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Vasodilators in Acute Heart Failure: Review of the Latest Studies

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Abstract Vasodilators play an important role in the management of acute heart failure (HF), particularly when increased afterload is the precipitating cause of decompensation. The time-honored approach to afterload reduction has been largely focused on use of intravenous nitrovasodilators, and, when properly dosed, this class of agents does provide substantial symptom relief for patients with acute hypertensive HF. Despite this, nitrovasodilators have never been shown to diminish mortality or provide any post-discharge outcome benefit leading to an ongoing search for viable and more effective alternatives. While no new vasodilators have been approved for use in acute HF since nesiritide more than a decade ago, a number of novel agents have been developed, with some showing significant promise in recent clinical trials. In this review, we summarize the latest study data as they relate to vasodilator therapy and provide a glimpse into the not too distant future state of acute HF care.

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Introduction

Along with diuretics, vasodilators are a mainstay in the management of acute heart failure (HF), particularly when accompanied by elevated blood pressure (BP). The primary intent of vasodilator therapy is to reduce systemic vascular resistance in an effort to offset impedance to forward cardiac flow. At present, vasodilator therapy is often reserved for those with marked hypertension and profound dyspnea on presentation; however, there remains a sizeable group of patients for whom modest, yet relatively excessive increases in afterload can precipitate acute onset of HF symptoms. Thus, while severely dyspneic HF patients with elevated BP have been shown to benefit from aggressive vasodilator therapy [1•, 2•], there is growing interest in the potential applicability of afterload reduction in a broader swath of the hypertensive phenotype.

Accordingly, there is a significant interest in better understanding the applicability of existing vasodilators and defining the potential utility of novel agents in development. To that end, a number of vasodilator trials have recently been conducted in patients with acute HF, several of which have targeted early enrollment in the emergency department (ED) when BPs tend to be at their maximum. Despite being based on a similar conceptual foundation, important differences in trial design and pharmacological targets exist, making direct, head-to-head comparisons difficult. Our primary purpose then for this review is to familiarize the reader with data from the latest vasodilator studies, highlighting respective hemodynamic effects of

differing agents while providing an overview, when available, of relevant outcomes.

Historical Perspective

Nitrovasodilators (nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, and sodium nitroprusside) have long been considered first-line agents for acute hypertensive HF. As a class, these drugs work by providing an exogenous source of nitric oxide (NO), which then binds to soluble guanylate cyclase (GC), producing cyclic GMP and vascular smooth muscle relaxation [3]. At low doses, this effect occurs predominantly in the venous circulation, resulting in increased capacitance and a marked reduction in preload, but at higher doses (≥150–250 mcg/min); arteriolar dilatation ensues, leading to substantial reductions in afterload [4]. This effect may be more pronounced when systemic vascular resistance is severely elevated [5] and appears to be mediated through a dose-dependent, differential effect on the pressure wave that is reflected back to the central circulation when peripheral arterioles recoil [6••]. Termed the *augmentation index*, this reflected wave affects the late systolic phase of cardiac contraction and represents a critical, yet modifiable variable in the ventricular/vascular coupling relationship.

Despite extensive real-world experience and some retrospective clinical data supporting the use of nitrovasodilators [7], related outcome data are lacking, and, as a class, this group of agents has not been shown to provide any significant benefit on mortality or hospital readmissions. As such, there has been substantial interest in identifying alternative vasodilators with the potential to improve outcomes. Nesiritide, a recombinant form of brain-natriuretic peptide (BNP) that has neurohormonal and vasodilator properties, was the first potential challenger to be developed and has been subject to extensive study since it first appeared on the market in 2001. Research involving nesiritide culminated in 2011 with publication of results from Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF), the largest investigation of acute HF treatment ever conducted (n receiving study drug = 7,007) that compared nesiritide (n = 3,496) with placebo (n = 3,511) in a prospective, randomized trial [8]. While the study was not specifically conducted in the ED setting, median time to patient randomization was relatively short in both arms (~15 h), and a similar proportion of patients in the nesiritide (15.7 %) and placebo (14.1 %) groups received open-label vasodilator therapy prior to administration of study medication. Patients treated with nesiritide did show a modest improvement in self-reported dyspnea at 6 and 24 h, but this finding did not meet the prespecified criteria for significance. Moreover, there was no difference in the co-primary endpoint of 30-day mortality or rehospitalization (9.4 vs. 10.1 %; $p = 0.31$) with relatively high but equivalent rates of renal impairment (any drop in estimated glomerular filtration rate >25 %) through 30 days (31.4 vs. 29.5 %; $p = 0.11$), signifying that nesiritide is safe but lacking in clinical efficacy. Of note, mean BP was not particularly high in either group (123 mmHg for nesiritide, 124 mmHg for placebo), and hypotensive episodes were significantly more common among those who received nesiritide (26.6 vs. 15.3 %; $P < 0.001$), suggesting that perhaps the wrong patient population (i.e., one for whom afterload was not a major component of the acute pathophysiology) was targeted for the trial.

