

STATE-OF-THE-ART PAPERS

Emerging Therapies for the Management of Decompensated Heart Failure

From Bench to Bedside

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While pharmaceutical innovation has been highly successful in reducing mortality in chronic heart failure, this has not been matched by similar success in decompensated heart failure syndromes. Despite outstanding issues over definitions and end points, we argue in this paper that an unprecedented wealth of pharmacologic innovation may soon transform the management of these challenging patients. Agents that target contractility, such as cardiac myosin activators and novel adenosine triphosphate-dependent transmembrane sodium-potassium pump inhibitors, provide inotropic support without arrhythmogenic increases in cytosolic calcium or side effects of more traditional agents. Adenosine receptor blockade may improve glomerular filtration and diuresis by exerting a direct beneficial effect on glomerular blood flow while vasopressin antagonists promote free water excretion without compromising renal function and may simultaneously inhibit myocardial remodeling. Urodilatin, the renally synthesized isoform of atrial natriuretic peptide, may improve pulmonary congestion via vasodilation and enhanced diuresis. Finally, metabolic modulators such as perhexiline may optimize myocardial energy utilization by shifting adenosine triphosphate production from free fatty acids to glucose, a unique and conceptually appealing approach to the management of heart failure. These advances allow optimism not only for the advancement of our understanding and management of decompensated heart failure syndromes but for the translational research effort in heart failure biology in general. (J Am Coll Cardiol 2006;48:2397–409) © 2006 by the American College of Cardiology Foundation

While recent times have witnessed great progress in reducing the mortality associated with chronic heart failure, progress in the management of decompensated heart failure (DHF) syndromes has languished, reflected by a limited therapeutic armamentarium and an equally sparse evidence-based literature. Initial stabilization and symptomatic improvement is achieved in the majority of patients with available interventions (1). However, rehospitalization and mortality rates remain high (30% to 60%) in the months after discharge (2–4). Within the next decade, a wealth of research activity and pharmacologic innovation may transform how we diagnose, classify, treat, and evaluate patients admitted for DHF. Ongoing pre-clinical and clinical studies are evaluating novel inotropic agents, diuretics and aquaretics, and modulators of myocardial metabolism (Fig. 1). This article provides an overview of promising drugs in development, offering mechanistic insights as well as data from animal and human trials.

CHALLENGES IN THE EVALUATION OF NOVEL THERAPIES

Decompensated heart failure represents an often amorphous clinical entity, a complex and heterogeneous group of syndromes encompassing numerous disease states with differing

presentations, outcomes, and optimal medical management. One approach to undifferentiated DHF considers several archetypal clinical syndromes, such as systemic volume overload, low cardiac output, and acute pulmonary edema (5). Systemic volume-overload heart failure represents a common clinical syndrome within DHF. These patients often carry a known diagnosis of heart failure and present with gradually worsening symptoms and signs of fluid overload such as edema, ascites, and dyspnea. In-hospital medical management principally involves intravenous diuretics and vasodilators. Low-output DHF is characterized by poor end-organ perfusion, manifest as hypotension, altered mental status, fatigue, and pre-renal azotemia. Congestion may or may not be present depending on, among other factors, the pulmonary lymphatic capacity. Patients with this type of heart failure often require invasive hemodynamic monitoring and positive inotropic therapy. Typically older, hypertensive patients with preserved systolic function and acute pulmonary edema comprise a third clinical syndrome of DHF. In these cases, vasodilators frequently achieve rapid resolution of symptoms. As a framework in evolution, this approach suffers from overlapping categories that prohibit the strict classification of patients presenting with features of more than one clinical syndrome, ultimately hindering its ability to guide management. Furthermore, the present method does not address differences between heart failure etiologies, a distinction that may prove critical for certain therapies, such as modulators of myocyte metabolism.

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Abbreviations and Acronyms

ANP	= atrial natriuretic peptide
ATP	= adenosine triphosphate
AVP	= arginine vasopressin
BNP	= brain natriuretic peptide
cAMP	= cyclic adenosine monophosphate
CI	= confidence interval
DHF	= decompensated heart failure
FFA	= free fatty acid
LTCC	= L-type calcium channel
NYHA	= New York Heart Association
PCWP	= pulmonary capillary wedge pressure
PKA	= protein kinase A
RyR	= ryanodine receptor

Another approach to differentiate DHF patients relies upon risk stratification, employing hemodynamic variables and laboratory values such as systolic blood pressure, blood urea nitrogen, and serum creatinine to identify groups at high risk for morbidity and mortality (6).

The absence of effective short-term surrogate end points poses another major challenge to evaluating new drugs for the management of DHF syndromes. Improved hemodynamic parameters, readily available measures in the inpatient setting, do not reliably translate into improved clinical outcomes longer term. Administration of nesiritide, for example, yields statistically significant improvements in pulmonary capillary wedge pressure (PCWP) and cardiac index at 6 h (7). However, recent meta-analyses suggest that nesiritide use may be associated with adverse events. One study observed a 52% (95% confidence interval [CI] 1.16 to 2.00) increase in the risk of worsening renal function, while another revealed a 74% (95% CI 0.97 to 3.12) increase in mortality at 30 days compared with non-inotrope-based control therapy (8,9). Although firm conclusions await the results of randomized, controlled studies, the findings are in contrast with the acute hemodynamic benefit observed with nesiritide infusion. Identifying convenient, short-term surrogate markers that accurately predict longer-term prognosis would facilitate the assessment and expedite the development of pharmacotherapies for DHF. The recent REVIVE (Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy) trials were some of the first to attempt a clinical composite end point that could account for the complex nature of DHF presentations, dividing patients into “better,” “worse,” or “unchanged” groups according to several variables. While this end point approximated the more objective plasma brain natriuretic peptide (BNP) measurement, it did not account for the greater number of adverse arrhythmic events or the higher mortality seen in the levosimendan group, leaving the question as to the ideal end point for such trials unanswered.

INOTROPIC THERAPIES

Augmenting systolic function with positive inotropic pharmacotherapy may be an appropriate management objective in selected patients presenting with low-output DHF.

