Right Ventricle: Wrong Targets?

Another Blow for Pharmacotherapy in Congenital Heart Diseases

Running title: Roche et al.; Right ventricle - wrong target?

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Journal Subject Codes: [11] Other heart failure; [41] Pediatric and congenital heart disease, including cardiovascular surgery

Key words: angiotensin converting enzyme inhibitors; congenital heart disease; Editorials; transposition of great vessels
Pharmacotherapeutic algorithms developed to treat heart failure in adults with acquired heart disease have often provided the template for treatment of ventricular dysfunction or heart failure symptoms in patients with underlying congenital heart disease. Superficially at least, this is not completely irrational, as ‘congenital’ patients often demonstrate similar levels of functional incapacity and a neurohormonal profile similar to that seen in ‘acquired heart failure’\(^1\). Scratch beneath the surface however, and the situation is much less clear. Systolic failure as the primary manifestation and driver of disease progression is rather rare, fundamentally the circulation in these patients is often quite different, and the rate of functional decline and adverse events tends to be substantially lower than that observed in the major studies of beta blockade and modifiers of the rennin-angiotensin system in acquired heart failure. Consequently there is an ever-increasing catalog of, albeit small, randomized controlled trials that have failed to show a significant clinical benefit of these therapies in congenital heart disease\(^2-6\). The study by van der Bom and colleagues, examining the role of valsartan in patients with a systemic right ventricle (RV) and published in this issue of *Circulation*\(^7\) can now be added to that list.

In congenital heart disease with a biventricular physiology, there are two main situations where the circulation depends on the RV’s ability to drive blood through the systemic vascular bed. These are transposition of the great arteries (TGA) after an atrial-level surgical correction and congenitally corrected transposition of the great arteries (ccTGA). In both settings the RV is positioned beneath the aortic valve and is at high risk for long-term failure, the incidence of which increase with age. In each subgroup systemic RV dysfunction usually precedes the onset of clinical heart failure and once symptoms do occur, they are a strong predictor of mortality\(^8\). By their mid-40s, over half of patients with ccTGA exhibit moderate-to-severe RV dysfunction and a similar proportion have developed clinical heart failure, outcomes that are strongly
associated with the presence and severity of tricuspid valve regurgitation\(^9\). The incidence of systemic RV dysfunction is similar for patients who have undergone atrial redirection procedures for TGA\(^10\). However, in this cohort clinical heart failure is somewhat less common and RV dysfunction predicts the risk of sudden cardiac death, which is the primary driver of mortality\(^8,11,12\). While the full arsenal of conventional heart failure therapy (lifestyle modification, medication, electrical therapies, transplant and ventricular assist device) can and have been employed in patients with a systemic RV, a lack of data specific to this population makes it difficult to know which strategy to adopt and who to target. Out of a desire to do something that might (even theoretically) help, when these patients develop more than mild systemic RV dysfunction or symptomatic heart failure, physicians often initiate medical treatment proven to be effective against heart failure in structurally normal hearts, usually an ACEi or ARB. A scientific understanding of not only the pathophysiology of functional decline, but also of the potential for such therapies to modify it underpins the success of such strategies in acquired heart failure. Unfortunately, for patients with a systemic RV, there is circumstantial evidence to suggest that neither the pathophysiology, nor the mechanism of action of treatment will be conducive of therapeutic success. For example, after atrial redirection procedures it appears that, consequent on the ‘conduit function’ of the baffles, it is a failure of atrioventricular coupling, with an inability to increase stroke volume with exercise or dobutamine stress\(^13,14\) which limits stroke volume and cardiac output responses. While this is demonstrably not an issue for those with ccTGA (who have normal stroke volume responses to exercise and dobutamine stress\(^15\)) evidence for primary RV myocardial failure is similarly lacking. Indeed, in an analysis of long-term outcomes in patients with ccTGA, those devoid of significant tricuspid (systemic) valve insufficiency remained free heart failure for decades\(^16\). Not only does this suggest that early
attention to valve function might be a better therapeutic target in the latter group, but on the basis of their pathophysiologic substrates, afterload reduction as a therapeutic target may be flawed for either group, at least in the short-term.

In this issue of Circulation, Van der Bom and colleagues present a study that furthers our understanding of heart failure management in adult congenital patients with a systemic RV. The investigators are to be congratulated for conducting a 3-year, prospective, multi-center, double-blind, placebo controlled trial of the angiotensin II type 1 receptor antagonist valsartan in patients with a systemic RV. This is no small achievement since well-designed trails in patients with congenital heart disease are notoriously difficult to complete\textsuperscript{17,18}. Although essentially a negative study, van der Bom et al’s work nonetheless provides an important message for clinical practice and also, once again, illustrates the complexities and challenges of studying patients with congenital heart disease.