The Future of Vasodilator Therapy

While the consideration of nesiritide as a nitrate substitute has served an important purpose, the advent of newer treatment options with potentially more attractive therapeutic profiles warrants a shift in focus. Though none has been as thoroughly evaluated as nesiritide, several have been subject to study in relatively large-scale trials with some showing significant promise for future clinical use.

Serelaxin

Relaxin is a naturally occurring peptide hormone released in pregnancy that helps regulate hemodynamic function and renovascular blood flow through a number of effects including stimulation of NO production, vascular endothelial growth factor, and matrix metalloproteinases and inhibition of endogenous vasoconstrictors (i.e., endothelin and angiotensin II) [9]. Such favorable characteristics led to the development of serelaxin, a pharmaceutical analog of relaxin, and initiation of a dose-finding pilot trial (Pre-RELAX AHF—Phase II Multicenter, Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Relaxin in Subjects With Acute Heart Failure) of 237 patients [10]. Based on a demonstration of greater dyspnea improvement with serelaxin and a trend toward reduction in the composite of cardiovascular death/readmission due to heart or renal failure at day 60 (2.6 vs. 17.2 %; $p = 0.053$), a follow-up study was designed.

Completed in 2012, the RELAXin in acute heart failure (RELAX-AHF) trial enrolled 1,161 acute HF patients with mild-to-moderate renal insufficiency and a systolic BP >125 mmHg (mean BP for the study cohort ~142/82 mmHg with no difference by group) and found a significantly greater decrease in one of two dyspnea endpoints (visual analog scale [VAS]) starting at 6 h and extending through day 5 for those who received serelaxin (n = 581)

compared with placebo ($n = 580$) [11•]. BP was more profoundly reduced in patients receiving serelaxin as well, decreasing approximately 13.5 mmHg from baseline by 6 h (vs. 9 mmHg) and 15.5 mmHg by 24 h (vs. 11 mmHg). Although more hypotensive episodes requiring a study-specified dose reduction were noted in the seralaxin group (29 vs. 18 %; $p = 0.0001$), there was no difference in hypotension-related adverse events (5 vs. 4 %; $p = 0.78$). Significant decreases in worsening heart failure, clinical signs of vascular congestion, adverse events related to renal impairment, and length of initial hospital stay were also seen in the serelaxin group, while the total dose of intravenous (IV) loop diuretic administered through day 5 was lower (161 vs. 213 mg; $p = 0.006$). Despite this, treatment with serelaxin did not increase days alive out of hospital, and there was no difference in cardiovascular death or hospital readmission for heart failure or renal failure up to day 60 between the serelaxin and placebo groups. However, serelaxin was associated with a significant reduction in both all-cause (6.1 vs. 9.6 %; $p = 0.028$) and cardiovascular (7.3 vs. 11.3 %; $p = 0.02$) mortality through 180 days, a pre-specified safety endpoint. This and other apparent clinical effects of serelaxin were consistent across multiple subgroups including those patients (7 % in each arm) who received IV nitrates concurrent with the study drug [12].

Whether the benefits shown in RELAX-AHF reflect a direct pharmacological attenuation of cardiac, renal, and hepatic stress or damage (as indicated by relative biomarker improvements from baseline to day 2 for patients treated with serelaxin) [13•], an effect resulting from earlier interruption of acute pathophysiology (median time to randomization in both arms was <8 h), the consequences of focused vasodilator administration in patients who truly have a hypertensive phenotype or some combination thereof are not known, but the identification of a therapy that can potentially reduce cardiovascular death in acute HF is an important advance [14]. To that end, an adequately powered multicenter mortality trial (RELAX-AHF 2) has been initiated ($n = 6{,}375$) with anticipated enrollment of the first patient by December 2014 (NCT01870778).

