

EDITORIAL COMMENT

Precision Medicine for Heart Failure

Back to the Future*

Arthur M. Feldman, MD, PhD



For nearly a half century, the primary focus of pharmacological development for the treatment of heart failure with reduced ejection fraction (HFrEF) has been the canonical receptor-G protein-adenylyl cyclase signaling system (1-4) and the accessory proteins that modify signaling by hydrolyzing cyclic adenosine monophosphate (cAMP) (phosphodiesterase), desensitizing the receptor to further catecholamine stimuli (G protein receptor kinases, or GRKs) (5), uncoupling the phosphorylated receptor from the G protein, and targeting it for internalization (β -arrestin) (6) or coupling the β -adrenergic receptor (β -AR) and the L-type Ca^{2+} channel (Bcl2-associated anthranogene 3, or BAG3) (7) (Figure 1). Maladaptive changes in the constituents of this signaling pathway are pathognomonic for HFrEF: a decrease in both β_1 -AR density and mRNA (8); uncoupling of β_1 -AR and β_2 -AR from downstream signaling; diminished G protein function (9); diminished levels of BAG3 (10); and an increase in GRK2 mRNA and in kinase activity (11,12).

The β -AR-Gs-AC signaling pathway was an early therapeutic target for patients with HFrEF; however, long-term β -AR stimulation proved toxic. Seeking an alternative approach to targeting the β -AR, scientists synthesized a compound (amrinone) with potent inotropic properties due to increased cAMP production secondary to inhibition of phosphodiesterase 3 (PDE3) (13). Milrinone, a more potent derivative of amrinone, showed similar hemodynamics when

administered intravenously (14). However, clinical trials of oral milrinone at a relatively high dose (40 mg/day) raised substantive concerns about its long-term use due to a 28% increase in mortality from all causes (15). Similarly, a comparison of oral milrinone, digoxin, and their combinations found that milrinone significantly increased exercise tolerance and reduced the frequency of substantial HF symptoms; however, it offered no advantage over digoxin (16). And finally, a 48-h infusion of milrinone failed to affect the length of the hospital stay, subsequent readmissions, or days in hospital (17). These negative results caused investigators to reassess the usefulness of inotropic agents and contributed to a shift to inhibiting β -adrenergic signaling— β -blockers having marked benefits in HFrEF.

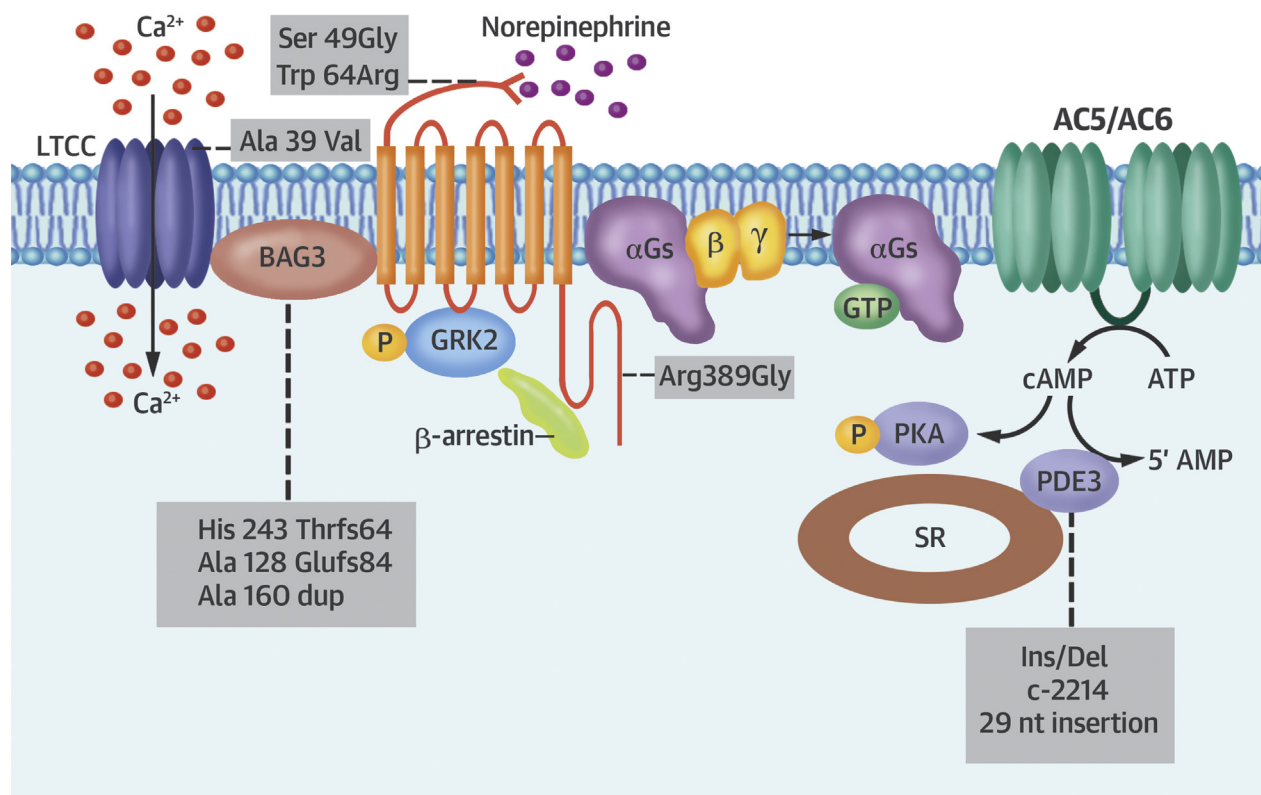
In addition to preventing the adverse biological effects of excessive adrenergic signaling, β -blockers also reverse some of the desensitization phenomena in the failing heart (18). This led investigators to theorize that a therapeutic strategy that combined a positive inotrope with a β -blocker might be beneficial in HFrEF (19). The rationale for this approach was that a PDE3I working beyond the level of receptor blockade would correct a fundamental molecular defect in the failing heart—decreased cAMP within the sarcoplasmic reticulum compartment—whereas β -blockade would inhibit adverse upstream signaling.

