EDITORIAL COMMENT

Potential of AT₁-R-Biased Agonists in Pediatric Heart Failure*

J. David Port, PhD

The pharmacological treatment of heart failure (HF) in adults, especially those with chronic HF with reduced ejection fraction (HFrEF), is well-worn territory (1). The use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ARBs), beta-adrenergic receptor blockers, aldosterone antagonists, and diuretic agents are the mainstays of pharmacological management. However, this is not to say that current therapeutic modalities are either optimal or that newer avenues need not be explored. For example, it is almost certain that pharmacogenetics will result in increased response rates to several drug classes in selected population. However, pharmacogenetics does not obviate the issue of nonresponders.

In contrast to adults, there are generally considered to be fewer evidence-based treatment options for HF in pediatric populations. Although pediatric HF is far less prevalent than adult HF (estimated at about 1:100,000), therapy for pediatric HF is considered an unmet need. In a recent review, Del Castillo et al. (2) summarized the currently available options for pediatric patients with HF, including several of those available to adults. These include inotropes such as dopamine, dobutamine, and epinephrine, with the standard caveats of increased heart rate and myocardial oxygen consumption. Also included are

angiotensin-converting enzyme inhibitors and ARBs. However, more recently, phosphodiesterase-3 inhibitors (PD3-I) such as milrinone have shown promise. So too have more novel agents, including the I_f current inhibitor ivabradine, gaining effectiveness by virtue of its ability to slow heart rate. Most recently, on the basis of the success of the PARADIGM-HF (Prospective Comparison of ARNI With ACEI to Determine the Impact on Global Mortality and Morbidity in Heart Failure) trial in adults, in which the ARB valsartan was used in fixed-dose combination with the neprilysin inhibitor sacubitril, the PANORAMA-HF (Study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of LCZ696 Followed by a 52-Week Study of LCZ696 Compared With Enalapril in Pediatric Patients With Heart Failure) study examined this same combination compared with enalapril in pediatric patients with HF due to systemic left ventricular (LV) systolic dysfunction (3). In 2019, the results of the trial led the U.S. Food and Drug Administration to extend approval of sacubitril/valsartan for pediatric HF.

One stark difference between adult and pediatric HF populations is the evidence-based efficacy of beta-blockers. To date, Shaddy et al. (4) have published the most definitive study demonstrating that the beta-blocker carvedilol is not particularly efficacious in pediatric HF. Although precedent setting, the carvedilol trial had limitations, including that it may have been underpowered and underdosed, and it included a cohort of patients with a broad spectrum of etiologies, including the single-ventricle congenital anomaly, thus complicating its interpretation with respect to specific subpopulations (5).

Angiotensin AT_1 receptors (AT_1-Rs) are canonical G protein–coupled receptors linked to $G_{q/11}$ and subsequently to PIP_2 hydrolysis, resulting in activation of serine/threonine kinase, protein kinase C, and an increase in intracellular calcium via the IP_3 receptor.

Thus, AT$_1$-R agonists, in addition to being profound vasoconstrictors, are, in a model system–dependent manner, positive inotropic agents. However, much like β-adrenergic receptors (β-AR), AT$_1$-Rs can be noncanonically (biased) coupled to β-arrestin signaling (6). In young mice, the AT$_1$-R/β-arrestin-2 complex has been shown to activate L-type calcium channels via casein kinase 2 (7), producing a positive inotropic effect.

In this issue of *JACC: Basic to Translational Science*, Kashihara et al. (8) examine the β-arrestin-biased angiotensin receptor (AT$_1$-R) agonist TRV027 (Trevena, King of Prussia, Pennsylvania) as a potential therapeutic agent in models of pediatric HF. Herein, the investigators demonstrate that "TRV027 causes a neonatal-specific, long-acting positive inotropic effect with minimum effect on heart rate, oxygen consumption, reactive oxygen species production, and aldosterone secretion." Thus, they posit that TRV027 could be used as an inotropic vasodilator specific for pediatric HF. It should be noted that on the basis of the aforementioned pharmacological properties, a clinical trial with TRV027 was conducted in adults with acute HF (BLAST-AHF [Biased Ligand of the Angiotensin Receptor Study in Acute Heart Failure]). Unfortunately, neither the primary nor the secondary endpoint was met, with the result that TRV027 was deemed to be clinically safe but not effective in adults with acute HF (9). Kashihara et al. (8) convincingly demonstrate in neonatal mice that TRV027 significantly increases left ventricular ejection fraction (LVEF) and that in the presence of atropine, propranolol alone or in combination with the α$_1$ adrenergic receptor blocker prazosin does not decrease this effect. Conversely, the positive inotropic effect of TRV027 was blocked by the ARB candesartan. Concordant with a neonatal-specific effect, the investigators demonstrate that both angiotensin II (AngII) and TRV027 increase LVEF in neonatal mice, whereas AngII but not TRV027 decreases LVEF in adult mice (see their Supplemental Figure 2). Although not explored directly, it is possible that the AngII-mediated decrease in LVEF in adult mice is secondary to increased afterload secondary to increased vasoconstriction, thereby decreasing left ventricular emptying. At a mechanistic level, the investigators demonstrate that in both neonatal mouse ventricular cardiac myocytes and human induced pluripotent stem cells differentiated into cardiac myocytes (hiPSC-CMs), TRV027 dramatically increases $\Delta F/F_0$, a measurement of calcium influx, without affecting time to peak tension (TTP). Furthermore, in a transgenic mouse model of congenital dilated cardiomyopathy, in which a mutant form of cardiac troponin C is expressed (cTnTΔK210), TRV027 was shown to increase LVEF.