Among current generation inotropic agents, heightened energy utilization and the coupling of contractility, chronotropy, and calcium represent significant limitations. First, drugs available to enhance contractility may induce maladaptive remodeling by imposing increasing metabolic demands on the failing heart. An open-label randomized study revealed a trend towards worsened 6-month survival after in-hospital infusion of dobutamine compared with nesiritide. Novel drugs targeting cardiac energetics as a means to improve systolic function are discussed in the following text (see the Metabolic Modulation section). Second, tachyarrhythmias contribute to the excess morbidity and mortality observed in clinical trials using available inotropic agents (10). Dopamine, dobutamine, epinephrine, and milrinone increase cyclic adenosine monophosphate (cAMP) levels within cardiac myocytes, resulting in activation of the cAMP-dependent protein kinase A (PKA) and phosphorylation of 2 key calcium channels, the L-type calcium channel (LTCC) and the ryanodine receptor (RyR) (11,12). Located on the myocyte cell membrane, LTCC mediates calcium entry from the extracellular space during the plateau phase, or phase 2, of the non-pacemaker myocyte action potential. In a process called calcium-induced calcium release, calcium influx via LTCC stimulates calcium release from sarcoplasmic reticulum stores by binding to the calcium receptor/calcium channel RyR located on the sarcoplasmic reticulum. Protein-kinase-A-mediated phosphorylation of LTCC and RyR induces conformational changes in both transmembrane channels promoting calcium flux into the cytosol. The rise in cytosolic calcium concentration promotes actin-myosin cross-bridging by displacing the inhibitory troponin-tropomyosin complex and results in myocyte shortening. However, the added contractility comes at a price—accumulation of calcium is arrhythmogenic, accounting for one possible mechanism for inducing delayed afterdepolarizations and triggered activity (13,14).

Despite the aforementioned considerations, data from the ADHERE (Acute Decompensated Heart Failure National Registry) indicate relatively frequent use of available inotropic agents, with milrinone or dobutamine administered to 10% of patients hospitalized for DHF (15). Importantly, the majority of these patients lacked evidence of hemodynamic compromise—only 10% manifest hypotension, 30% had impaired renal function, and 30% to 40% experienced dyspnea at rest—suggesting perhaps overenthusiastic use of inotropic therapy. Developing drugs that improve myocyte contractility without perturbing the cellular electrophysiological balance remains an elusive goal in the management of DHF. Two novel therapies attempting to dissociate inotropy and arrhythmogenicity are cardiac myosin activators and istaroxime.

CARDIAC MYOSIN ACTIVATORS

Cardiac myosin activators directly target the force-generating cardiac enzyme, myocardial myosin ATPase,

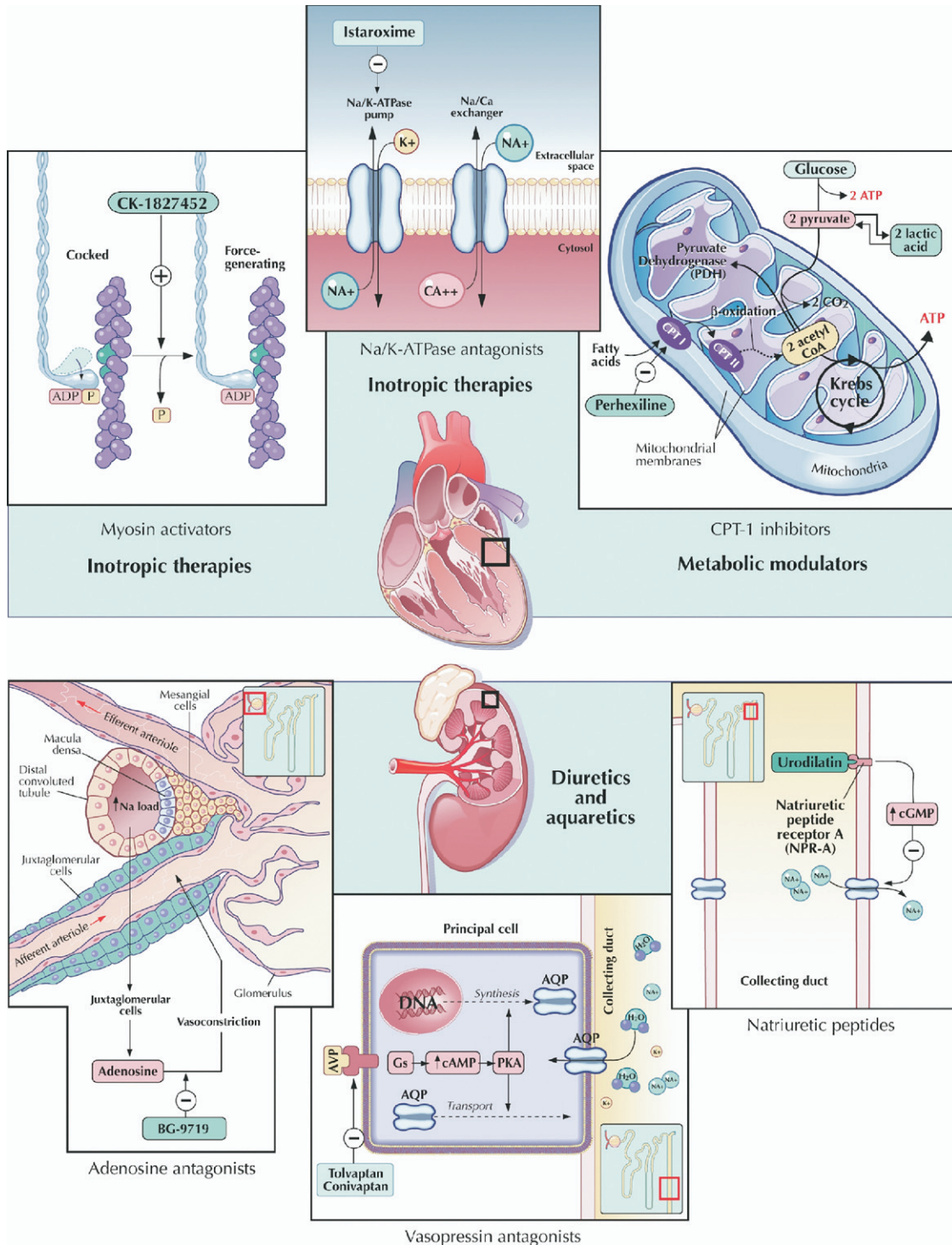


Figure 1. Overview of emerging pharmacotherapies for the management of acute decompensated heart failure. ADP = adenosine diphosphate; AQP = aquaporin-2; AVP = arginine vasopressin; cAMP = cyclic adenosine monophosphate; cGMP = cyclic guanosine monophosphate; CPT-1 = carnitine palmitoyl transferase-1; Gs = stimulatory G-protein; Na/K-ATPase = adenosine triphosphate-dependent transmembrane sodium-potassium pump; PKA = protein kinase A. Illustration by Rob Flewell.

