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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

**Table 2**
Clinical studies investigating the effects of ACE inhibitory and angiotensin II blocking treatments in adult congenital heart disease.

| Reference | Design | Treatment | Duration | Population | N | Findings |
|---|---|---|---|---|---|---|
| Hopkins, 1996 [29] | Prospective cohort study | Enalapril (2.5 mg/day)<br>Captopril (6.25 mg × 3/day) | 399 ± 313 days | Cyanotic CHD patients with:<br>– Anatomical obstruction of RVOT<br>– Eisenmenger syndrome<br>Mean age: 32 ± 9 years<br>NYHA class: II–III | 10 | Treatment with enalapril/captopril caused:<br>– Improvement in NYHA class<br>– A trend towards an increase in oxygen SAT and a decrease in systolic BP<br>Treatment was discontinued in 3 patients |
| Kouatli, 1997 [27] | Randomized, double blind, placebo-controlled, crossover trial | Enalapril (0.2–0.3 mg/kg/day) | 10 weeks | Fontan patients (4–19 years after surgery)<br>Mean age: 14.5 ± 6.2 years<br>NYHA class: I | 18 | Compared to placebo treatment with enalapril caused:<br>– A decrease in the mean percent increase in cardiac index from rest to max exercise<br>– No difference in HR, BP, cardiac index or diastolic filling patterns at rest<br>– No difference in exercise variables |
| Hechter, 2001 [32] | Retrospective observational cohort study | Various ACE inhibitors and dosages | Minimum 6 months | Patients with systemic RV after atrial switch repair of TGA<br>Mean age: 31 years (range 26–42 years)<br>NYHA class: N/A | 14 | Treatment with ACE inhibitor caused:<br>– No changes in resting variables (HR, systolic BP, LVEF and RVEF)<br>– No changes in max exercise variables (max HR, max systolic BP, max oxygen uptake, max LVEF and max RVEF)<br>Some patients improved max oxygen uptake and exercise duration |
| Lester, 2001 [31] | Randomized placebo-controlled crossover study | Losartan (25–50 mg/day) | 8 weeks | Patients with systemic RV after atrial switch repair of TGA<br>Age: >13 years<br>NYHA class: N/A | 7 | Compared to placebo treatment with losartan caused:<br>– Improvement in exercise duration and increased RVEF<br>– Reduced systemic AV-valve regurgitant volume and area<br>– Decreased systolic BP<br>No adverse effects of the treatment were found |
| Ohuchi, 2001 [28] | Prospective cohort study<br>(Subgroup analysis of case control study) | Enalapril (0.1 mg/kg/day) | 6.8 months | Fontan patients<br>Mean age: 14 ± 3 years<br>NYHA class: N/A | 18 | Treatment with enalapril caused:<br>– No change in EF of the systemic ventricle (the same as non-treated controls)<br>– No changes in cardiac autonomic nervous activity (incl. HR variability and baroreflex sensitivity) |
| Robinson, 2002 [33] | Prospective cohort study | Enalapril (0.5 mg/kg/day) | 12 months | Patients with systemic RV after atrial switch repair of TGA<br>Mean age: 13.8 ± 3 years<br>NYHA class: I | 8 | Treatment with enalapril caused:<br>– Increased body mass index and decreased max oxygen uptake<br>– No change in other exercise variables<br>– Increase in resting respiratory rate<br>– Decreased BP |
| Dore, 2005 [34] | Randomized double-blind, placebo-controlled, crossover, clinical trial | Losartan (50–100 mg/day) | 106 ± 6 days | Patients with systemic RV because of:<br>– Atrial switch repair of TGA<br>– Congenitally corrected TGA<br>Mean age: 30.3 ± 10.9 years<br>NYHA class: I–II | 29 | Compared to placebo losartan treatment caused:<br>– No effect on max oxygen uptake or exercise duration<br>– No effect on systolic BP or HR at rest or during exercise<br>– No effect on RVEF or NT-pro-BNP levels<br>– A trend towards increased levels of AngII |
| Therrien, 2008 [35] | Randomized, double blind, placebo-controlled clinical trial | Ramipril (10 mg/day) | 12 months | Patients with systemic RV after atrial switch repair of TGA<br>Mean age: 26 ± 2 years<br>NYHA class: I–II | 17 | Compared to placebo ramipril treatment caused:<br>– No effect on exercise capacity or quality of life<br>– No improvement in RVEF or RV volumes |
| Van der Bom, 2012 [36] | Randomized, double blind, placebo-controlled clinical trial | Valsartan (160 mg × 2 /day) | 3.2 years | Patients with systemic RV because of:<br>– Atrial switch repair of TGA<br>– Congenitally corrected TGA | 88 | Compared to placebo valsartan treatment caused:<br>– Steady RV EDV and mass (increase in the placebo group)<br>– No effect on RVEF, exercise capacity or |

(continued on next page)

