regimen over the other. While this study suggests equivalence, results are unlikely to represent a clinically relevant comparison as the median dose of NTG was quite low (2.5 mcg/min vs. 3 mg of morphine and 80 mg of furosemide).

The second prospective study was a non-randomized, open label evaluation comparing 29 patients with severe hypertensive AHF (mean [standard deviation (SD)] arterial pressure = 157.2 [25.7] mm Hg) who received bolus, high-dose NTG (2 mg every 3-5 min as needed for 30 min) to 45 historical controls with hypertensive AHF (mean [SD] mean arterial pressure = 151.8 [24.5] mm Hg) treated by NTG infusion alone (mean [confidence interval(CI)] initial rate = 31.7 [26.0-37.3] mcg/min) [4]. Dose range for the 29 patients who

received both infusion and bolus was mean [CI] initial rate = 23.6 [15.4 – 31.9] mcg/min for infusion and mean [SD] cumulative dose = 6.5 [3.5] mg over 30 min for bolus. Compare to historical controls, the AHF patients treated with both infusion and bolus required endotracheal intubation (13.8% vs. 26.7%), noninvasive ventilation (6.9% vs. 20.0%), and intensive care unit admission (37.9% vs. 80.0%) less often. Moreover, mean total hospital length of stay was 2 days shorter (4.1 vs. 6.2 days) and biomarker evidence of myocardial infarction was less common (17.2% vs. 28.9%) in those treated by bolus high-dose NTG. Importantly, hypotension occurred in only one high-dose NTG patient and relatively few in either group developed worsening renal function (13.8% vs. 15.6%). Hemodynamic data were also provided for those who received high-dose NTG, showing substantial improvements in mean arterial pressure, heart rate, respiratory rate and oxygen saturation by 1 hour.

The third study was a retrospective comparison of patients (n=430) treated for AHF in the ED of a single institution over one year, 46 of whom (10.7%) received IV NTG in addition to furosemide therapy.[15] While no data on blood pressure or symptom change were provided, those treated with both NTG (range: 5-15 mcg/min) and furosemide (mean [SD] dose: 75 [44] mg) had a significantly shorter mean [SD] hospital length of stay than patients who received neither NTG nor furosemide (n=257), or furosemide (mean [SD] dose: 59 [28] mg) alone (n=127) in the ED (6 [4] vs. 8 [8] vs. 9 [12] days, respectively)(Table 1). In addition, the use of NTG and furosemide was associated with a substantially greater reduction in BNP levels during the course of treatment. Administration of NTG and furosemide was also reported to confer a survival advantage over 36 months on Cox proportional hazard regression analysis, but the validity of this is questionable as models were not adjusted for disease severity, propensity for NTG treatment, or furosemide dose, and outpatient management during the follow-up period was not accounted for.

The fourth study was the Vasodilation in the Management of Acute CHF (VMAC) trial. [16] This was a phase III study that included 204 patients who received IV nesiritide, 143 who received NTG and 142 who were given placebo in addition to standard care. Patients who received NTG had modest but not statistically significant improvements in pulmonary capillary wedge pressure (PCWP) at three hours (mean [SD] dose: 29 [38] and 42 [61] mcg/min in the patients without [n=60] and without [n=83] a pulmonary artery catheter in place, respectively) compared to those who received placebo but there was no difference in global clinical status or dyspnea over this time period. However, there was a significant improvement in PCWP at three hours in a small (n=9) subset of patients treated at a single enrolling site with more aggressively dosed NTG (mean [SD]: 155 [73] mcg/min).

The fifth study was a secondary analysis from the VMAC study which evaluated changes in left ventricular filling pressure between high-dose nitroglycerin (mean dose of 161 mcg/min at 6 hours) and nesiritide [17]. There was not a significant change in PCWP in the high-dose nitroglycerin group, while the nesiritide group did have a significant change. However, whether patients continued to have nitroglycerin aggressively titrated is unclear.