accelerating its activity in order to enhance contractility. Molecular events underlying muscle contraction begin with binding of adenosine triphosphate (ATP) to the globular head domain of myosin, resulting in its dissociation from actin (16,17) (Fig. 2). Rapid hydrolysis of ATP to adenosine

diphosphate and phosphate induces flexion of the myosin head. Upon release of phosphate, conformational changes in the myosin head result in a high-affinity interaction with the adjacent actin unit. Extension of the myosin head—the so-called power stroke—follows, resulting in displacement

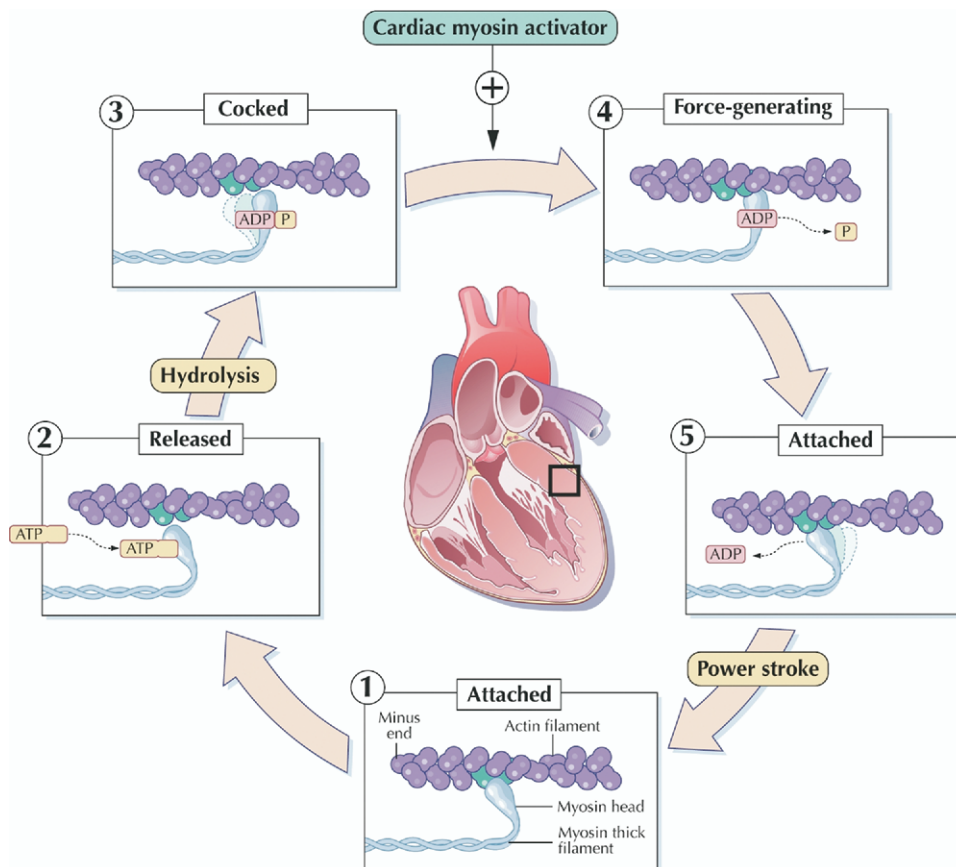


Figure 2. The myosin ATPase cycle. Cardiac myosin activators appear to accelerate the rate-limiting step, hastening the transition of myosin from the weakly filament-bound to the strongly filament-bound state. ADP = adenosine diphosphate; ATP = adenosine triphosphate. Illustration by Rob Flewell.

of actin by approximately 10 nm. The cycle then concludes in the rigor state after adenosine diphosphate leaves its binding cleft.

Several small molecules have been developed that target myocardial myosin ATPase, including CK-0689705, CK-1122534, CK-1213296, and CK-1827452. In vitro and in vivo studies using rat and dog models of heart failure demonstrate that these novel agents increase fractional shortening of ventricular myocytes in a dose-dependent manner without altering intracellular calcium levels (18–22). Beta-blockade does not abrogate the inotropic effect, supporting a mechanism of action independent of adrenergic activation (18). Transient kinetic analysis of individual steps in the cardiac myosin cycle reveal that these compounds accelerate the rate-limiting, third step of the enzymatic process, hastening the transition of myosin from the weakly filament-bound to the strongly filament-bound state (23). An intravenous formulation of CK-1827452 is currently in phase I clinical development as a potential treatment for patients with DHF. While cardiac myosin activators provide a mechanism for decoupling contractility and chronotropy, it remains unclear whether fueling an accelerated myosin ATPase cycle will incur a significant metabolic cost. If so, the accompanying increased oxygen consumption may have a detrimental effect on the failing heart.

ISTAROXIME: Na/K-ATPase INHIBITOR

Istaroxime (PST-2744), a novel Na/K-ATPase inhibitor chemically unrelated to cardiac glycosides, augments myocardial contractility by stimulating calcium entry via the sarcolemmal Na/Ca-exchanger. In vitro and in vivo analyses of istaroxime therapy in guinea pigs and dogs revealed dose-dependent increases in inotropic activity as measured by the maximum rate of pressure rise in the left ventricle (dP/dt_{max}) (24,25). Unlike available inotropic therapies, however, preliminary data suggest that istaroxime may permit cytosolic calcium accumulation while avoiding a proarrhythmic state. Compared with digoxin, istaroxime demonstrated a significantly greater ratio of proarrhythmic dose to inotropic dose as well as a more rapid onset and decay of effect, suggesting both a wider margin of safety and a more predictable pharmacokinetic profile. Another study compared istaroxime and dobutamine in a canine model of chronic ischemic heart failure (26). The change in dP/dt_{max} after treatment was equivalent between subjects administered istaroxime and dobutamine (+51%) (Fig. 3); however, peak heart rate was significantly higher with dobutamine infusion (160 vs. 120 beats/min). Measurements of cardiac output were not obtained. In cardiomyopathic hamsters, istaroxime improved survival as well as contractility and lusitropy (27). Untreated mortality at 52 weeks of age was 100%,

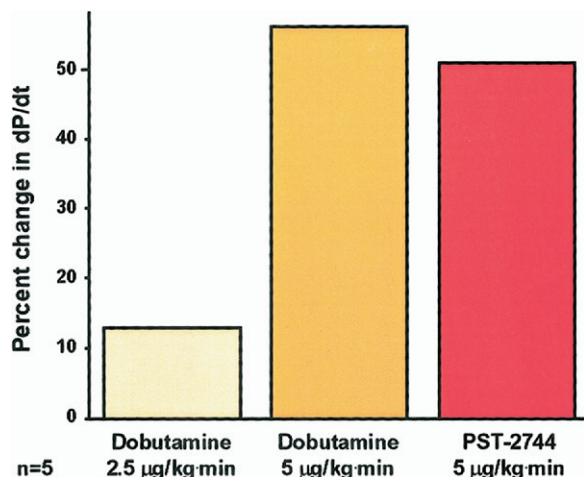


Figure 3. Change in left ventricular dP/dt_{max} comparing istaroxime (PST-2744) to dobutamine in 5 dogs with chronic ischemic heart failure. No difference was found between PST-2744 and 5 $\mu\text{g}/\text{kg}/\text{min}$ dobutamine. Both significantly increased dP/dt_{max} ($p < 0.05$). Reproduced with permission (26).

