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# The renin–angiotensin–aldosterone-system and right heart failure in congenital heart disease

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ABSTRACT

Adults with congenital heart disease represent a rapidly growing patient group. Dysfunction of the right ventricle is often present, and right heart failure constitutes the main cause of death. Heart failure therapies used in acquired left heart failure are often initiated in adults with right heart failure due to congenital heart disease, but the right ventricle differs substantially from the left ventricle, and the clinical evidence for this treatment strategy is lacking.

In this review, we identified existing clinical studies evaluating the effects of ACE inhibitors, angiotensin II receptor blockers and aldosterone antagonists in adults with congenital heart disease by a systematic literature search. From 13 identified studies no clear evidence of beneficial effects was found, but the design of the studies limits the validity of the results. The studies in general include low numbers of patients, have short follow-up periods and evaluate surrogate endpoints instead of hard clinical endpoints. Specific evaluation of symptomatic patients with a systemic right ventricle indicates that these patients may benefit from RAAS inhibitory treatments, but this requires further investigation.

To conclude, existing studies do not support the use of RAAS inhibitory treatments in right heart failure due to congenital heart disease but contain important limitations. Hence, there is a need for new well-designed trials including higher numbers of patients and validated endpoints to optimize and guide future treatment of this patient group.


## 1. Background

Right heart failure is a frequent complication in adults with congenital heart disease (CHD) and constitutes the main cause of death in this patient group [1]. Right heart failure has been studied sparsely compared to left heart failure, and as a consequence, no treatment exists that effectively targets the failing right ventricle (RV). Left heart failure knowledge and treatment guidelines are often extrapolated to conditions with a failing right heart, but this generalization implies major issues and contrasts current recommendations. Hence, there is a fundamental need for thorough evaluation of current knowledge and treatment practice. This review evaluates the existing studies investigating the role of the renin–angiotensin–aldosterone-system (RAAS) in right heart failure due to CHD and the effects of RAAS inhibitory treatments.

### 1.1. The right ventricle versus the left ventricle

The RV differs substantially from the left ventricle (LV). They compose different anatomical structures, with the right ventricle being a crescent shaped, thin-walled compliant chamber contracting in the longitudinal direction, as opposed to the ellipsoid, thick-walled left ventricle, which primarily contracts with a radial motion [2]. Consequently the RV is more sensitive to changes in afterload than the LV [3]. The RV and the LV derive from different embryological cell lineages [4] and express distinctive gene patterns [5]. When subjected to pressure overload, the expression of genes essential to adaptive remodeling correlates with the degree of hypertrophy in the LV. In the RV, on the other hand, maladaptive factors related to apoptotic pathways are activated, and genes necessary for the contractile performance of the cardiomyocytes are relatively down regulated [6]. Adrenergic $\alpha_1$-receptor stimulation increases contractility in the LV, but in the RV contractility is impaired [7]. The ventricles may also respond very differently to the same therapeutic agent. Epoprostenol is life saving in pulmonary arterial hypertension and associated RV dysfunction but increases mortality in acquired left heart failure [8].

### 1.2. Right heart failure in congenital heart disease

Of all major congenital abnormalities, CHD accounts for approximately one-third [9], and the incidence of moderate to severe CHD is approximately 6 in 1000 live births, the majority with the need for structural and/or medical interventions. A few years ago many of these children died at an early age due to acute or chronic heart failure,

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but today, with better surgical and transcatheter techniques and intensive care, more patients with CHD survive into adulthood, forming a new and growing population of adults with CHD. Consequently, adults with CHD now outnumber children with CHD [10].

Adults with CHD predominantly develop failure of the RV, which may be induced by pressure overload or volume overload (Table 1). Surgical procedures e.g. atrial switch repair of transposition of the great arteries, after which the RV becomes the systemic ventricle, may also contribute to the pathology. In general the RV tolerates volume overload better than pressure overload [11], but all the defects listed in Table 1 may lead to deterioration of RV function and the development of symptomatic right heart failure with exercise intolerance, fatigue, fluid retention and dyspnea.

Right heart failure in adults with CHD is often associated with arrhythmias, pulmonary hypertension and the presence of remaining anatomical abnormalities including stenoses, valve regurgitations and residual shunts. Arteriosclerosis and subsequent myocardial ischemia is much less frequent in adults with CHD than adults with acquired left heart failure, but still a higher prevalence of traditional cardiovascular risk factors including hypertension, obesity and dyslipidemia has been observed in adults with CHD compared to the general population [12]. Together these factors add to the complexity of the management of this patient group and should be kept in mind when applying treatment strategies.