Isosorbide dinitrate—Similar to NTG, only two studies of ISDN met criteria for inclusion. The first was a prospective, randomized trial (Table 1), and provides perhaps the

best supporting evidence for use of nitrate therapy in AHF.[6] A total of 104 patients (52 in each arm) with cardiogenic pulmonary edema were randomized in the ambulance to receive low dose furosemide (40 mg one time) and high-dose ISDN (3 mg by repeat bolus every 5 minutes) or high-dose furosemide (80 mg by repeat every 15 min) and low-dose ISDN (continuous infusion started at 1 mg/h with ability to increase by 1mg/h every 10 min). The study found those who received high-dose ISDN (mean [SD] dose = 11.4 [6.8] mg along with 56 [28] mg furosemide) were less likely to require mechanical ventilation (13.4% vs. 40.3%; difference = -26.9%; 95% CI -42.1% to -10.0%) or have biomarker evidence of myocardial infarction (17.3% vs. 36.5%; difference = -19.2%; 95% CI -35.0% to -2.1%) than patients who were randomized to the high-dose furosemide (mean [SD] dose = 200 [65] mg) arm. Blood pressure change over time was similar between groups with no difference in the proportion who experienced excessive (defined as > 30%) reductions in mean arterial pressure. Improvements in respiratory rate and oxygen saturation were significantly better in those who received high-dose ISDN.

The second study, a retrospective analysis of AHF at a single hospital center, was designed primarily to assess the safety of bolus ISDN when administered to patients 75 years of age or older.[18] While the study was hampered by clear imbalances between patients, those who received bolus dose ISDN (n=25; mean [SD] total dose = 3.8 [1.9] mg) were no more likely than those who were treated without bolus ISDN (n=112; 16% treated with a continuous ISDN infusion) to have an excess decrease in blood pressure or develop hypotension, suggesting the relative safety of modestly dosed ISDN in this population.

Isosorbide mononitrate—Closely related to ISDN but infrequently used, isosorbide mononitrate (ISMN) also improves symptoms in patients with severe cardiogenic pulmonary edema (Table 1). In a single center, open label study of AHF patients, ISMN administered as a bolus with subsequent continuous infusion resulted in a significant reduction in mean [SD] respiratory rate (from 36 [7] to 27 [8] breaths/min; difference = 9; 95% CI 5 to 14) and the degree of hypoxemia (PaO₂ 53.9 [5.7] torr vs. 61.9 [13.4] torr; difference = 8.0; 95% CI 2.0 to 14.0) by 2 hours.[19] Further, despite a high degree of respiratory distress at baseline, only six patients (25%) required mechanical ventilation with most (n=14) of the non-intubated patients exhibiting dyspnea relief within 15 minutes of bolus administration. Blood pressure also steadily declined with a 9.7% reduction in mean [SD] arterial pressure by one hour (from 124 [28] mm Hg to 112 [15] mm Hg; difference = -12; 95% CI -1 to 25) and a maximal response at six hours. Of note, blood pressure effects were most prominent in the subset of patients (n=13) whose baseline systolic blood pressure exceeded 160 mm Hg, and overall there was only one episode of hypotension. While no comparator group was included, all 24 patients received furosemide (mean [SD] dose at 6 hrs = 53.9 [28.6] mg) prior to inclusion and continued to be severely symptomatic, suggesting benefit with ISMN above and beyond diuretic monotherapy.

In summary, these level 2 and 3 studies suggest that nitrates, as a group, are safe in the setting of AHF with efficacy signals that suggest short-term clinical benefit, particularly when administered by at higher doses by bolus, to patients with severe dyspnea and markedly elevated blood pressure.

Nesiritide

Nesiritide is a recombinant human b-type natriuretic peptide (BNP), and its effects on cardiovascular physiology are thought to mimic those of the endogenous hormone. BNP is released primarily from the myocardium in response to increased ventricular wall stress and volume overload. As such, BNP levels are known to rise in AHF. Beyond acting as a diagnostic and prognostic marker, BNP serves a compensatory purpose, mainly via its vasodilatory and natriuretic effects. A total of 20 nesiritide articles met the inclusion criteria for our review: 12 randomized controlled trials, 6 retrospective evaluations, 2 secondary analyses of prospective randomized data (Table 1).