Ularitide

While nesiritide is the prototypical exogenous natriuretic peptide (NP), several other variants exist, including ularitide, a synthetic analog of urodilatin, which is an atrial-NP derivative. Much like nesiritide, the main pharmacological effects of ularitide include vasodilation (especially in the renal, pulmonary and coronary vasculature), diuresis, natriuresis, and inhibition of the renin–angiotensin–aldosterone system (RAAS) [15, 16]. Phase I ($n = 18$) [17] and phase II ($n = 168$) [18•] studies of ularitide in patients with acute HF showed favorable, dose-dependent hemodynamic effects and consistent improvements in dyspnea without inducing renal dysfunction. As a follow-up to this preliminary work, the Trial of Ularitide's Efficacy and Safety in Patients With Acute Heart Failure (TRUE-AHF), a phase III randomized study of ularitide versus placebo, was initiated in the fourth quarter of 2012 (NCT01661634). The primary endpoint is a hierarchic clinical composite that includes a patient-centered assessment of clinical progress, demonstrated lack of improvement or worsening of HF requiring a prespecified intervention, and death. Recruitment is currently on-going with targeted enrollment of 2,116 patients from centers across North America, Europe, and Latin America.

Cenderitide

Cenderitide is another NP derivative, representing a chimer of *c*-type and *Dendroaspis* NP (an isolate from the green mamba snake) [19]. Though still considered a vasodilator, the profile of this agent more accurately reflects its peptide constituents, combining preferential cardiac unloading, venodilating, and antifibrotic properties of CNP that result from dual GC receptor activation with the potent natriuretic and diuretic effects of DNP [20]. While preliminary study of cenderitide focused on development of an IV formulation for patients with acute HF and renal dysfunction, the drug has since been repositioned as a continuous subcutaneous infusion for use in the post-acute HF hospitalization period (i.e., initiated upon hospital discharge). A phase I pharmacokinetic and pharmacodynamics study ($n = 58$) of this approach was completed in 2011, showing dose-dependent effects on BP over 24 h of infusion with systolic BP reductions ranging from −16 (SD 12) to −28 (SD 1) mmHg and good bioavailability in 58 (45 cenderitide and 13 placebo) chronic HF patients [21]. A phase II trial targeting enrollment of approximately 300 patients to evaluate cardiac remodeling, renal function, rehospitalization, and mortality as endpoints after 90 days of continuous cenderitide therapy via subcutaneous pump in patients post-admission for acute HF was planned for 2012 but has yet to be initiated.

Clevidipine

Clevidipine is a fourth generation IV dihydropyridine calcium channel blocker (CCB) that has recently emerged as a potential option for BP control in patients with hypertensive HF. While there has been historical concern with administration of CCBs in the setting of acute HF, data from a subset of patients ($n = 19$) in the VELOCITY (The Evaluation of the Effect of Ultra-Short-Acting Clevidipine in the Treatment of Patients With Severe Hypertension) trial suggested potential utility for newer IV preparations

[22], prompting development of PRONTO (An Efficacy and Safety Study of Blood Pressure Control in Acute Heart Failure—A Pilot Study).

Designed as a randomized, open-label phase IIIa trial of clevidipine ($n = 51$) versus standard of care ($n = 53$) for patients with acute HF who had dyspnea >50 on a 100 mm VAS and a systolic BP >160 mmHg, PRONTO completed enrollment in 2012 [23]. Patients that received clevidipine were more likely to have their BP reduced to a predefined target range by 30 min (70.5 vs. 36.6 %; $p = 0.002$) and experienced more rapid improvements in dyspnea (mean [SD] VAS at 1 h: 21.7 [18.8] mm vs. 33.4 [24.9] mm; $p = 0.02$) than the standard of care group [86.8 % of whom received either nitroglycerin (56.6 %) or nicardipine (30.2 %)]. BP reduction was also more profound (−36 vs. −22 mmHg at 30 min), and overshoot beyond the BP target range occurred more frequently (29.4 vs. 1.9 %; $p < 0.001$) in those who were treated with clevidipine, but few patients in either arm (3 clevidipine, 1 standard of care) developed actual hypotension (systolic BP <90 mmHg) over the 3-h observation period. Of note, the mean (SD) times to study drug administration were 3.2 (1.9) and 2.7 (1.8) h for the clevidipine and standard of care arms ($p = 0.24$), respectively, making PRONTO one of the earliest intervention trials in acute HF to date.