compared with 54% among hamsters administered istaroxime. Although encouraging, the exact mechanism by which istaroxime achieves uncoupling of calcium and arrhythmogenicity remains unclear. Electrophysiologic studies in guinea pig ventricular myocytes suggest one possible mechanism: suppression of the transient inward calcium current directly involved in the genesis of delayed afterdepolarizations (28). While studies have been promising to date, istaroxime remains in the early stages of pre-clinical research.

DIURETICS, AQUARETICS, AND NATRIURETICS

Conventional diuretics such as loop and thiazide diuretics remain the mainstay of therapy for the management of fluid overload in both systemic volume overload and acute pulmonary edema DHF, administered to 87% of hospitalized patients according to the national ADHERE registry (29). However, these drug classes suffer from inherent limitations, achieving water loss via excretion of solute at the expense of glomerular filtration. Impaired glomerular filtration mediated by loop diuretics arises from indirect sequelae of volume depletion as well as direct detrimental effects on nephron function, including decreased glomerular blood flow. Adenosine receptor blockade may overcome this limitation, achieving diuresis and maintaining glomerular filtration by improving renal blood flow. The second mechanistic disadvantage described in the preceding text, solute-driven volume loss, results in hyponatremia and hypokalemia. Numerous studies suggest that these metabolic derangements have profound clinical significance, either as the cause of morbidity and mortality or as surrogate markers for poor outcomes (30–32). Furthermore, by inhibiting sodium transport in the macula densa (33), loop diuretics such as furosemide directly activate the renin-angiotensin-aldosterone system (34–37) responsible for cardiac remodeling and the progression of heart failure (38). Novel

vasopressin receptor antagonists, on the other hand, promote solute-free water diuresis, or aquaresis, and may, therefore, correct hypervolemia while simultaneously preserving an appropriate electrolyte milieu and minimizing renin release (39). Finally, a number of atrial natriuretic peptide (ANP) analogues are under active investigation, including urodilatin. While nesiritide, or recombinant B-type natriuretic peptide, significantly reduces PCWP via pulmonary vasodilation and diuresis (7,40), meta-analyses of randomized, controlled trials suggest a possible association with worsened renal function and an increased risk of death (8,9). Ongoing clinical studies attempt to clarify the effects of nesiritide and explore other natriuretic peptides for the management of pulmonary and systemic congestion. Peripherally inserted veno-venous ultrafiltration, as a mechanical approach to fluid overload, lies beyond the scope of our pharmacotherapeutic discussion, and promising results from recent trials have been reviewed elsewhere (41–43).

ADENOSINE ANTAGONISTS

Four distinct receptor subtypes—A1, A2a, A2b, and A3—mediate the effects of adenosine on the kidney, heart, and blood vessels (44). Current research efforts in the management of DHF focus on the beneficial effects of A1-receptor blockade on renal blood flow. Inhibition of adenosine pathways in the kidney does not target tubular function, but rather improves glomerular filtration by exerting a direct beneficial effect on glomerular blood flow and interrupting tubuloglomerular feedback (44,45). Stimulation of renal A1-receptors induces afferent arteriolar constriction (46), post-glomerular vasodilation (47), and mediates tubuloglomerular feedback, the macula densa mechanism by which increased sodium delivery to the proximal tubule leads to decreased glomerular filtration rate (48). Selective A1-receptor blockade attenuates these potentially detrimental effects in animal and human studies, suggesting a potential therapeutic role in the treatment of DHF.

In a rat model of dilated cardiomyopathy, administration of BG-9719, a selective A1-receptor antagonist, achieved diuresis while maintaining stable renal and cardiac function (49). When added to chronic furosemide therapy, BG-9719 augmented renal blood flow and glomerular filtration rate. Similarly, BG-9719 doubled urine output and increased creatinine clearance in pigs with rapid pacing-induced systolic dysfunction (50). Invasive hemodynamic monitoring in pigs treated with BG-9719 revealed significantly decreased PCWPs without adverse effects on cardiac output, mean arterial pressure, or heart rate.

Human studies of adenosine antagonists in heart failure have also yielded promising results. In one crossover trial comparing furosemide and BG-9719, both agents induced natriuresis in 12 patients with New York Heart Association (NYHA) functional class III or IV heart failure, but only BG-9719 preserved baseline glomerular filtration rate (51). Another study examined the renal activity of BG-9719

alone and in combination with 80 mg of intravenous furosemide in 63 patients admitted with symptomatic heart failure (25). Patients were deemed eligible for the randomized, placebo-controlled, double-blind trial provided they were categorized as NYHA functional class II, III, or IV, had a documented ejection fraction less than or equal to 40%, and remained edematous despite a daily furosemide dose of at least 80 mg. The trial examined three BG-9719 dosing regimens, 7-h infusions designed to yield serum concentrations of 0.1, 0.75, or 2.5 $\mu\text{g}/\text{ml}$. BG-9719 alone tripled urine output compared with placebo without effecting a decrease in glomerular filtration rate or potassium loss (Fig. 4). Furosemide alone augmented urine output 8-fold while significantly reducing glomerular filtration rate. BG-9719 added to intravenous furosemide further increased diuresis and, more importantly, reversed the decline in renal function such that no difference in glomerular filtration rate was observed between the combination and placebo groups.

Despite the diuretic advantages of renal A1-receptor blockade, the complexity of adenosine physiology necessitates further trials to prove that adenosine antagonism yields no adverse clinical consequences. In an apparent pharmacologic paradox, A1-receptor agonists are simultaneously under development as cardioprotective therapy in heart failure. Activation of cardiac A1-receptors inhibits norepinephrine and endothelin release and may thereby antagonize neurohormonal axes involved in myocardial hypertrophy and remodeling (52). In a murine model of pressure overload heart failure, administration of 2-chloroadenosine, a selective A1-receptor agonist, attenuated cardiac hypertrophy, pulmonary edema, and systolic dysfunction induced by transverse aortic constriction (53). In addition, adenosine has been identified as a critical trigger substance for ischemic pre-conditioning (54). Sublethal ischemia increases myocardial levels of adenosine, which, via stimulation of A1- and A3-receptors, triggers an intracellular cascade conferring a protected phenotype resistant to further ischemic insult. If A1-receptors on myocardial cells indeed serve a significant cardioprotective role, therapeutic inhibition of the A1-receptor in DHF may require renal specificity to achieve diuresis without compromising cardiac function.