Nesiritide's beneficial hemodynamic effects are well established. Several studies have confirmed its ability to significantly reduce (PCWP) [17, 20-23]. The use of nesiritide in patients with AHF is also associated with reductions in endogenously produced BNP, a laboratory value used clinically as a surrogate for cardiovascular congestion [24, 25]. Several small studies have shown a benefit of adding nesiritide to standard therapy on patient-reported relief of dyspnea [20, 26], but additional studies provided little support for nesiritide in reducing the frequency of rehospitalization [27-34] or mortality [26-28] in patients with AHF (Table 1). The previously mentioned VMAC study included 204 patients who received IV nesiritide [16] and demonstrated a statistically significant improvement in dyspnea at three hours post infusion in patients treated with nesiritide over those treated with NTG or placebo – leading to FDA approval of nesiritide for use in the United States. However, subsequent meta-analyses raised safety concerns [35, 36], which led to a pivotal mortality study, the Acute Study of Clinical Effectiveness of Nesiritide in Heart Failure (ASCEND-HF) [28]. ASCEND-HF included patients randomly assigned treatment with nesiritide (n=3496) or placebo (n=3511) in addition to standard therapy. No statistically significant differences at the pre-specified alpha levels were achieved for the primary study endpoints, including rehospitalization, self-reported dyspnea at both six and 24 hours post-infusion, or self-reported overall wellbeing, though statistically significant improvements in dyspnea were observed. Although initial studies did not demonstrate any increased risk of hypotension [29, 30, 37, 38], ASCEND-HF revealed a significantly increased risk of both symptomatic and asymptomatic hypotension among patients randomized to nesiritide.[28] There were no differences in mortality or renal dysfunction in ASCEND. More recent studies found no significant difference among low-dose dopamine, low-dose nesiritide and placebo in improving clinical outcomes in AHF patients with renal dysfunction. [39-41]

Several studies discussed use of nesiritide specifically in an ED or ED Observation Unit (EDOU) population.[27, 30, 31] Miller et. al. conducted a double-blind randomized controlled trial of nesiritide plus standard therapy (n=53) versus standard therapy (n=48) and evaluated the relative effects on ED readmission in AHF patients. The study found an absolute acute symptom relief of 8.9% between the 2 groups (95% CI –3.3% to 24.2%). Hypotension occurred more frequently in the nesiritide-treated group but ED return visit or hospitalization at 30 days was non-significantly higher for nesiritide (41.5%) than placebo (39.6%; absolute difference 1.9%; 95% CI –17.2% to 21.1%). Peacock et al. conducted a multicenter randomized controlled trial evaluating safety and efficacy of nesiritide when added to standard care for AHF patients admitted to an EDOU. The study found a non-

significant difference in subsequent hospital admission rate among patients who received nesiritide (55.3% for standard of care vs. 48.8% for nesiritide; difference = -6.5%; 95% CI -18.5% to 0.6%). Secondary outcome measures for patients receiving nesiritide versus standard care included fewer inpatient hospitalizations within 30 days (22.7% standard care, 10.2% nesiritide; difference = -12.5%; 95% CI -21.7% to 3.3%) and shorter duration of hospitalization (median LOS 2.5 days for nesiritide vs. 6.5 days for standard of care). Styron et al. reported results of a retrospective evaluation of a single center's experience with the effect of nesiritide on readmission and mortality rates in patient with AHF and failed to detect a significant difference between any endpoint based on results of logistic regression analysis. It is important to note that there was no accompanying increase in mortality

In summary, nesiritide does not appear to worsen mortality or renal function; however, its use is associated with an increased incidence of hypotension. It should not be routinely used in AHF management, and if used, careful monitoring for hypotension is suggested.

ACE Inhibitor – Enalaprilat

While the use of ACE inhibitors has received widespread acceptance for treatment of hypertension and chronic HF, the utility of intravenous formulations for AHF has received little study. This is due, in part, to concerns regarding hypotension, renal injury, and deleterious effects on electrolytes. ACE inhibition for chronic heart failure, however, does have positive effects on both preload and afterload without an unfavorable impact on myocardial oxygenation.[42]

Given these observations, a small randomized, double-blind, placebo-controlled trial tested the efficacy and safety of IV enalaprilat in 20 patients with acute pulmonary edema unrelated to AMI.[43] Compared with placebo, enalaprilat led to greater reduction in PCWP (37% versus 10%) as well as improved renal blood flow. Trends were noted for decreased myocardial workload. No patients had excessive hypotension or adverse effects. The authors concluded that intravenous enalaprilat is effective and well tolerated in select patients with acute pulmonary edema. Unfortunately, the study size and drug administration between 6 and 18 hours after the acute episode make it difficult to translate these results to ED patients with AHF.

An ED study evaluating the efficacy and tolerability of intravenous enalaprilat in differing doses (0.625, 1.25, 2.5, and 5mg) for hypertensive crises included 14 AHF patients among 65 enrollees.[44] In this small AHF cohort, 64% (n=9) responded favorably according to pre-set criteria, no significant difference was noted for dose level, and no severe side effects were noted. While the authors concluded enalaprilat is safe and moderately effective for hypertensive crises in general, the small size of the AHF cohort and lack of physiologic description also prove difficult to use these results to inform current ED practice.

