Review Articles

Review of Vasodilators in Acute Decompensated Heart Failure: The Old and the New

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ABSTRACT

Despite substantial improvements in treatment for chronic heart failure, morbidity and mortality for acute decompensated heart failure (ADHF) remain high. Treatment of ADHF is focused on controlling symptoms rather than improving long-term outcomes. The vasodilators nitroglycerin (NTG) and sodium nitroprusside (SNP) have been used in ADHF for decades, but, since the development of nesiritide 10 years ago, interest in new vasodilators has grown. Therapies that improve not only hemodynamics and symptoms but also long-term outcomes are in high demand, and numerous new vasodilatory agents have been investigated, including various natriuretic peptides, soluble guanylyl cyclase agents, renin-angiotensin-aldosterone system−modifying agents, and others. A review of the literature shows that few of them rise to the challenge set by NTG and SNP. (*J Cardiac Fail 2013;19:478−493*)
Key Words: Nitroglycerin, sodium nitroprusside, natriuretic peptide.

Almost 1 million patients yearly receive a primary diagnosis of acute decompensated heart failure (ADHF) at hospital discharge in the United States (US),[1] with the direct cost of these hospitalizations reaching $209 billion in 2010.[2] In-hospital mortality varies among recent registries from ∼3% to 5%,[3,4] a decrease from the 8% rate found in a Medicare beneficiary registry from 1991 to 1994,[5] but long-term statistics remain bleak, with rehospitalization rates of 25%−40% and post-hospitalization mortality rates of 10%−20% 2−3 months after discharge.[3,6,7]

ADHF results in poor outcomes for many reasons, including the natural course of the disease and the age and comorbidities of those most affected,[1,8] with a paucity of treatment shown to decrease morbidity and mortality.[3] Management of ADHF focuses on improving symptoms by relieving congestion rather than improving long-term outcomes, which may be appropriate to a certain extent:

> [B]oth patients and physicians desire therapies that improve signs, symptoms, and/or quality of life, assuming an acceptable safety profile. Expecting therapies used for 48 hours to improve outcomes at 2 to 6 months in a complex, heterogeneous substrate […] may set the bar too high.[9]

ADHF is a complex syndrome rather than a single pathologic entity, aising from a variety of etiologies manifesting as diverse clinical presentations in patients with systolic dysfunction as well as in those with preserved ejection fraction (EF).[8,10,11] Various forces are involved in the pathophysiology of ADHF, ranging from molecular and immunologic disturbances to ischemic and mechanical dysfunction.[12] Many of these derangements are driven by neurohormones, including the renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system, antidiuretic hormone (ADH), natriuretic peptides (NPs), and endothelins.[12,13] As shown in Figure 1, neurohormones can affect cardiac function either directly or by modulating preload, afterload, natriuresis, and diuresis. In ADHF, many neurohormones are elevated, resulting in increased afterload and preload, decreased natriuresis and diuresis, and decreased ventricular contractility.[12−14]

First-line management for ADHF consists of intravenous diuretic therapy, which improves ventricular contraction and decreases heart failure (HF) symptoms via natriuresis and diuresis. Heart Failure Society of America (HFSA)

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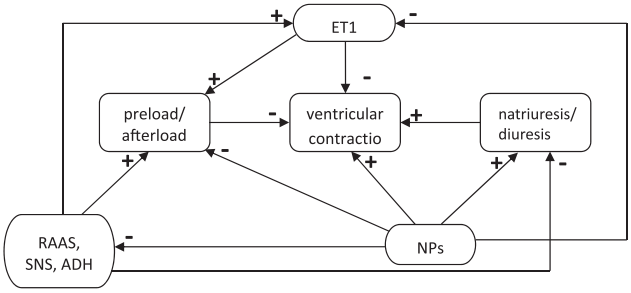

Fig. 1. Neurohormonal effects on cardiac function.[12–14,16] In acute decompensated heart failure, the RAAS, the SNS, ADH, and ET1 act to increase preload and afterload and decrease natriuresis and diuresis, thereby decreasing ventricular contraction. NPs counteract these effects, improving ventricular contractions via vasodilatation. ADH, antidiuretic hormone; ET1, endothelin-1; NPs, natriuretic peptides; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system.

guidelines suggest considering a vasodilator for symptoms of congestion, particularly in the setting of acute pulmonary edema or severe hypertension.[15] As illustrated in Figure 2, most vasodilators act via cyclic guanosine monophosphate (cGMP) to increase intracellular calcium, thereby causing smooth muscle relaxation and vasodilation.[16] This results in decreased preload and afterload, thereby causing improved contractility.[12] A combination of diuretic and vasodilator therapy has also been shown to rapidly decrease neurohormonal activation, including NPs, endothelin, and norepinephrine.[14]