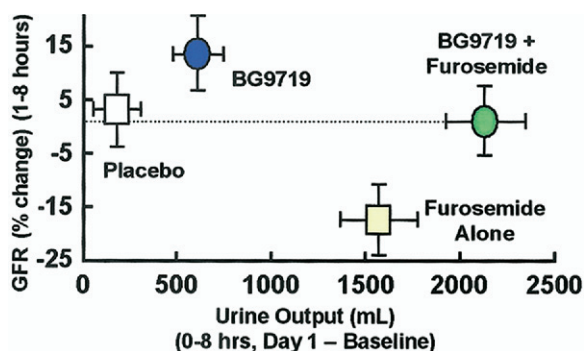


Figure 4. Adenosine antagonist BG9719 augments diuresis and preserves glomerular filtration rate (GFR) when administered alone or in combination without furosemide. Reproduced with permission (25).

VASOPRESSIN ANTAGONISTS

Arginine vasopressin (AVP), also known as antidiuretic hormone, is critical to the regulation of fluid balance, augments vascular tone in heart failure, and may play a role in myocardial remodeling (55). Arginine vasopressin exerts its cardiorenal effects through 2 receptor subtypes (56). V2-receptors located on renal collecting duct principal cells mediate the primary physiologic action of AVP, free water reabsorption (55). Binding of AVP to V2-receptors stimulates the synthesis of aquaporin-2 water channel proteins and promotes their transport to the apical surface (Fig. 5). At the cell membrane, aquaporin-2 permits selective free water reabsorption down the medullary osmotic gradient, ultimately decreasing serum osmolality and increasing fluid balance. V1a-receptors on peripheral arterial and coronary smooth muscle cells effect cAMP-independent vasoconstriction, explaining the utility of AVP in shock states (57). The functional significance of V1a-receptors on cardiomyocytes remains unclear. In animal models, stimulation of this receptor population promotes fibroblast proliferation and protein synthesis, suggesting a role in myocardial hypertrophy and remodeling (58–61).

Patients with heart failure consistently exhibit elevated circulating levels of AVP in proportion to disease severity (34,61–65). In the SOLVD (Studies of Left Ventricular Dysfunction) trial, plasma levels of AVP, along with renin and norepinephrine, were significantly higher in patients with left ventricular dysfunction compared with control subjects, and higher still in patients with overt DHF (34). As with other neurohormonal axes in heart failure, activation of the AVP pathway is hypothesized to represent a maladaptive response leading to worsened congestive symptoms and ultimately disease progression. Impaired systolic function and depressed cardiac output activate pressure-sensitive baroreceptors in the carotid artery, which, in turn, stimulate AVP release from the posterior pituitary (38). V2-receptor-mediated aquaporin-2 expression promotes free water reabsorption, aggravating the existing fluid imbalance (66–69). In addition to inappropriate volume retention, AVP may worsen hemodynamics in heart failure. Intravenous AVP infusion in patients with chronic heart failure augmented systemic vascular resistance, decreased cardiac output, and increased PCWP in a dose-dependent fashion, presumably as a result of V1a-receptor-mediated vasoconstriction (56,70). Growing evidence suggests that AVP itself, not simply its attendant abnormal loading conditions, may effect structural changes in the myocardium via V1a-receptor activation. When administered to cultured rat cardiomyocytes, AVP stimulated protein synthesis and fibroblast proliferation (58–61,71,72). Selective V1a-receptor antagonism abrogated these effects and, in one in vivo study of myocardial infarcted rats, prevented deterioration in systolic function (73). In human heart failure and remodeling, the pathophysiologic significance of AVP and the myocyte V1a-receptor subpopulation remain undeter-

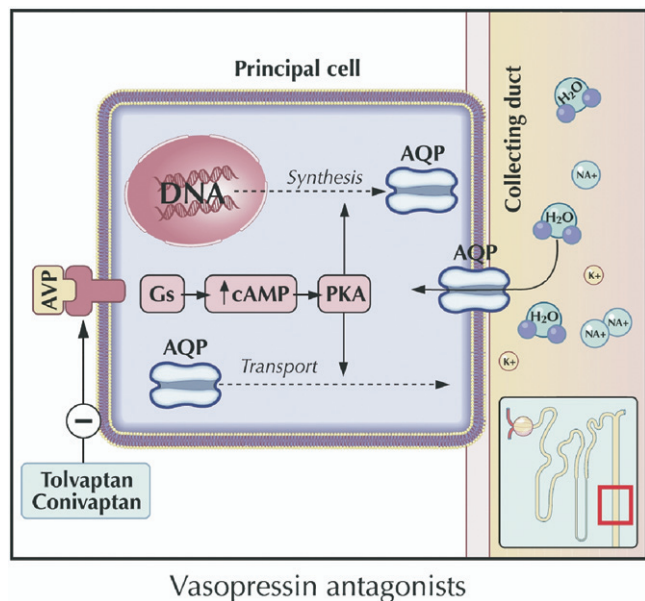


Figure 5. Vasopressin (AVP) stimulates synthesis of aquaporin-2 (AQP) water channel proteins and their transport to the apical surface of collecting duct principal cells. Other abbreviations as in Figure 1. Illustration by Rob Flewell.

mined. The posited harmful effects of excess AVP in heart failure provide the rationale for the development of AVP antagonists as novel therapeutic agents for the management of DHF (74).