While both studies receive an evidence grade of two, they are relatively small and were not specifically conducted in the ED. Their findings suggest enalaprilat is safe, well tolerated, and may be efficacious in AHF patients, but a larger cohort is necessary before definitive conclusions can be drawn about its efficacy in ED patients with AHF.

Hydralazine

Hydralazine for treatment of AHF has been poorly studied. A small randomized trial was performed to compare the differential hemodynamic effects of ISDN (50-200 mcg/kg/h infusion) with hydralazine (0.15 mg/kg IV bolus) in patients with acute myocardial infarction (AMI) complicated by left ventricular failure.[45] In a post-hoc analysis of a randomized, controlled trial that received a level 3 evidence grade 18 subjects randomly received each medication separately in two consecutive 90-minute periods (n=12), or in combination in a single 90-minute period (n=6). Over the three hours of treatment and compared to one hour prior to infusion, both reduced systemic arterial pressure and vascular resistance, only isosorbide dinitrate reduced LV filling pressure, and only hydralazine increased cardiac output and stroke volume. In combination, reduced LV filling pressures, systolic and diastolic arterial pressures, and total systemic vascular resistance (SVR), as well as increased cardiac output and stroke volume were noted. The investigator's concluded the combination appeared to be of greater benefit for this population, than either alone, as long as the fall in blood pressure can be tolerated.

This study's size, timing, evidence grade, and the very select group of post-AMI patients, make it difficult to inform the utility of intravenous hydralazine for ED treatment of AHF. An ongoing study incorporating the use of hydralazine to reduce preload and afterload in hospitalized patients with AHF may provide insight into its safety and efficacy.[46]

Relaxin

While topical and sublingual nitrates have formed the cornerstone for AHF management, current research has turned towards synthetic peptides with favorable hemodynamic profiles. [1] The newest agent in this limited class is relaxin, a recombinant analog of the endogenous human peptide relaxin-2. This vasoactive peptide helps mediate the maternal hemodynamic adjustments to pregnancy, specifically by augmenting cardiac output and renal perfusion while decreasing afterload via improved arterial compliance.[47] A small hemodynamic study suggests relaxin decreases PCWP to a greater degree over the first eight hours of infusion when compared to placebo.[48]

The Pre-RELAX-AHF and RELAX-AHF trials were conducted in a double-blind, placebo-controlled fashion to assess the dosing, safety, and efficacy of relaxin in normotensive to hypertensive patients with mild to moderate renal impairment presenting with clinical and radiographic evidence of AHF. Patients were randomized within 16 hours of presentation, with some US patients enrolled in the ED setting. Protocol-defined safety parameters included down-titration of drug or cessation for significant decreases in systolic blood pressure. The primary endpoint in both studies was improvement in dyspnea as evaluated with serial assessments on two separate validated scales.

In the Pre-RELAX-AHF trial,[49] a Phase IIb study with an evidence grade of 2, the doses evaluated had comparable lowering of systolic blood pressure (roughly 13 mm Hg) in both the placebo and relaxin groups. The total incidence of hypotension overall was infrequent, but stopping criteria likely prevented significant hypotension. A better balance between dyspnea improvement and hypotension resulted in the 30 µg/kg/day dose being chosen to

move forward for the Phase III Relax-AHF trial, which received an evidence grade of 1. A total of 1,161 patients were evaluated in the RELAX-AHF trial.[5] Subjects randomized to relaxin were found to have a significantly greater decrease in dyspnea on a visual analog scale through 5 days. While the dyspnea improvement was statistically significant, whether this difference (less than 10 mm) at various time points was clinically meaningful is unclear. However, no difference was seen by 7-point relative Likert scale, which required patients to be improved at all three time points (6, 12 and 24 hours) when compared to placebo. Clinical signs of congestion were improved more rapidly in the relaxin group and total dose of intravenous loop diuretic was significantly lower. The total length of index hospitalization and coronary care unit stays were significantly decreased in the relaxin group. Compared to prior trials of other vasoactive drugs, patients were enrolled much sooner (16 hours or less, mean ~6.6 hours) and many were enrolled within the ED setting.

