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RAAS Inhibitors for Right Ventricular Dysfunction in Tetralogy of Fallot: Quo Vadis?

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Tetralogy of Fallot (TOF) is the most common form of cyanotic congenital heart disease, occurring in 1 in ~2500 births and comprising ~6% of all forms of critical congenital heart disease. Named for Étienne-Louis Arthur Fallot, who described the "blue malady" in 1888, the classic "tetralogy" consists of a ventricular septal defect, pulmonary outflow tract obstruction, aortic overriding, and right ventricular (RV) hypertrophy.[1] After repair, RV dilation and dysfunction may be produced, in part, by ischemia-reperfusion injury, surgical scarring, RV volume overload from pulmonary regurgitation, and residual RV outflow obstruction. Pulmonary valve replacement has not been shown to improve RV function, arrhythmias, or other outcomes, despite improving pulmonary regurgitation and reducing RV volumes.[2] In an attempt to halt or reverse the progression from compensated RV function to RV failure, treatment with renin-angiotensin-aldosterone system (RAAS) inhibitors has crept into the practice of treatment of adults with TOF and other congenital heart defects associated with RV dysfunction.

However, little is known about the RV molecular response to stress and its progression from a compensated state to failure.[3] Standard left ventricular heart failure drugs (e.g., β–blockers, angiotensin converting enzyme [ACE] inhibitors, angiotensin II receptor blockers [ARBs]) have shown mixed results in their ability to improve function or survival in patients with systemic RV failure in the setting of congenital heart disease,[4–7] suggesting fundamental differences in the mechanisms of right vs. left ventricular failure. Changes in shape, structure and loading conditions between the right and left ventricles were once thought to be the primary reason for these differences.[8] However, it is now appreciated that the right and left ventricle diverge early in development, before afterload differences become operative. The first and second heart fields lead to the differentiation of left and right ventricular cardiomyocytes during early development, with subsequent chamber-specific differences in cell signaling and Ca^{2+} handling, suggesting subtle but critical differences between the two ventricles at the cellular level as well.[9] Data from animal models of RV stress have shown that the two ventricles exhibit similar alterations in genes regulating

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extracellular matrix and cytoskeletal remodeling. However, there are important differences between the left ventricle and right ventricle in genes regulating reactive oxygen species production and antioxidant protection, angiogenesis, energy production and mitochondrial function.[10] These results confirm differences at the cellular and molecular level in the mechanisms leading to failure of the left vs. right ventricle that could impact the effectiveness of the drugs used to treat heart failure.

In left ventricular failure, neurohormonal activation via the RAAS is a positive mediator of cardiac fibrosis. The RAAS was also shown to be activated in RV failure in the setting of pulmonary hypertension.[11] Treatment with losartan decreased hypertrophy and restored normal RV-pulmonary arterial coupling in these patients.[12] In contrast, there are conflicting results on ACE inhibition in pulmonary hypertension patients, thought to be related to breakthrough aldosterone signaling. In preclinical models of RV afterload, treatment with losartan led to an improvement in fibrosis and cardiac hypertrophy.[13]

In this issue of Circulation, Bokma *et al.* show a lack of efficacy of RAAS inhibition in patients with repaired TOF.[14] The REDEFINE trial was a multicenter, prospective, randomized, double-blind, placebo-controlled study of losartan, 150 mg/day, vs. placebo in 95 adults with TOF and RV dysfunction, defined as an RV ejection fraction < 50%. Subjects with severe pulmonary valvular stenosis or regurgitation were excluded. The primary outcome was the change in RV ejection fraction by cardiac MRI between baseline and 18–24 months. Statistical analyses were performed according to intention-to-treat. The trial found no significant benefit of losartan treatment on RV ejection fraction, or on any of the secondary endpoints in this trial. Moreover, adverse effects necessitated discontinuation of losartan in four of 47 patients (9%), two of whom had kidney toxicity and two with liver dysfunction. Although small and underpowered to explore important subgroups, this trial is the largest to be published, and addresses an important problem in the burgeoning population of adults with congenital heart disease.

The REDEFINE trial should be interpreted in light of some limitations. It was powered for 90 subjects, and fewer patients were treated per protocol. Nonetheless, the effect size was sufficiently small that inclusion of a greater number of subjects would have been highly unlikely to have changed the conclusion that losartan did not have a beneficial effect on RV ejection fraction in the overall group with mild right ventricular dysfunction. Moreover, only subjects with the most severe pulmonary regurgitation or stenosis were excluded. It is possible that lesser but nonetheless important residual hemodynamic lesions may have contributed to the variance in RV outcomes. Moreover, marked right bundle branch block is common in repaired TOF and can lead to RV electromechanical dysynchrony.[15] The effects of moderate pulmonary regurgitation or stenosis, as well as of electromechanical dyssynchrony, may have diminished the effect of RAAS inhibition on RV function.

Based upon the results of the REDEFINE trial, the authors conclude that losartan and agents promoting RAAS inhibition should not be routinely prescribed for asymptomatic patients with mild RV failure after repair of TOF. Whereas this is true for the 18- to 24-month follow-up time point of this study, it is not known whether RAAS inhibition prior to the development of RV dysfunction would be beneficial. The authors saw an improvement in

RV ejection fraction in a subgroup of patients with non-restrictive physiology together with incomplete remodeling, as defined by QRS fragmentation on ECG. This subgroup analysis was not pre-specified and hence analyses must be viewed as exploratory. However, the findings could suggest that once RV fibrosis has developed, as the molecular correlate of restrictive physiology, it cannot be reversed with ARBs, but that institution of ARBs prior to the development of fibrosis might be beneficial. It is also possible that longer-term administration of ARBs might be required to limit the slow progression of RV fibrosis in these patients. Because the extent of fibrosis was not evaluated in the study protocol for cardiac MRI, this explanation remains speculative.

Further questions remain. It is uncertain whether RAAS inhibition might have been beneficial in those with more severe RV dysfunction and/or with heart failure symptoms greater than NYHA class 2 (the sickest group in the current study). Selection of more symptomatic patients with worse RV function but lesser degrees of pulmonary stenosis and regurgitation could have increased the effect size of treatment. It remains uncertain whether ARBs would be more beneficial in patients with volume overload, compared with pressure overload; patients with severe pulmonary regurgitation, a common sequel in patients with TOF repaired with a trans-annular patch, were not included in the current study. Another unanswered question is whether longer-term RAAS inhibition (>5 years), compared with 18 to 24 months in the current trial, would be more effective at preventing progressive RV dysfunction. Finally, the results of the REDEFINE cannot be extrapolated to RV failure in the setting of a systemic RV (e.g. hypoplastic left heart syndrome, L-transposition of the great arteries), in which ARB-induced afterload reduction may play a role.

In summary, the REDEFINE trial has shown that ARBs have little role in preventing progression of right heart failure in patients with TOF and mild right ventricular dysfunction. Indeed, the degree to which the RAAS is altered in CHD patients with RV failure remains to be determined, as reliance on data from studies on left ventricular failure can be misleading. Further research is needed to elucidate the basic mechanisms of RAAS activation in the stressed right ventricle, and to study circulating biomarkers of RAAS activation and of RV fibrosis. The results of such studies should be completed before we close the door on the possibility that RAAS inhibition can be beneficial for some patients with RV failure in repaired TOF. New animal models of RV failure simulating residual lesions seen after CHD and new models of pulmonary hypertension are beginning to unravel the molecular mechanisms of RV failure. These studies may pave the way toward developing RV-specific heart failure therapies and designing future clinical trials.

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