Clinical society practice guidelines specifically mention the vasodilators nitroglycerin (NTG) and sodium nitroprusside (SNP), which have been used in ADHF for 30 years, and nesiritide, which has been in use for a decade.[10,15] Numerous new vasodilatory agents have been developed and investigated in the past 10 years in the search for therapies that might improve not only hemodynamics and symptoms but long-term outcomes as well. We reviewed published randomized controlled trials (RCTs) and selected observational trials of vasodilators used in the management of ADHF, including nitric oxide (NO) donators, NPs, soluble guanylyl cyclase (sGC) agents, RAAS-modifying agents, endothelin antagonists, relaxin, and hydralazine. Appraisal of the literature shows that few agents rise to the challenge set by NTG and SNP.

Methods

Pubmed was searched from 1982 to the present for experimental clinical trials in humans with ADHF reporting relevant clinical outcomes with the use of the phrase (“heart failure” NOT chronic) AND “drug name.” The following drug names were used: “aliskiren,” “BAY 58-2667,” “carperitide,” “CD-NP,” “cinaciguat,” “enalapril,” “hydralazine,” “nesiritide,” “nitroglycerin,” “nitroprusside,” “tezosentan,” “relaxin,” “ularitide,” and “urodilatin.” The search was limited to articles in the English language. References from potentially relevant articles and from review articles were searched to identify additional studies. Clinicaltrials.gov was searched for ongoing trials, and manufacturers of the various drugs were contacted directly to request information regarding current and ongoing trials. ADHF was defined as worsening of HF signs or symptoms requiring hospitalization and intravenous therapy (the signs and symptoms reported varied among trials). Relevant clinical outcomes included hemodynamic effects, change in dyspnea or clinical status, change in creatinine (Cr), worsening HF, total or cardiovascular (CV) mortality, and readmission. Trials that focused solely on pharmacodynamics, pharmacokinetics, and safety were excluded. The quality of each trial was assessed based on randomization, blinding, and handling of patient attrition in analysis with the use of the Jadad scale.[17] A trial with a Jadad score of ≥3 was considered to be of reasonable

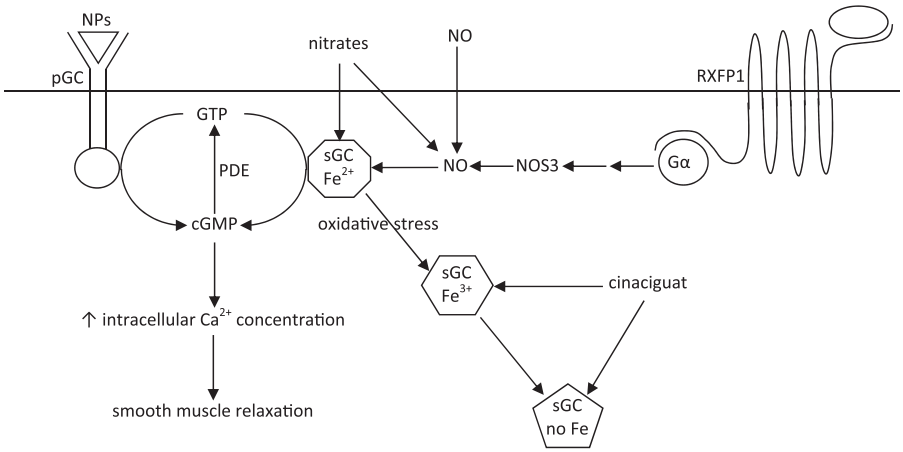

Fig. 2. Mechanisms of action of selected vasodilators.[13,16,20,21,29,56,78] NO and nitrates diffuse across the cell membrane and convert GTP to cGMP via sGC bound to a reduced heme moiety. cGMP increases intracellular calcium, thereby resulting in smooth muscle relaxation and vasodilatation. Cinaciguat acts via sGC bound to an oxidized heme moiety or with no heme moiety, while NPs act via membrane-bound pGC. Relaxin binds RXFP1, a G-coupled protein receptor, to activate NOS3 and increase intracellular NO. cGMP, cyclic guanosine monophosphate; Gα, guanine nucleotide-binding protein; GTP, guanosine triphosphate; NPs, natriuretic peptides; NO, nitric oxide; NOS3, endothelial nitric oxide synthase; PDE, phosphodiesterase; pGC, particular guanylyl cyclase; RXFP1, relaxin/insulin-like family pepide receptor 1; sGC, soluble guanylyl cyclase.