Despite the improvement in the above clinical parameters relaxin demonstrated no benefit in the composite endpoint of hospital readmission for heart or renal failure by day 30 or 60. All-cause cardiovascular death and total days survived outside of the hospital from the index admission to day 60 were also not significantly different between the two groups. Although no differences in the composite 60 day outcome were seen, a statistically significant improvement in cardiovascular and all-cause mortality was observed at 180 days.

The overall adverse event profile was small and suggested a high margin of safety, but this may have been impacted by the protocol driven decreases in infusion rates for pre-specified decreases in blood pressure. A pre-specified analysis of cardiac, renal, and hepatic function noted a significant decrease in hs-Troponin T, NT-pro-BNP, serum creatinine, and hepatic transaminase levels, all of which are markers that correlate with mortality.[50] Recently the FDA voted against the approval of relaxin for a worsening HF indication so it remains unavailable for clinical use. Further study is underway to determine if the mortality benefits are replicable.[51]

Clevidipine

Clevidipine is a short-acting intravenous dihydropyridine calcium channel blocker. It was first evaluated in a secondary analysis (level of evidence 3) of 19 patients with AHF from a prospective, single arm, open label study of ED patients with systolic blood pressure over 180 mmHg. [52] Blood pressure control within 30 minutes of drug initiation was the primary endpoint. Of the 19 AHF patients who received clevidipine, the median time to reach prespecified target systolic blood pressure was 11.3 minutes (95% CI, 7-19). There were no treatment-related adverse events. Clevidipine was subsequently studied in a randomized, open label, active comparator study (level of evidence 2) in ED patients with AHF and systolic blood pressure over 160 mmHg. Co-primary endpoints were median time to, and percent of patients attaining, a systolic blood pressure within a pre-specified target blood pressure range (TBPR) at 30 minutes. Dyspnea reduction was the main secondary endpoint. Of 104 patients (mean [SD] age 61 [14.9] years, 51.9% female, 79.8% African American), 51 received clevidipine and 53 standard care intravenous vasodilators. Baseline mean [SD] systolic blood pressure and dyspnea as measured by 100 mm visual analog scale were 186.5 [23.4] mmHg and 64.8 [19.6] mm, respectively. More clevidipine patients

(70.5%) reached TBPR than SOC (36.6%), $p=0.002$ and clevidipine was faster to TBPR, $p=0.0006$. At 45 minutes, clevidipine patients had greater mean [SD] VAS dyspnea improvement than SOC, -37.1 [20.9] vs -27.9 mm [21.7], $p=0.02$, and this difference remained significant up to 3 hours. Overall, 16 patients exceeded their lower TBPR limit; 15 clevidipine and 1 SOC ($p<0.001$) by a mean [SD] of 8.7 [4.7] and 13 mmHg, respectively. No patient had hypotensive symptoms while on study drug. There were five deaths within 30 days of treatment (3 clevidipine, 2 SOC, $p=0.615$), none during study drug administration.

In summary, clevidipine's rapid reduction of blood pressure appears to be associated with dyspnea improvement. However, as the study was open-label, measurement bias in ascertainment of dyspnea scores may have occurred.[53] Furthermore, whether this improvement was sustained beyond 12 hours, or whether more rapid BP improvement translates to improved outcomes beyond the initial management phase was not studied. Regardless, if used clinically, cautious titration is necessary as evidenced by the significantly greater blood pressure overshoot in this cohort compared to standard care. [54]

Discussion

Our systematic review of the literature found few high quality AHF studies performed in the ED. The majority of these investigations were performed in the inpatient setting with patients who had likely already undergone initial stabilization prior to enrollment, making it difficult to generalize their results to patients presenting acutely to an ED. A recent review of vasodilator use in all hospitalized HF patients found similar results.[55] Further, many were retrospective analyses or cohort studies which were not designed a priori to investigate a primary AHF endpoint in ED patients. However, studies which enrolled patients within 24 hours of ED presentation provide evidence of blood pressure and dyspnea improvement, but lack conclusive evidence regarding their impact on long term outcomes such as hospital readmission and mortality rates. Studies which enrolled patients in the ED, or in an ED associated observation unit,[27, 30, 31] showed neutrality or only modest benefits of adding IV vasodilators in comparison to standard care alone. None of the large, multicenter investigations of IV vasodilators, such as ASCEND-HF or RELAX-AHF, specifically mandated ED enrollment, though some were conducted across numerous sites internationally and did enroll ED patients. Interestingly, a statistically significant improvement in symptoms might be easier to achieve in an ED based "therapy naïve" population, and thereby maximally symptomatic upon enrollment, and thus the ED may be an ideal setting for future drug efficacy investigations [56, 57].