Six centers in the Netherlands took part in the study and potential participants were identified from CONCOR, the Dutch national registry and DNA-bank of ACHD patients. Eighty-eight patients with a systemic RV in the setting of ccTGA or TGA after atrial redirection procedure were recruited and randomized in a 1:1 distribution to receive either placebo or 160mg valsartan twice a day for three years. Participants who were taking an ACEi prior to enrollment desisted for four weeks before the study began. Investigations were performed at baseline and as close to three years after enrollment as possible. The primary endpoint was RV ejection fraction (RVEF), measured by cardiac magnetic resonance imaging or computer tomography as determined by clinical factors such as the presence of a pacemaker. Valsartan was well tolerated and there were no excess adverse events int he valsartan group. At a mean follow-up of 3.2 years, RVEF remained unchanged in both the placebo patients (37.6±6.5% vs. 36.7 ±6.1%,
p=0.23) and those taking valsartan (34.9 ±7.4% vs. 35.1±9.6%, p=0.79) and the difference in RVEF between the two groups was not statistically significant. No statistical differences were found between the placebo and valsartan groups regarding changes in the degree of tricuspid regurgitation, parameters of exercise capacity, quality of life scores or neurohormonal activation during the course of the study and the groups showed no differences in the occurrence of clinical endpoints. Positive findings of the study relate to indices ventricular remodeling, which suggest valsartan may have tempered progression of RV dilatation and hypertrophy. However, only absolute values for these measurements are reported and it is unclear whether these findings would persist were the data presented in the more usual format, indexed for body surface area.

The investigators performed additional subgroup analyses and here the important finding was that in symptomatic patients RVEF and VO$_2$peak declined during follow up in the placebo group (36.9 ±8.8% vs. 33.6±7.5%, p<0.01 and 27.0±6.6ml/kg/min vs. 22.5±7.3ml/kg/min, p<0.01) whereas they remained unchanged in patients taking valsartan (33.4±9.6% vs. 34.8±10.9%, p=0.46 and 20.1±5.2ml/kg/min vs. 18.7±4.6ml/kg/min, p=0.58). As can be seen, both RVEF and VO$_2$ were lower at baseline in the valsartan patients however. The authors conclude that their data fails to support the routine use of losartan in asymptomatic patients with a systemic RV but that therapy might be more appropriate is specific subgroups, especially those with symptoms.

The current study is important because it is one of only three prospective trials testing the effect of pharmacological treatment in patients with a systemic RV$^{4-6}$. Moreover, it includes the largest number of patients studied to date and the longest duration of follow-up. Of the previous studies, two considered the effects of RAAS blockade$^{5,6}$. In a crossover study design, Dore et al. compared the effects of twice daily losartan 50mg and placebo in 29 adults with either ccTGA or Mustard baffle$^5$. After 15 weeks of treatment there were no differences in measures of exercise
capacity, neurohormonal activation, echocardiographically assessed ventricular function or tricuspid regurgitation. Therrien et al. studied the effects of ramipril therapy or placebo in 17 patients treated for one year using MRI to assess RVEF, a cardiopulmonary exercise test and the Minnesota Living with Heart Failure Questionnaire; again there were no benefits seen in the treatment group. Non-randomized studies of RAAS antagonism in the systemic RV have included few patients with limited follow-up (n=7 follow-up 8 weeks, n=14 follow-up 18 months, n=9 follow-up 1 year). Only Lester et al. found noted benefit after treatment and theirs was the smallest study with the shortest duration of follow-up. With clear methodological advantages, van der Bom et al. have confirmed and strengthened existing data, and the available evidence simply does not support the routine use of ACEi or ARBs in patients with a systemic RV.

It is time to ask whether the strength of this evidence is sufficient to dismiss potential theoretical benefits of ACEi and ARBs (reduction of fibrosis, inhibition of hypertrophy, reduction of sudden death) in this population and to change current clinical practice. Herein lies the problem with research in small and heterogenous patient groups. With the initial intent of recruiting >128 patients and using a multi-centre approach, van der Bom and colleagues only managed to enroll 88 study participants out of 323 potentially eligible candidates. Of these, only 62 both continued the study medication until completion and underwent final evaluation. Compare this to VA1-HeFt, which included 5010 patients with left ventricular dysfunction and found that 160mg of valsartan twice daily produced a 13% lower risk of the combined clinical end-point. The original power calculation for the present study suggested a minimum of 102 patients were required for 80% power to detect a difference in ejection fraction of 5.6%. It is therefore quite possible that van der Bom et al’s trial was simply underpowered to detect
clinically relevant effects of valsartan therapy. One suspects that this argument, and the desire to ‘do good’ may remain stimuli for clinicians to continue treating these patients with conventional heart failure medications. Indeed, almost 60% of over 500 Fontan patients studied by The Pediatric Heart Network were receiving ACEi24, despite the only randomized, placebo controlled, cross-over trial of their use showing reduced cardiac output response to exercise during active treatment3. Alternatively, congenital heart disease specialists might abandon their slavish pursuance of therapies developed for treatment of heart failure with a completely different morphologic and pathophysiologic substrate, and instead identify new and more directly relevant targets for intervention. At the very least, the time is ripe for funding agencies and researchers to re-aim their focus on development of novel therapeutic solutions.

Conflict of Interest Disclosures: None.

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2005;112:2411-2416.


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Circulation. published online December 17, 2012;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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