Tolvaptan (OPC-41061) is a selective V₂-receptor antagonist, binding 29 times more avidly to V₂-receptors than to V_{1a}-receptors (75). In the rat model, oral administration of tolvaptan achieved significant and sustained dose-dependent aquaresis without affecting serum concentrations of sodium or creatinine (75). Equipotent doses of furosemide, however, decreased serum sodium concentration and increased serum creatinine concentration (76). Moreover, while the loop diuretic augmented renin activity and circulating levels of aldosterone, no such activation of the renin-angiotensin-aldosterone axis was noted in rats treated with tolvaptan (76). The ACTIV in CHF (Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure) trial evaluated the effects of tolvaptan in patients hospitalized with DHF and a systolic ejection fraction less than 40% (77). At randomization, mean ejection fraction was 24%, and all subjects were NYHA functional class III or IV. Adding tolvaptan to standard therapy significantly increased mean 24-h urine volume (Fig. 6) and decreased body weight compared with placebo. Despite these aquaretic benefits, administration of tolvaptan was not associated with an improvement in the primary combined clinical end point, defined as death, hospitalization for heart failure, or unscheduled presentation for heart failure requiring escalation of therapy. With regard to adverse events, sudden cardiac death was observed in 5 patients treated with tolvaptan and 1 patient in the placebo group. A large phase III trial, EVEREST (Efficacy

of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan), is underway to further examine the effect of tolvaptan on cardiovascular mortality and heart failure hospitalization (78). Limited information exists regarding the effects of V₂-receptor blockade on renal hemodynamics and neurohormonal activity in patients with heart failure. A recent crossover study of 14 patients demonstrated that tolvaptan, unlike furosemide, did not impair renal blood flow or increase renin activity and circulating norepinephrine levels (79). In addition to tolvaptan, other selective V₂-receptor antagonists currently undergoing clinical investigation include SR-121463 and AVPA-985 (55,80).

Simultaneous blockade of V_{1a}- and V₂-receptors would theoretically yield advantages over V₂-receptor antagonism, namely, inhibition of V_{1a}-mediated arterial vasoconstriction and myocardial remodeling (59,60,81). Conivaptan (YM087) is a dual antagonist demonstrating 10 times the affinity for V_{1a}-receptors compared with V₂-receptors (55). In experimental models of ischemic and non-ischemic heart failure, conivaptan achieved significant aquaresis while decreasing systemic vascular resistance and improving systolic function (82-84). Selective V₂-receptor blockade alone did not augment cardiac performance. As noted in the preceding text, conivaptan inhibited AVP-induced protein synthesis in the rat cardiomyocyte model, suggesting a potential therapeutic role in the inhibition of myocardial hypertrophy (59,85). To date, few trials have examined the effects of conivaptan in congestive heart failure patients. One short-term study enrolled patients with symptomatic systolic heart failure on appropriate therapy including a loop diuretic, angiotensin-converting enzyme inhibitor, and beta-blocker (86). At randomization, mean ejection fraction was 23%, and the majority of subjects were classified as NYHA functional class III. Conivaptan significantly increased urine

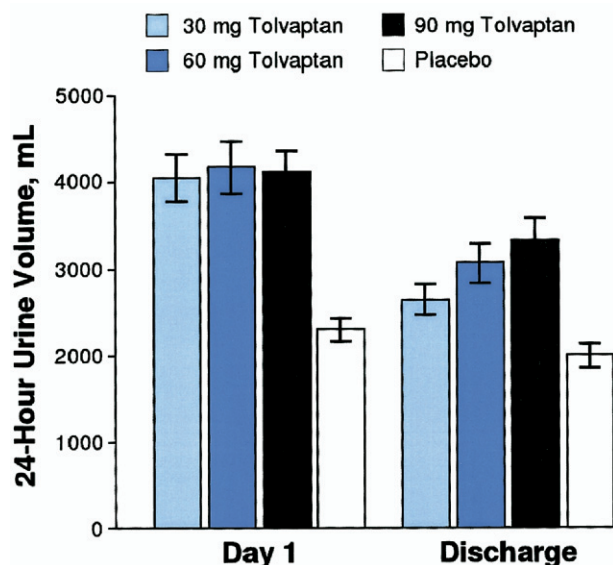


Figure 6. Tolvaptan therapy increased 24-h urine volume compared with placebo in patients hospitalized for decompensated heart failure. Reproduced with permission (77).

output in a dose-dependent manner compared with placebo and reduced PCWP and right atrial pressure. Adverse events occurred less frequently after acute conivaptan therapy compared with placebo. Notably, systemic vascular resistance and cardiac index were not different between the conivaptan and placebo groups. Baseline levels of AVP were low in the study population, potentially masking a vasodilatory benefit of V1a-receptor inhibition. Patients hospitalized for DHF and, in particular, patients administered V2-receptor antagonists exhibit higher AVP levels that may provoke undesired vasoconstriction. Hemodynamic consequences of V1a/V2-receptor antagonists as well as their effects on myocardial remodeling require further elucidation in long-term studies, ideally comparing dual V1a/V2- and selective V2-receptor blockade. The ADVANCE (A Dose Evaluation of a Vasopressin Antagonist in CHF undergoing Exercise) trial is currently examining the effect of conivaptan on functional capacity, measured by peak oxygen consumption, in patients with heart failure (87).

URODILATIN (ULARITIDE)

Atrial, or A-type, natriuretic peptide is synthesized in specialized atrial myoendocrine cells as the prohormone ANP-(1-126), processed into the biologically active 28-amino acid ANP-(99-126), and released into the circulation in response to atrial stretch (88). Binding to natriuretic peptide type A receptors activates coupled guanylate cyclase and stimulates the formation of cyclic guanosine monophosphate. Downstream pathways effect peripheral vasodilatation and inhibit renal sodium reabsorption. Administration of intravenous ANP in pre-clinical and clinical studies decreases PCWP and systemic vascular resistance, reduces plasma levels of renin and aldosterone, and increases urine output (89,90). However, the hemodynamic and neurohormonal benefits of ANP are blunted in DHF patients compared with normal subjects (90). Mechanisms of impaired ANP response in heart failure include down-regulation of ANP receptors and increased activity of neutral endopeptidase, the enzyme responsible for ANP degradation (91).

In 1988, a unique, renally synthesized isoform of ANP was isolated from human urine (92). Distal tubular cells produce the 32-amino acid ANP, termed urodilatin, and secrete the peptide into the tubular lumen, where it travels to the inner medullary-collecting duct and binds to natriuretic peptide type A receptors to promote sodium excretion (88). Unlike ANP-(99-126), the active circulating isoform, urodilatin possesses a TAPR-NH₃ terminal extension that confers resistance to biological inactivation by neutral endopeptidase. Both experimental animal models and early clinical trials demonstrated therapeutic effects of urodilatin, which significantly enhanced diuresis and natriuresis and reduced PCWP and systemic vascular resistance to a greater extent than ANP-(99-126) (93–100).