Standard care in AHF patients currently consists of intravenous diuretics and intravenous vasodilators in those with elevated blood pressure. Our review suggests current practice is not based on large-scale, high-quality randomized trials, but rather clinical dogma. Data for the nitrates as a class suggest they are safe and efficacious and, when vasodilators are indicated, are currently the most common choice.[1] Nitrates are also the agent most often used as the comparator arm when studying other vasodilators. Despite this, they have not been subject to a randomized trial to determine their efficacy when used with (or without) diuretics, and their impact on mortality is unclear. The use of hydralazine and enalaprilat

for afterload reduction intuitively makes sense, but data about their efficacy and safety is extremely limited. Nesiritide has been studied in a large-scale outcome trial. It has no deleterious effect on renal function or mortality, but was associated with more hypotension than placebo. Further, its relative lack of efficacy relative to standard care and cost relegate it to a second-line therapy. Clevidipine has potent effects on blood pressure and is associated with dyspnea reduction. However, the potential to decrease blood pressure too rapidly suggests close monitoring is necessary. [52, 54] The RELAX AHF trial has promising results, but greater enrollment of ED patients in a large-scale trial is needed before firm conclusions can be made about its role in ED patients with AHF and its impact on mortality. Further, other important ED-centric endpoints need exploration, such as relaxin's impact on LOS and the clinical efficacy of using it over a shorter time frame and in an observation unit.

Other limitations inhibit our ability to make solid conclusions regarding use of IV vasodilators in ED AHF patients. Small sample sizes and single center enrollment for the majority of ED-based studies remain major barriers in determining the most effective and safe treatment for AHF patients. Further, most studies are underpowered, include homogenous patient populations, and may only track patients during their time in the ED, thus making generalizations regarding patient outcomes over time difficult.

Conclusions

This systematic review of reported literature found that IV nitrovasodilators used in the treatment of AHF in the ED and ED-like settings do provide improvement in short-term symptoms and appear safe to administer. Other commonly used vasodilators such as hydralazine and enalaprilat have very little published data about their safety and efficacy. Future research efforts need to enroll greater numbers of patients in the ED setting to assess the specific impact of vasodilator therapy on both short-term and long-term efficacy and safety.

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Figure 1.

Table 1

Article Data Extraction Summary Table

Author (year)	Study Type	Study Quality	Patient N	Intervention	Primary Outcomes
Nitroglycerin					
Aziz (2011)	Retrospective Cohort Study	3	430	No diuretics (dose based on patient response)/no nitrates (drip titrated to reach SBP of 120mmHg) OR diuretics only OR nitrates only	Composite: All-cause mortality and ADHF readmission
Beltrame (1998)	Prospective, open-label Randomized controlled Trial	2	69	Furosemide bolus 40 mg OR NTG 2.5 µg/min with N-acetylcysteine at 6.6 µg/min over 24 hours	Change in short term respiratory variables
Elkayam	Post-hoc subgroup analysis of a prospective randomized controlled trial	3	27	High-dose nitroglycerin (mean of 161 mcg/min at 6 hours) OR nesiritide (0.01 mcg/kg/min)	Left ventricular filling pressure
Levy (2007)	Nonrandomized, open-label, single arm study	3	29	Nitroglycerin (starting dose 0.3 to 0.5 µg/kg/min, with titration allowed in increments of 20 µg/min every 1 to 3 minutes thereafter at the discretion physician. Max rate fixed at 400 µg/min.) or no intervention	Time to intubation, adverse events
VMAC (2002)	Randomized Controlled Trial	1	489 (494)	Nesiritide (2 mcg/kg bolus and 0.01 mcg/kg per minute infusion) OR nitroglycerin OR placebo added to standard medications	Absolute change in PCWP and patient's evaluation of dyspnea 3 hours after medication initiation
Isosorbide Dinitrate					
Cotter (1998)	Prospective, Randomized Controlled trial	2	110	Isosorbide dinitrate, 3 mg bolus administered intravenously every 5 min OR furosemide 80 mg bolus administered intravenously every 15 min, as well as isosorbide dinitrate 1 mg/h, increased every 10 min by 1 mg/h	Pulmonary edema
Freund (2011)	Observational case series	3	136	ISDN continuous infusion OR bolus	Hypotension, Hospital Length of Stay, Hospital Mortality
Isosorbide Mononitrate					
Harf (1988)	Prospective Cohort	2	24	ISDN IV bolus of 10 mg + 1 mg/mL concentration for 24 hours	Hemodynamic effects
Nesiritide					
Arora (2007)	Retrospective Chart Review	3	206	Nesiritide dose given at either 0.01, 0.015, 0.02, 0.03 µg/kg/min OR Therapy at discretion of physician	Renal function
Bartone (2008)	Retrospective Chart Review	3	75	Usual care OR Nesiritide bolus (2 µg/kg) and continuous infusion (0.01 µg/kg/min) doses per hospital protocol	Short term change in hemodynamic values
Burger (2001)	Post-hoc subgroup analysis of a prospective Randomized Controlled Trial	3	261	IV dobutamine (dosing at investigators discretion) OR nesiritide 0.015 µg/kg/min infusion, preceded by a 0.3 µg/kg IV bolus OR nesiritide 0.030 µg/kg/min infusion, preceded by a 0.6 µg/kg IV bolus	Ventricular arrhythmia