The findings of Kashihara et al. (8) suggest substantial promise for a novel new therapy in pediatric HF, but they should be interpreted with the following caveats in mind. It is certainly encouraging that an AT$_1$-R-biased ligand that produces a sustained inotropic effect without unduly elevating myocardial oxygen consumption (MVO2) and without several of the other less salutary effects of G$_q$-coupled receptors, in general. In particular, it would be interesting to compare TRV027 with any number of other agents, including the combination of sacubitril/valsartan or the PD3-I milrinone, in the cTnTΔK210 cardiomyopathy model. Although not a perfect recapitulation of pediatric HF, it could be argued that the transgenic model may be closer to the clinical condition than either cultured neonatal ventricular cardiomyocytes or hiPSC-CMs. In the case of the former, although neonatal mouse ventricular cardiac myocytes are a neonatal model, there are distinct and manifest differences in cardiac signaling between rodents and humans. Given that hiPSC-CMs display an immature, fetal-like cardiomyocyte structural and electrophysiological phenotype, one could argue that their demonstrated immature nature (nonterminally differentiated phenotype) would be an appropriate experimental model system; however, many other aspects of induced pluripotent stem cells (iPSCs) may be limiting in translating the model to pediatric humans.

In summary, the current paper by Kashihara et al. (8) demonstrates an innovative approach to finding potential solutions to an unmet need. Although TRV027 does not appear to be the agent of choice for acute HF in adults, the unique gene expression patterns and signaling pathways in pediatric hearts (10) have the potential to yield surprising results.

AUTHOR DISCLOSURES

ADDRESS FOR CORRESPONDENCE: Dr. J. David Port, Department of Medicine, Division of Cardiology, and Department of Pharmacology, University of Colorado School of Medicine, 4200 East Ninth Avenue, Denver, Colorado 80045. E-mail: david.port@ucdenver.edu.

REFERENCES

1. Bristow MR, Port JD, Kelly RA. Treatment of heart failure: pharmacological methods. In: Braunwald E, Zipes DP, Libby P, editors. Heart Disease: A Textbook of Cardiovascular Medicine. 6th ed. Orlando, Florida: W.B. Saunders, 2001: 562-99.

2. Del Castillo S, Shaddy RE, Kantor PF. Update on pediatric heart failure. Curr Opin Pediatr 2019;31: 598-603.

3. Shaddy R, Canter C, Halnon N, et al. Design for the sacubitril/valsartan (LCZ696) compared with enalapril study of pediatric patients with heart failure due to systemic left ventricle systolic dysfunction (PANORAMA-HF study). Am Heart J 2017;193:23-34.

4. Shaddy RE, Boucek MM, Hsu DT, et al. for the Pediatric Carvedilol Study Group. Carvedilol for children and adolescents with heart failure: a randomized controlled trial. JAMA 2007;298: 1171-9.

5. Miyamoto SD, Sucharov CC, Woulfe KC. Differential response to heart failure medications in children. Prog Pediatr Cardiol 2018;49:27-30.

6. Port JD, Sucharov CC, Bristow MR. Adrenergic receptor signaling in heart failure. In: Felker GM, Mann DL, editors. Heart Failure: A Companion to Braunwald's Heart Disease. 4th ed. Philadelphia, pulmonary artery: Elsevier, 2020:91-102.

7. Kashihara T, Nakada T, Kojima K, Takeshita T, Yamada M. Angiotensin II activates CaV 1.2 Ca^{2+} channels through beta-arrestin2 and casein kinase 2 in mouse immature cardiomyocytes. J Physiol 2017;595:4207-25.

8. Kashihara T, Kawagishi H, Nakada T, et al. β-Arrestin-biased AT₁ agonist TRV027 causes a neonatal-specific sustained positive inotropic effect without increasing heart rate. J Am Coll Cardiol Basic Trans Science 2020;5:1057-69.

9. Pang PS, Butler J, Collins SP, et al. Biased ligand of the angiotensin II type 1 receptor in patients with acute heart failure: a randomized, double-blind, placebo-controlled, phase IIB, dose ranging trial (BLAST-AHF). Eur Heart J 2017;38: 2364-73.

10. Tatman PD, Woulfe KC, Karimpour-Fard A, et al. Pediatric dilated cardiomyopathy hearts display a unique gene expression profile. JCI Insight 2017;2:e94249.