Pharmacologic application of urodilatin to the management of DHF began with the evaluation of ularitide, its synthetic equivalent, in the SIRIUS (Safety and Efficacy of an Intravenous Placebo-Controlled Randomized Infusion of Ularitide in a Prospective Double-blind Study in Patients with Symptomatic, Decompensated Chronic Heart Failure) trial (101). The randomized, double-blind, placebo-controlled study examined the effects of 24-h ularitide infusion in the setting of DHF. The study population consisted of 24 patients with NYHA functional class III to IV symptoms, a mean cardiac index of 1.9 l/min/m², and a mean PCWP of 26 mm Hg without evidence of cardiogenic shock. The benefits of higher doses of ularitide, 30 ng/kg/min, included early significant decreases in PCWP compared with placebo, later decreased N-terminal pro-BNP compared with baseline, a trend towards decreased systemic vascular resistance and increased cardiac index, improved dyspnea self-assessment scores, and an apparent decreased need for diuretic and nitrate therapy (Fig. 7). Hemodynamic improvements, however, were transient, failing to persist throughout the 24-h drug infusion, and at many time points did not achieve statistical significance compared with placebo. Moreover, the administration of ularitide at 30 ng/kg/min effected significant reductions in systolic blood pressure, averaging 17 mm Hg, after 6 h. To clarify the safety and efficacy of ularitide, a larger trial aptly named SIRIUS II enrolled 221 patients presenting with DHF (102). Compared with placebo, 24-h infusion of ularitide at 15 and 30 ng/kg/min achieved significant increases in cardiac index and decreases in systemic vascular resistance starting at 1 h after initiation of therapy and persisting over 24 h. At these doses, ularitide also significantly reduced N-terminal pro-BNP at 24 h compared with placebo but did not alter 30-day survival or improve renal function. As in SIRIUS I, however, ularitide produced a dose-dependent decrease in systolic blood pressure, with 16% of patients in the 30 ng/kg/min group experiencing hypotension.

Ongoing concerns regarding the safety and efficacy of another natriuretic peptide, nesiritide, provide pause for thought regarding more detailed study of ularitide (8,9,103). As noted above, short-term improvements in hemodynamic parameters alone are no longer felt to be sufficient to support clinical use. In addition, the rationale behind supplementing a neurohormonal system that is already maximally up-regulated endogenously has yet to be proven. Additional studies are required to establish safety as well as a therapeutic benefit in terms of clinical end points. Recently, a large-scale, multicenter trial has been proposed using an intermediate dose of ularitide, 15 ng/kg/min, in an attempt to improve congestive symptoms and signs in patients with DHF.

METABOLIC MODULATION

Optimizing myocardial energy utilization represents a unique and conceptually appealing approach to the management of heart failure. In the normal adult human heart,

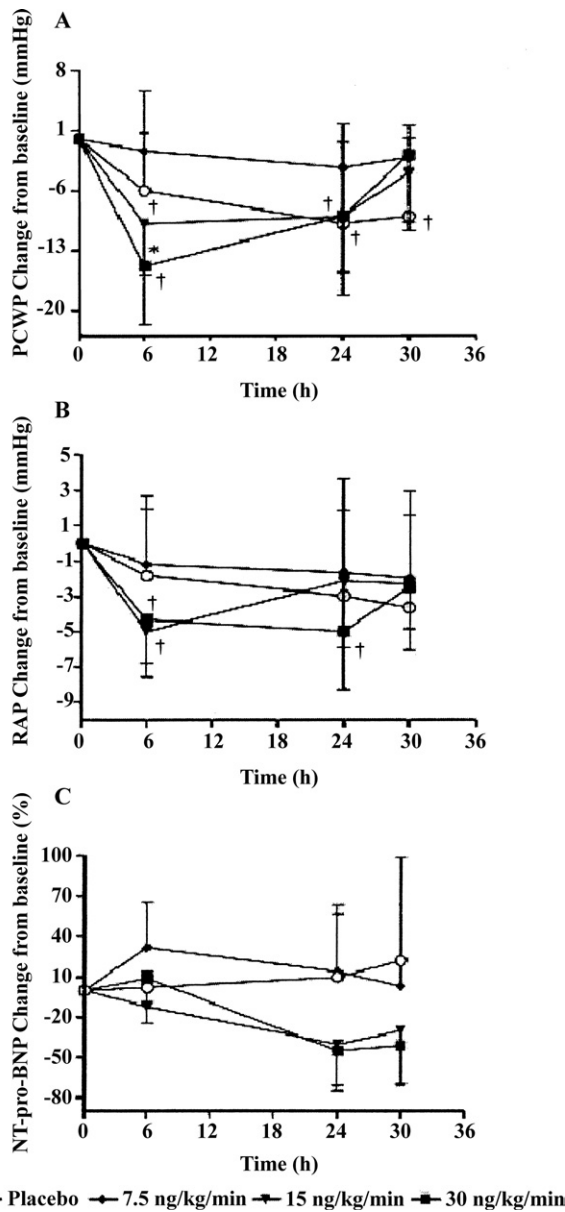


Figure 7. Changes from baseline during 24-h placebo or urodilatin infusion, and after discontinuation. **p* < 0.05 versus placebo; †*p* < 0.05 versus baseline. NT-pro-BNP = N-terminal pro-B-type natriuretic peptide; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure. Reproduced with permission (101).

the majority (60% to 90%) of ATP production results from free fatty acid (FFA) metabolism, with only 10% to 40% of myocardial energy generated by glucose (104,105). Utilization of FFAs is ordinarily advantageous, providing more ATP per gram of metabolic fuel than carbohydrate catabolism. However, under ischemic conditions with oxygen as the limiting substrate, glycolysis becomes the more efficient pathway, requiring 10% to 15% less oxygen compared with FFA breakdown (105,106) (Table 1). Furthermore, FFA oxidation during ischemia inhibits pyruvate dehydrogenase, resulting in increased conversion of pyruvate to lactate, progressive tissue acidosis, and impaired myocyte contractility (107-111). In principle, shifting energy utilization

from FFAs to glucose would optimize metabolic efficiency, reverse abnormalities in the cellular milieu, and improve cardiac function.

PERHEXILINE

Attempts at therapeutic metabolic manipulation were first applied to the symptomatic relief of angina, frequently with striking effect. First discovered in the 1960s, perhexiline, the most extensively studied modulator of myocyte energetics, promotes glucose utilization through inhibition of carnitine palmitoyl transferase-1, an enzyme critical to mitochondrial uptake of FFAs (104). Several randomized studies demonstrated that perhexiline use at doses of 100 to 200 mg twice daily achieved reductions exceeding 50% in the frequency of anginal episodes and the use of sublingual nitroglycerin, as well as significant improvements in exercise tolerance (112-116). Treatment with perhexiline yielded benefits even among patients with recurrent angina despite maximal medical management with beta-blockers, nitrates, and calcium-channel blockers. In one randomized, double-blind, placebo-controlled trial of 17 patients with refractory angina on combination therapy, 65% of patients administered perhexiline for 3 months noted improvements in ischemic symptoms during exercise, compared with 18% of patients given placebo (117).