Author (year)	Study Type	Study Quality	Patient N	Intervention	Primary Outcomes
Burger (2002)	Prospective Randomized Controlled Trial	1	255	1 of 2 doses of intravenous nesiritide (0.015 or 0.03 g/kg/min) or dobutamine (5 g/kg/min)	Heart Rate, Ventricular Arrhythmia
Chow (2011)	Prospective, open label randomized	2	89	Nitroglycerin initiated at 10 µg/min, titrated by physician to dyspnea relief or hypotension, max 200 µg/min OR nesiritide 2µg/kg optional bolus followed by 0.01 µg/kg/min for at least 48 hours	Renal function, biomarkers
Colucci (2000)	Randomized Controlled Trial	2	127	Nesiritide 0.015 g/kg per min infusion, preceded by a 0.3 µg IV bolus OR nesiritide 0.030 g/kg per min infusion, preceded by a 0.6 µg IV bolus OR placebo + bolus	Hemodynamic measures, dyspnea
Fu (2012)	Prospective Controlled Trial	2	140	Nesiritide (0.5 ~ 1.0 mg for 10-15 hours once daily for 13 days) + standard care or Standard care	Medical Research Council Scales, Edema, Dyspnea
Lenz (2004)	Retrospective case-control study	3	216	Nesiritide OR standard care (Dose information not reported)	Resource Utilization (Length of Stay, Number of Tests) and adverse events
Lewis (2003)	Retrospective Review of Reported Cases	3	55	Nesiritide (initial bolus of 2µg/kg followed by continuous dose of 0.01 µg/kg/min for 24 hr, then reevaluated with option to titrate up if needed) or milrinone (regimen not reported)	Infusion duration, length of stay, readmission
Miller (2008)	Prospective, Randomized Double-Blinded Placebo Controlled Trial	2	101	Nesiritide 0.01 µg/kg per min infusion, preceded by a 0.2 µg/kg intravenous bolus OR placebo + standard therapy	Re-admission or hospitalization at 30 days
O'Connor (2011)	Randomized placebo controlled Trial	1	7141	Optional IV bolus of nesiritide (2 µg/kg) then continuous infusion 0.010 µg/kg/min for 24 hours up to 7 days OR matching placebo	Dyspnea, rehospitalization, death
Owan (2008)	Randomized controlled Trial	2	72	Nesiritide (bolus of 0.2 mg/kg followed by 0.01 mg/kg/min) or Standard therapy	Renal function
Peacock (2005)	Randomized Controlled Trial	2	250	Standard care plus nesiritide 0.01 g/kg per min infusion, preceded by a 2 µg/kg IV bolus OR placebo + standard care	Admission, Length of Stay, Re-admission
Sakr (2008)	Randomized Controlled Trial	2	34	Standard therapy + nesiritide 0.01 µg/kg per min infusion, preceded by a 2µg/kg IV Bolus OR standard therapy	Hospital Length of stay and readmission
Scroggins (2005)	Retrospective analysis	3	132	Nesiritide vs. Milrinone (no treatment regimen reported)	Cost Effectiveness
Silver (2002)	Post-Hoc Analysis, Randomized Controlled Trial	3	251	Nesiritide (0.015 g/kg per min infusion, preceded by a 0.3 g/kg IV Bolus OR 0.030 g/kg per min infusion, preceded by a 0.6 g/kg IV bolus OR Investigator chosen IV vasodilator Dobutamine)	Infusion duration, Length of Stay, Readmission, Mortality at 6 months
Styron (2009)	Retrospective cohort	3	595	Nesiritide OR other regimen (dosing information not given)	30 and 180 day mortality
VMAC (2002)	Randomized Controlled Trial	1	489 (494)	Nesiritide (2 mcg/kg bolus and 0.01 mcg/kg per minute infusion) OR nitroglycerin OR placebo added to standard	Absolute change in PCWP and patient's evaluation of dyspnea 3 hours after