Although results are encouraging, PRONTO was insufficiently powered for outcome data beyond BP and dyspnea control, and generalizability is limited by enrollment of a predominantly (∼80 %) African-American cohort. A follow-up, phase IIIb trial (PRONTO II—A Randomized Parallel Group Controlled Comparison Study of Clevidipine Versus Placebo or Standard of Care for Dyspnea and Blood Pressure Control in Acute Heart Failure) was recently launched with targeted enrollment of 500 patients based on stratified (120–140 and >140–160 mmHg) BP criteria. Patients will be recruited from centers in the US and Australia with a projection for the first patient to be enrolled in December 2013.

TRV120027

TRV120027 is a beta-arrestin biased angiotensin II type 1 receptor (AT1R) ligand that has recently been developed for potential use in patients with acute HF. Completely novel in its pharmacology, TRV120027 acts like a conventional angiotensin receptor blocker, inhibiting angiotensin II-mediated vasoconstriction while concurrently enhancing cardiomyocyte contractility through biased, G-protein independent activation of the beta-arrestin signaling pathway [24]. Canine models of tachypacing-induced HF show a dose-dependent decrease in mean arterial pressure and pulmonary capillary wedge pressure (PCWP) with an increase in cardiac output and renal blood flow, suggesting that TRV120027 provides effective cardiac unloading while preserving renal function, even in animals who were administered furosemide [24, 25•]. Importantly, apparent BP effects of TRV120027 are rapid in onset and relatively short in duration, providing an ideal hemodynamic profile for use in acute HF. While human experience with TRV120027 is limited, a phase II double-blind, placebo-controlled, dose-ranging study targeting enrollment of approximately 500 patients hospitalized for acute HF is set to begin in early 2014 (NCT01187836).

Nicorandil

Introduced in the late 1980s, nicorandil (*N*-[2-hydroxyethyl] nicotinamide nitrate) is an agent with nitrate-like properties that activates adenosine triphosphate-sensitive potassium channels, resulting in balanced venous and arterial vasodilation [26]. While no large-scale trials of nicorandil in acute HF exist, it has been evaluated in several small studies that consistently demonstrate a controlled reduction in BP and PCWP with an absence of hemodynamic tolerance [26–29]. A greater relative decrease in NT-proBNP levels [30•] and a potential reduction in the rate of death or rehospitalization for HF through 180 days (adjusted hazard ratio = 0.179, $p < 0.0001$) [31] have also been shown with nicorandil treatment, though confirmation would require a well-designed prospective study.

Cinaciguat

As described, nitrovasodilators exert their effect by upstream activation of cGMP through binding of NO to soluble GC, a heterodimeric enzyme consisting of an alpha and beta subunit. Actual binding of NO occurs at a prosthetic heme molecule located within the beta subunit but only when the heme iron is in it ferrous state. Thus, nitrovasodilators can be rendered largely ineffective during times of oxidative stress when the redox potential shifts soluble GC heme to its ferric form [32]. Cinaciguat, an NO-independent direct activator of oxidized and heme-free soluble GC, is not affected by changes in the redox potential and has been shown to have potent, sustained preload and afterload reducing effects when administered to a non-randomized group of patients ($n = 60$) with acute HF [33].

Based on this, the COMPOSE program, a set of three randomized, double-blind, placebo-controlled, fixed-dose, multicenter, multinational phase IIb trials aimed at defining the potential role of cinaciguat in acute HF, was developed [34]. Designed to study invasive hemodynamic (COMPOSE 1 and 2) and self-reported dyspnea (COMPOSE EARLY) endpoints separately, the COMPOSE program targeted a total enrollment of 320 patients. Unfortunately, the higher dose range of cinaciguat (50, 100 and 150 mcg/h)

was associated with an excess of non-fatal adverse BP events leading to premature termination of both COMPOSE 1 and COMPOSE EARLY with only 12 (out of 100) and 62 (out of 160) patients enrolled, respectively. Much of this was driven by COMPOSE EARLY, where hypotension developed in 27.9 % (vs. 5.3 % in placebo patients) of those treated with cinaciguat, and serious treatment-emergent adverse events occurred in 16.3 % (vs. 10.5 % in the placebo group). While relative improvements in PCWP were found in the hemodynamic arm, there was no apparent effect on the cardiac index, and no evidence of dyspnea benefit was seen, leading study investigators to doubt the utility of the cinaciguat for acute HF going forward. Thus, while interest remained in COMPOSE 2 as it targeted a lower dose range (10 and 25 mcg/h), the study was shut down with only four (out of 60) patients enrolled for projected futility. It is noteworthy that the mean (SD) systolic BP in the cinaciguat arm of COMPOSE EARLY was only 136.7 (12.3) mmHg [vs. 132.4 (16.2) mmHg in placebo patients], and the mean (SD) baseline dyspnea VAS score was 44.1 (24.7) mm [vs. 50.2 (23.8) in the placebo group], suggesting that the study enrolled a population that may have been less likely to benefit from the targeted intervention.