To test this hypothesis, 2 separate clinical trials were undertaken with the PDE3 inhibitor (PDE3I) enoximone: the ESSENTIAL (Studies of Oral Enoximone Therapy in Advanced Heart Failure) 1 and 2 trials were carried out in Europe and the United States, respectively. Low-dose enoximone proved safe, but the pre-defined primary outcomes were not achieved. Important differences were seen between the ESSENTIAL-1 and ESSENTIAL-2 trials: there were more women and more minority enrollees

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FIGURE 1 Schematic Representation of the β -AR-Gs Protein-AC Signaling System



Boxes show selected common (>1%) genetic variants that modify the function of the indicated component. AC = adenylyl cyclase; α GS = alpha guanine nucleotide binding protein; ATP = adenosine triphosphate; β = guanine nucleotide binding protein beta subunit; BAG3 = Bcl2-associated anthanogene 3; β -AR = beta-adrenergic receptor; GRK = G protein receptor kinase 2; Gs α = guanine nucleotide-binding protein alpha subunit; Ins/Del = insertion/deletion; LTCC = L-Type Ca^{2+} channel; nt = nucleotide; p = phosphate; PDE3 = phosphodiesterase 3; PKA = protein kinase A; SR = sarcoplasmic reticulum; γ = guanine nucleotide binding protein gamma subunit.

in the ESSENTIAL-1 trial, suggesting that different populations might have varying responses to a PDE3I (20). Additionally, African-American patients had a lower 60-day mortality and better overall clinical outcomes in unadjusted analysis (21). Amrinone also showed variable effects on vasodilation and inotropy across different HFrEF patients enrolled in an early study of amrinone (22). In aggregate, these results suggested that genetic variants might alter response to PDEIs in unique populations.

Regardless of whether positive inotropes including PDE3Is are beneficial or harmful to the natural history of HFrEF, they remain a necessary component of the therapeutic armamentarium of Stage D heart failure. For example, the INTERMACs registry (Interagency Registry for Mechanically Assisted Circulatory Support) reported that 29% of Stage D patients were “stable but inotrope-dependent,” supporting the

need for a safer inotrope or more optimal use of current agents (23).

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In this issue of the *Journal*, Sucharov et al. (24) report the presence of a 29-nucleotide insertion in the promoter region of the human *PDE3A* gene (c.-2214) that includes an ATF3 binding site (25). When ATF3 binds the insertion domain of the promoter, it inhibits transcription promoted by a downstream cAMP response element (CRE). Administration of a PDE3I leads to an increase in cAMP, which in turn drives the subsequent expression and enzyme activity of PDE3. In the absence of the insertion (the deletion-Del-allele), this increase in PDE3A activity will cancel the effect of the PDE3I and may account for tolerance or even tachyphylaxis to the administered PDE3I. Heart failure patients who are

homozygous for the insertion would be expected to have a more robust and sustained response to a PDE3I, whereas individuals homozygous for the deletion would be expected to develop tolerance. A prospective clinical trial is needed to confirm this hypothesis; however, this finding opens the door to the possible use of a PDE3I with a β -blocker in patients with an insertion homozygous or possibly heterozygous genotype.