Author (year)	Study Type	Study Quality	Patient N	Intervention	Primary Outcomes
				medications	medication initiation
Wang (2004)	Prospective Randomized Control Crossover Trial	2	15	Nesiritide 0.01 µg/kg per min infusion, preceded by a 2 µg/kg IV Bolus OR placebo bolus and infusion	Renal Function
Witeles (2007)	Randomized, double blind, placebo controlled, clinical trial	2	75	Nesiritide infusion (2 µg/kg IV bolus followed by continuous 0.01 µg/kg/min × 48h) OR matching placebo (5% dextrose in water mimicking same dosing as above)	Renal Function
Enalaprilat					
Anane (1996)	Prospective, randomized, double blind placebo controlled Trial	2	20	IV Enalaprilat 1 mg infused over 2 hours	Hemodynamic and neurohormonal effects
Hirschl (1995)	Randomized controlled Trial	2	65	IV Enalaprilat 0.625, 1.25, 2.5 or 5.0 mg (Bolus)	Blood pressure reduction Adverse Effects
Hydralazine					
Nelson (1984)	Post-hoc Analysis of Randomized controlled Trial	3	18	ISDN (50 µg/kg/h titrated to 200 µg/kg/h) followed by Hydralazine OR hydralazine bolus (0.15 mg/kg) + ISDN OR simultaneous hydralazine + ISDN	Hemodynamic effects (improved blood pressure)
Relaxin					
Ponikowski (2014)	Multi-center prospective, randomized, double blind, placebo controlled trial	2	71	Placebo or Relaxin 30 µg/kg per day administered intravenously for 20 h continuously	Hemodynamic effects
RELAXIN II Study (2014)	Phase III, Multi-center prospective, randomized, double blind, placebo controlled Trial	-	6375-ongoing	Placebo or serelaxin 30 µg/kg per day administered intravenously for up to 48 h continuously	Mortality
Teerlink (2009)	Phase II, Double-blind, randomized, placebo-controlled Trial	2	230	Placebo (20mM sodium acetate solution with pH of 5, indistinguishable from relaxin) or Relaxin (1 of 4 regimens: 10 30, 100, or 250 µg/kg)	Dyspnea
Teerlink (2012)	Phase III, Multi-center prospective, randomized, double blind, placebo controlled Trial	1	1161	Placebo or Relaxin 30 µg/kg per day administered intravenously for up to 48 h continuously	Dyspnea
Clevidipine					
Peacock (2010)	Prospective Cohort	3	19	Clevidipine at 2 mg/h infusion, could be titrated by doubling the infusion every 3 to a max of 32 mg/h, then continued for 18-96 hours	Percentage of patients with blood pressure within a prespecified target range at 30 minutes
Peacock (2014)	Prospective, Randomized, Open-Label, Active Comparator Trial	2	104	Clevidipine at 2 mg/h infusion, could be titrated by doubling the infusion every 3 to a max of 32 mg/h for up to 96 hours or until the target blood pressure reduction was met	Co-primary of median time to and percent of patients attaining blood pressure reduction to a prespecified target range at 30 minutes

Table 2

Risk of Bias Summary table *

Description	Yes	No	Unclear
Sequence generation	7	10	13
Allocation concealment	6	16	9
Blinding of participants, personnel and outcome assessors	8	16	6
Incomplete outcome data adequately addressed	18	8	7
Free of Selective outcome reporting	17	9	6
Free of Other sources of bias	3	24	3

* Papers included multiple times if they have multiple outcomes that meet different levels of bias criteria. (4-6, 14, 15, 17, 18, 20, 22-25, 28-32, 35, 36, 40, 41, 45, 46, 54-61)