### 1.3. The renin–angiotensin–aldosterone-system and heart failure

Renin is released from the juxtaglomerular cells of the kidneys in response to low pressures. It is converted to angiotensin I by Angiotensinogen produced by the liver, which is then converted to angiotensin II by angiotensin converting enzyme (ACE) in the lungs. The hemodynamic effects of angiotensin II include stimulation of aldosterone production and systemic vasoconstriction and, consequently, fluid retention and increased systemic blood pressures. But it also has a number of direct cardiac effects. Angiotensin II induces hypertrophy and apoptosis of the cardiomyocytes, and it is the most important regulator of the development of myocardial fibrosis. These effects are main components of cardiac remodeling, which is a maladaptive response causing ventricular dilatation and cardiac dysfunction [13]. Aldosterone influences blood pressure regulation by increasing reabsorption of water and sodium in the kidneys, but it also promotes cardiac fibrosis and endothelial dysfunction. The improved survival in patients with left heart failure treated with the aldosterone antagonists is believed to be due to diuretic effects, reduced fibrosis and improved endothelial function [14,15].

**Table 1**
Etiology and mechanisms of right ventricular overload in congenital heart disease.

| | |
|---|---|
| Pressure overload | Right ventricular outflow obstruction |
| | • Right ventricular outflow tract obstruction |
| | • Pulmonary valve stenosis |
| | • Pulmonary atresia |
| | • Pulmonary arterial stenosis |
| | Systemic right ventricle |
| | • Congenitally corrected transposition of the great arteries |
| | • After atrial switch repair of transposition of the great arteries |
| | • Right ventricle in a univentricular circulation |
| | Pulmonary arterial hypertension |
| Volume overload | Left-to-right shunt |
| | • Atrial septal defect □ |
| | • Atrioventricular septal defect |
| | • Total or partial anomalous pulmonary venous return |
| | Pulmonary regurgitation |
| | • After Fallot repair |
| | Tricuspid valve regurgitation |
| | • Ebstein´s anomaly |
| | • Due to right ventricular dilatation |

Large randomized controlled trials have demonstrated solid beneficial effects of RAAS inhibition in acquired left heart failure with an average reduction in 1-year mortality of 16% after treatment with ACE inhibitors [16]. Prevention of the deleterious effects induced by increased activation of the RAAS is now a keystone in the treatment of acquired left heart failure, but the role of the RAAS and the therapeutic potential of RAAS inhibition in right heart failure caused by CHD remain unclear.

### 1.4. The right ventricle and the renin–angiotensin–aldosterone-system

Studies indicate that the RAAS exerts effects on the RV along with its effects on the LV. In experimental studies, failure of the RV is associated with increased activation of the RAAS [17], but when investigating the effects of RAAS inhibition results are contradictory [18–20]. In humans, the density of angiotensin II receptors is the same in the RV as in the LV of the healthy heart [21], and in failing hearts the angiotensin II receptor subtype 1 is selectively down regulated both in the failing RV and the failing LV [22]. In patients with mild hypertension RAAS inhibition improved RV myocardial performance index (an echocardiographic measure of combined systolic and diastolic function) unrelated to the reduction in blood pressure [23], and in a large cross sectional study the use of RAAS inhibitors was associated with changes in RV morphology independent of LV effects [24]. In adults with CHD, the activity of neurohormonal systems including the RAAS is increased. Bolger et al. studied 53 patients with CHD comprising 4 anatomical groups (single ventricle physiology, tetralogy of Fallot, systemic right ventricle and others (including septal defects and patent ductus arteriosus)) and compared them to healthy controls. Neurohormonal activation occurred in a similar way across different anatomical groups suggesting the molecular mechanisms involved in the development of heart failure in CHD to be independent of the anatomical defect. Furthermore, the neurohormonal activation was very alike the activation seen in adults with acquired left heart failure suggesting that adults with CHD may benefit from neurohormonal blocking treatments like patients with acquired left heart failure [25]. A more recent study compared 104 adults with CHD and RV dysfunction (primarily tetralogy of Fallot and pulmonary atresia) to healthy controls. They found no differences in angiotensin II and aldosterone levels between the CHD group and the controls [26]. This incongruence with previous findings may be explained by different compositions of the study populations. While Bolger et al. included patients with both left and right cardiac lesions; Lemmer et al. primarily investigated patients with lesions compromising the RV.

Thus, the role of RAAS activation in right heart failure associated with CHD remains unclear, specific studies are needed to evaluate the effects of RAAS inhibition in patients with CHD.

## 2. What do we know?

Using Pubmed, we performed a systematic literature search to identify studies investigating the effects of ACE inhibitors or angiotensin II receptor blockers in adults and older children (age > 13) with CHD and right heart failure conducted between 1995 and 2015. Additionally, all relevant reference lists were screened manually. Studies investigating adults with types of CHD that involves an increased load on the RV and thereby potentially the development of RV dysfunction and failure were included. The RV overloading condition could be due to the original defect or post-surgical. Case reports have been excluded from this review.

### 2.1. Existing clinical studies of RAAS inhibition in adult congenital heart disease

From the literature search, 13 studies investigating the effects of RAAS inhibition in patients with CHD were identified (Tables 2 and 3). Patients with a univentricular heart and a passive blood flow to support