In the 1970s and 1980s, reports of hepatotoxicity and peripheral neuropathy with long-term perhexiline use tempered initial enthusiasm for the novel antianginal agent (118-121). Toxicity arises as a result of phospholipid accumulation mediated by carnitine palmitoyl transferase inhibition, which occurs primarily among patients with slowed hepatic metabolism (CYP2D6) of perhexiline (122-128). Further studies demonstrated that cautious dose titration to maintain plasma concentrations between 150 to 600 ng/ml appears to avoid serious adverse sequelae (129). Post-marketing surveillance data from Australia reveal a dramatic decline in the incidence of peripheral neuropathy and hepatitis with the advent of therapeutic monitoring (130). Nonetheless, perhexiline use remains restricted to severe, refractory ischemic symptoms, and its availability currently limited to Australia, New Zealand, and several European countries (104).

The improved safety profile provided by therapeutic monitoring has prompted renewed interest in perhexiline, in particular in another metabolically stressed state, heart failure. In theory, optimization of cardiac energetics would benefit not only ischemic, but non-ischemic cardiomyopathy. Numerous studies in heart failure patients without

Table 1. The Theoretical ATP Yield of Complete Oxidation of Glucose and the Free Fatty Acid Palmitate

Substrate	Substrate Efficiency (mol ATP/mol Substrate)	Oxygen Efficiency (mol ATP/mol O)
Glucose	36	3.0
Palmitate	129	2.6

ATP = adenosine triphosphate.

significant coronary artery disease have revealed regional myocardial hypoperfusion, attributed to increased oxygen demand from tachycardia and heightened wall stress and decreased oxygen supply due to endothelial dysfunction and elevated filling pressures (131–133).

While no study has yet examined the utility of perhexiline in patients hospitalized for DHF, one small, short-term clinical trial suggests a significant benefit in patients with chronic heart failure (134). Fifty-six optimally medicated patients with ischemic or non-ischemic heart failure, left ventricular ejection fraction <40%, and NYHA functional class II or III symptoms were randomized to receive perhexiline or placebo. Serial measurements of blood perhexiline levels guided dose titration to prevent toxicity, with a goal concentration of 0.15 to 0.59 ml/l. After 8 weeks, perhexiline-treated ischemic and non-ischemic groups demonstrated a 43% relative increase in left ventricular ejection fraction (absolute 10 percentage points) and 17% increase in peak exercise oxygen consumption (Fig. 8). In comparison, prior studies have shown an increase in peak exercise oxygen consumption of 13% to 20% associated with angiotensin-converting enzyme inhibitor therapy (135) and 8% with biventricular pacing (136). Perhexiline increased peak systolic velocity at rest and maximal dobutamine stress by 15%

and 25%, respectively, and significantly improved quality of life as measured by the Minnesota Living with Heart Failure Questionnaire. Administration of placebo was not associated with improvements in any of the pre-specified clinical end points. Adverse events were infrequent and limited to transient nausea and dizziness, with no cases of hepatotoxicity or peripheral neuropathy observed. Although limited in size and duration, this study advances the hypothesis that an innovative therapeutic mechanism—metabolic modulation—may potentially serve as a future treatment of heart failure of either ischemic or non-ischemic etiology. In addition to perhexiline, other agents directed at optimizing myocyte energetics include trimetazidine, ranolazine, and etomoxir (104).

SUMMARY

While some have decried the absence of pharmacologic innovation in heart failure, we argue in this paper that there is cause for optimism. New inotropic agents may avoid arrhythmia by directly targeting cardiac myosin. Novel Na/K-ATPase inhibitors may augment myocardial contractility without the adverse effect profile of cardiac glycosides. Adenosine receptor blockade may improve glomerular filtration and diuresis by exerting a direct beneficial effect on glomerular blood flow. Vasopressin antagonists promote free water excretion without compromising renal function and may simultaneously inhibit myocardial remodeling. Novel natriuretic peptides may improve pulmonary congestion via vasodilation and enhanced diuresis. Metabolic modulators may optimize myocardial energy utilization by shifting ATP production from FFAs to glucose.

While debate as to the exact nature and definition of DHF syndromes will undoubtedly continue, and while the most appropriate end point in acute heart failure clinical trials will remain the subject of many editorials to come, we demonstrate here that even as these issues are resolving, the pipeline of pharmacologic innovation continues to offer us new hope that short-term improvements in hemodynamics, volume status, and clinical symptoms can lead ultimately to the holy grail of improved outcome for our patients.

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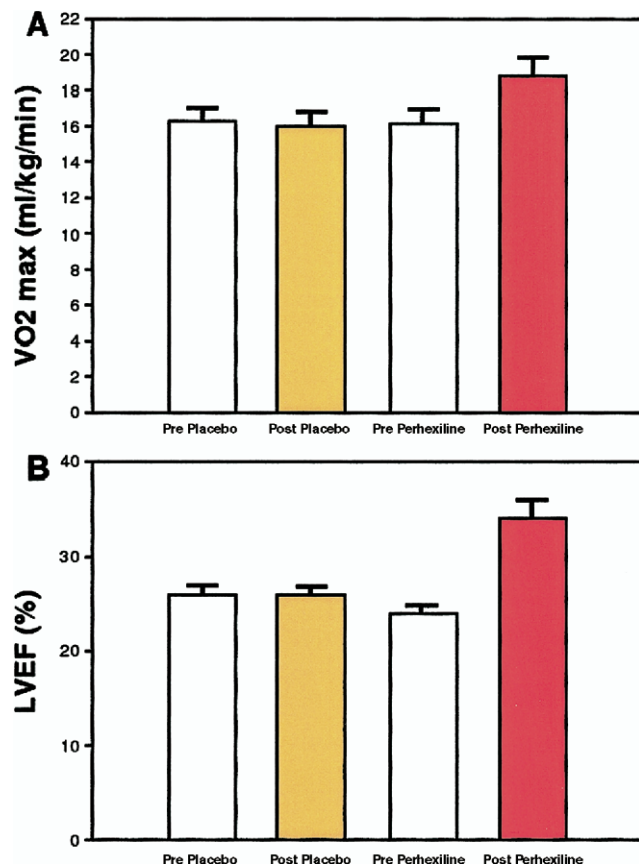


Figure 8. Effect of perhexiline treatment on peak exercise oxygen consumption (VO₂ max) and left ventricular ejection fraction (LVEF) in congestive heart failure patients. *p* < 0.001 in both cases. Reproduced with permission (134).

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