The results of Sucharov et al. (24) are consistent with the growing recognition that genetic variants in genes encoding proteins of the β -AR-Gs-AC signaling cascade can modify outcomes and response to pharmacological therapy. For example, single nucleotide polymorphisms common in β_1 -AR or β_2 -AR (26) alter function and may exhibit specificity for therapeutic agents (27,28). For example, the β_1 -AR-Arg389Arg genotype does not influence response to metoprolol (29), but rather enhances response to the β -blocker bucindolol when compared with patients in the Gly carrier subgroup (30). Genetic variations in G protein β -3 subunit (31) or NOS3 (32) predict enhanced benefit of fixed-dose isosorbide dinitrate and hydralazine in HFREF patients of African ancestry, and genetic

variants in BAG3 found in individuals of African ancestry with HFREF are associated with a worse outcome (33). Large deletions or truncations in BAG3 are also causative of a dilated cardiomyopathy (34).

The approach that Sucharov et al. (24) used to interrogate the biology of the PDE3A genetic variant, including expression screening, DNA sequencing, and microsomal fractions from failing human heart, is novel. This in vitro approach may prove useful for evaluating what will undoubtedly be an increasing number of genetic variants as studies such as the National Institutes of Health-sponsored "All of Us," which plans to genotype 1 million Americans, gain traction (35). Nonetheless, prospective studies in humans will also be needed to confirm the biology observed in vitro before precision medicine can become a reality.

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REFERENCES

- Sutherland EW. Studies on the mechanism of hormone action. *Science* 1972;177:401-8.
- Rodbell M. Nobel lecture. Signal transduction: evolution of an idea. *Biosci Rep* 1995;15:117-33.
- Gilman AG. Nobel lecture. G proteins and regulation of adenyl cyclase. *Biosci Rep* 1995;15: 65-97.
- Lefkowitz RJ. A brief history of G-protein coupled receptors (Nobel lecture). *Angew Chem Int Ed Engl* 2013;52:6366-78.
- Traynham CJ, Hullmann J, Koch WJ. Canonical and non-canonical actions of GRK5 in the heart. *J Mol Cell Cardiol* 2016;92:196-202.
- Noor N, Patel CB, Rockman HA. Beta-arrestin: a signaling molecule and potential therapeutic target for heart failure. *J Mol Cell Cardiol* 2011;51:534-41.
- Feldman AM, Gordon J, Wang J, et al. BAG3 regulates contractility and Ca(2+) homeostasis in adult mouse ventricular myocytes. *J Mol Cell Cardiol* 2016;92:10-20.
- Bristow MR, Feldman AM. Changes in the receptor-G protein-adenyl cyclase system in heart failure from various types of heart muscle disease. *Basic Res Cardiol* 1992;87 Suppl 1:15-35.
- Feldman AM, Cates AE, Veazey WB, et al. Increase of the 40,000-mol wt pertussis toxin substrate (G protein) in the failing human heart. *J Clin Invest* 1988;82:189-97.
- Myers VD, McClung JM, Wang J, et al. The multifunctional protein BAG3: a novel therapeutic target in cardiovascular disease. *J Am Coll Cardiol Basic Trans Science* 2018;3:122-31.
- Ungerer M, Bohm M, Elce JS, Erdmann E, Lohse MJ. Altered expression of beta-adrenergic receptor kinase and beta 1-adrenergic receptors in the failing human heart. *Circulation* 1993;87:454-63.
- Ungerer M, Parruti G, Bohm M, et al. Expression of beta-arrestins and beta-adrenergic receptor kinases in the failing human heart. *Circ Res* 1994;74:206-13.
- Alousi AA, Farah AE, Leshner GY, Opalka CJ Jr. Cardiotonic activity of amrinone-Win 40680 [5-amino-3,4'-bipyridine-6(1H)-one]. *Circ Res* 1979;45:666-77.
- Baim DS, McDowell AV, Cherniles J, et al. Evaluation of a new bipyridine inotropic agent-milrinone-in patients with severe congestive heart failure. *N Engl J Med* 1983;309:748-56.
- Packer M, Carver JR, Rodeheffer RJ, et al. Effect of oral milrinone on mortality in severe chronic heart failure. The PROMISE Study Research Group. *N Engl J Med* 1991;325:1468-75.
- DiBianco R, Shabetai R, Kostuk W, Moran J, Schlant RC, Wright R. A comparison of oral milrinone, digoxin, and their combination in the treatment of patients with chronic heart failure. *N Engl J Med* 1989;320:677-83.
- Felker GM, Benza RL, Chandler AB, et al. Heart failure etiology and response to milrinone in decompensated heart failure: results from the OPTIME-CHF study. *J Am Coll Cardiol* 2003;41:997-1003.
- Heilbrunn SM, Shah P, Bristow MR, Valentine HA, Ginsburg R, Fowler MB. Increased beta-receptor density and improved hemodynamic response to catecholamine stimulation during long-term metoprolol therapy in heart failure from dilated cardiomyopathy. *Circulation* 1989;79:483-90.
- Lowes BD, Shakar SF, Metra M, et al. Rationale and design of the enoximone clinical trials program. *J Card Fail* 2005;11:659-69.
- Metra M, Eichhorn E, Abraham WT, et al. Effects of low-dose oral enoximone administration on mortality, morbidity, and exercise capacity in patients with advanced heart failure: the randomized, double-blind, placebo-controlled, parallel group ESSENTIAL trials. *Eur Heart J* 2009;30:3015-26.
- Echols MR, Felker GM, Thomas KL, et al. Racial differences in the characteristics of patients admitted for acute decompensated heart failure and their relation to outcomes: results from the OPTIME-CHF trial. *J Card Fail* 2006;12:684-8.
- Konstam MA, Cohen SR, Weiland DS, et al. Relative contribution of inotropic and vasodilator effects to amrinone-induced hemodynamic improvement in congestive heart failure. *Am J Cardiol* 1986;57:242-8.
- Kirklin JK, Naftel DC, Kormos RL, et al. Third INTERMACS annual report: the evolution of destination therapy in the United States. *J Heart Lung Transplant* 2011;30:115-23.
- Sucharov CC, Nakano SJ, Slavov D, et al. A PDE3A promoter polymorphism regulates cAMP-induced transcriptional activity in failing human myocardium. *J Am Coll Cardiol* 2019;73:1173-84.
- Miyamoto SD, Sucharov CC, Woulfe KC. Differential response to heart failure medications in children. *Prog Pediatr Cardiol* 2018;49:27-30.