Concurrent with the COMPOSE program, another phase IIb, randomized, placebo-controlled trial of cinaciguat was conducted enrolling 139 patients with acutely decompensated chronic HF who were hospitalized, had a pre-existing need for right heart catheterization, and a PCWP $\geq$18 mmHg [35]. A significant improvement in PCWP at 8 h, the primary endpoint, was seen with cinaciguat [mean PCWP decrease: -7.7 mmHg (baseline $= 25.7 + 5.0$ mmHg) vs. -3.7 mmHg (baseline $= 25.0 + 5.3$ mmHg); $p < 0.0001$]. Statistically significant improvements were also noted for a number of secondary hemodynamic endpoints including the cardiac index, systemic vascular resistance, pulmonary vascular resistance, and right atrial pressure. However, as with COMPOSE EARLY, systolic BP decreased to a much greater extent in the cinaciguat group [-21.6 (SD 17.0) mmHg vs. -5.0 (SD 14.5) mmHg; $p < 0.0001$], and development of hypotension (predefined as systolic BP <90 mmHg or a reduction from baseline of $\geq$40 mmHg, or an adverse event related to hypotension) was far more common (73.2 vs. 25.5 %), leading to early termination of the trial. As with other unsuccessful vasodilator trials, BP at enrollment for this study cohort was not elevated [mean (SD) systolic BP = 123 (17) mmHg in both arms], and the excess rate of hypotension may represent sampling bias rather than a truly harmful drug effect.

Bay 1021189

While enthusiasm may have dampened for cinaciguat, the SOluble Guanylate Cyclase stimulatoR in heArT failure patientS (SOCRATES) program is set to begin with two concurrent phase II studies evaluating the use of BAY 1021189, an oral soluble GC stimulator, in patients with acute worsening of chronic HF. Soluble GC stimulators have a dual effect, increasing cGMP production by sensitizing the enzyme to endogenous NO through a stabilization of the NO-soluble GC complex and by directly binding to soluble GC through a different binding site [32]. The SOCRATES studies target a total enrollment of 880 patients (470 in a preserved and 410 in a reduced ejection fraction cohort) with a primary endpoint of change in log-transformed NT-ProBNP at 12 weeks and first projected enrollment in early 2014.

CXL-1020

Least studied of any agent mentioned, CXL-1020 is a pure nitroxyl (HNO) donor that provides direct positive cAMP-independent lusitropic and inotropic effects as well as combined venous and arterial dilation [36]. Preliminary study of CXL-1020 in humans ($n = 31$) with stage D chronic HF showed dose-dependent effects on myocardial contractility (increase), left heart failing pressures (decrease), and systemic vascular resistance (decrease), leading to a balanced unloading of the left ventricle in the setting of decompensated systolic dysfunction [36]. Further human study of CXL-1020 is underway, though no plans for a large-scale clinical trial have been announced.

Conclusions

A number of agents can produce afterload reduction, yet only a handful have been rigorously tested in the setting of acute HF, and head-to-head comparison trials are sorely lacking. As shown by this review, we are entering a new era of study with earlier enrollments, larger trials, and a broader selection of drug classes. Many of the agents discussed offer promise beyond conventional therapy, and it is our hope that at least a few survive the test of time.

Compliance with Ethics Guidelines

Conflict of Interest P. Levy is a board member for the Society of Cardiovascular Patient Care and a consultant for Cornerstone Therapeutics, Novartis Pharmaceuticals, and Trevena, Inc. He has also received grant funding from Cardiorentis, Inc., Bayer Schering Pharma, Nile Therapeutics, and Novartis Pharmaceuticals. S. Laribi punctually received fees as consultant from Novartis. Dr. Mebazaa reports personal fees from Cardiorentis, lecture fees from Orion, and personal fees from Bayer, outside the submitted work.

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.

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