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A novel way of modification of AT₁ angiotensin receptors to alleviate pediatric heart failure

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The treatment of pediatric heart failure (PHF) is a long-standing unmet medical need because of a great variety of its pathogenesis and pathophysiology rendering large-scale clinical trials difficult. In order to overcome this issue, we conducted basic experiments and found that cardiac AT₁ angiotensin receptors (AT₁R) and their downstream β -arrestin 2 play a prosurvival role in the pre-weaning period of mice. Specifically, angiotensin II activated L-type Ca²⁺ channels through the AT₁R/ β -arrestin 2 pathway in murine cardiac myocytes (CM) before weaning. A peptidyl β -arrestin-biased AT₁R agonist (BBA), TRV027 significantly increased the peak twitch Ca²⁺ transients in mouse neonatal CMs as well as human iPS cell-derived CMs with fetal to neonatal phenotype. TRV027 evoked a characteristic, strong, long-lasting positive inotropic effect (~8 h) in pre-weaning mice without little increasing heart rate, cardiac oxygen consumption, ROS production, and aldosterone secretion. Finally, daily administration of TRV027 but not an AT₁R antagonist from postnatal day 1 significantly improved the survival rate of knock-in mice bearing a genetic mutation causing human congenital dilated cardiomyopathy. In this symposium, we will refer to these and other lines of evidence indicating that PHF before weaning should be treated with BBA but not ARB.