26. Taylor MR, Bristow MR. The emerging pharmacogenomics of the beta-adrenergic receptors. *Congest Heart Fail* 2004;10:281-8.
27. Turki J, Lorenz JN, Green SA, Donnelly ET, Jacinto M, Liggett SB. Myocardial signaling defects and impaired cardiac function of a human beta 2-adrenergic receptor polymorphism expressed in transgenic mice. *Proc Natl Acad Sci U S A* 1996;93:10483-8.
28. Mason DA, Moore JD, Green SA, Liggett SB. A gain-of-function polymorphism in a G-protein coupling domain of the human beta1-adrenergic receptor. *J Biol Chem* 1999;274:12670-4.
29. White HL, de Boer RA, Maqbool A, et al. An evaluation of the beta-1 adrenergic receptor Arg389Gly polymorphism in individuals with heart failure: a MERIT-HF sub-study. *Eur J Heart Fail* 2003;5:463-8.
30. Liggett SB, Miale-Perez J, Thaneemit-Chen S, et al. A polymorphism within a conserved beta(1)-adrenergic receptor motif alters cardiac function and beta-blocker response in human heart failure. *Proc Natl Acad Sci U S A* 2006;103:11288-93.
31. McNamara DM, Taylor AL, Tam SW, et al. G-protein beta-3 subunit genotype predicts enhanced benefit of fixed-dose isosorbide dinitrate and hydralazine: results of A-HeFT. *J Am Coll Cardiol HF* 2014;2:551-7.
32. McNamara DM, Tam SW, Sabolinski ML, et al. Endothelial nitric oxide synthase (NOS3) polymorphisms in African Americans with heart failure: results from the A-HeFT trial. *J Card Fail* 2009;15:191-8.
33. Myers VD, Gerhard GS, McNamara DM, et al. Association of variants in BAG3 with cardiomyopathy outcomes in African American individuals. *JAMA Cardiol* 2018;3:929-38.
34. Dominguez F, Cuenca S, Bilinska Z, et al. Dilated cardiomyopathy due to BLC2-associated athanogene 3 (BAG3) mutations. *J Am Coll Cardiol* 2018;72:2471-81.
35. National Institutes of Health. All of Us Research Program. Available at: <https://allofus.nih.gov/about>. Accessed December 2, 2018.

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