**Table 2** (*continued*)

| Reference | Design | Treatment | Duration | Population | N | Findings |
|---|---|---|---|---|---|---|
| | | | | Mean age: 33 ± 10 years<br>NYHA class: I–IV | | quality of life<br>– A trend towards decreased systemic BP<br>In the subgroup of symptomatic patients there was no reduction in RVEF in valsartan group but significant reduction in the placebo group<br>The same incidence of adverse effects and clinical events in the valsartan and the placebo group was reported |
| Babu-Narayan, 2012 [30] | Randomized, double-blind, placebo-controlled clinical trial | Ramipril (10 mg/day) | 26.3 ± 2.6 weeks | Patients with repaired ToF with moderate/severe pulmonary regurgitation and RV dilatation<br>Mean age: 30.1 ± 10.3 years<br>NYHA class: I–II | 64 | Compared to placebo ramipril treatment caused:<br>– Improved RV and LV long axis shortening<br>– No change in RVEF, RV mass or RV volumes<br>– No change in neurohormone levels, NYHA class, or exercise capacity<br>In the subgroup with restrictive RV, ramipril improved LV systolic function<br>No adverse effects were reported |
| Tutarel, 2012 [37] | Retrospective observational case control study | Enalapril (10 mg × 2/day) | 13.3 ± 4 months | Patients with systemic RV after atrial switch repair of TGA<br>Mean age: 25.2 ± 3.5 years<br>NYHA class: II | 14 | Enalapril treatment caused:<br>– Decrease in NT-pro-BNP levels (increase in control group)<br>– No change in max oxygen uptake, NYHA class or RV function<br>No adverse effects on heart failure symptoms or renal function were reported |

CHD: congenital heart disease; RVOT: right ventricular outflow tract; SAT: oxygen saturation; HR: heart rate; BP: blood pressure; NYHA: New York Heart Association; TGA: transposition of the great arteries; RV: right ventricle; LVEF: left ventricular ejection fraction; RVEF: right ventricular ejection fraction; AngII: angiotensin II; EDV: end diastolic volume; ToF: tetralogy of Fallot; LV: left ventricle; ESV: end systolic volume.

the pulmonary circulation after the Fontan procedure demonstrated no improvement of RV function after treatment with ACE inhibitors [27,28]. An adverse reduction in the mean percent increase in cardiac index from rest to max exercise with enalapril treatment was observed [27].

In cyanotic CHD patients, ACE inhibition improved NYHA class in 8 out of 10 patients, but treatment was discontinued in 3 patients due to increased fatigue symptoms, although no decrease in arterial oxygen saturation was detected in any of the patients [29]. Compared to placebo, treatment with ramipril did not improve NYHA class in patients with repaired tetralogy of Fallot and subsequent pulmonary regurgitation and RV dilatation. An improvement in RV and LV long axis shortening was observed, but the treatment did not improve other measures of RV function or morphology [30].

A number of studies have investigated the effects of RAAS inhibition in patients with a systemic RV after atrial switch repair of transposition of the great arteries (Mustard or Senning operation). Although a small crossover study (n = 7) reported improved exercise duration and RV ejection fraction with losartan treatment [31], most studies have found no beneficial effect of RAAS inhibition in patients with systemic RV on neither RV function nor exercise capacity [32–35]. One study even observed a decrease in maximal oxygen uptake with enalapril treatment [33]. A larger randomized controlled trial (n = 88) comparing valsartan to placebo found that while RV end diastolic volume and mass increased in the placebo group, there were no adverse changes in the treatment group [36]. In the subgroup of symptomatic patients, RV ejection fraction decreased in the placebo group but remained stable in the valsartan group. In a recent retrospective study evaluating only symptomatic patients (NYHA class II) with systemic RV, a decrease in plasma levels of NT-pro-BNP with enalapril treatment compared to an increase in the non-treated control group was observed [37]. Hard clinical endpoints were only evaluated by one study [36]. In patients with systemic RV, the overall risk of clinical events (composite endpoint of hospitalization due to heart failure, arrhythmias, reoperation or death) was the same for the treatment group and the placebo group. Treatment with aldosterone antagonists has only been investigated in very few studies (Table 3). Short-term treatment with spironolactone did not improve endothelial function in Fontan patients [38]. In patients with systemic right ventricular morphology, 12 months treatment with eplerenone did not change RV mass or function, nor did it affect heart failure or collagen turnover biomarker levels [39].

## 3. Discussion

Until now studies investigating the effects of RAAS inhibition in adults and older children with CHD have found no overall convincing beneficial effects in this patient group (Table 2). ACE inhibitors, angiotensin II receptor blockers and aldosterone antagonists seem to be well tolerated as the studies in general report no adverse effects of the treatments.

### 3.1. Limitations of clinical studies

The clinical studies performed so far may carry important limitations. Firstly, they include very few patients (between 7 and 88). This may have led to insufficient power to detect effects (beneficial or adverse) of the treatments. Despite being a growing patient group, the number of adults with CHD is still very low compared to the number of patients with acquired left heart failure. Conducting larger trials in adults with CHD is therefore challenging and requires broad multicenter collaborations. Additionally, adults with CHD are young and otherwise healthy people, who normally experience very few symptoms. This may decrease their motivation for participating in clinical studies further complicating the inclusion process [36].

Secondly, the treatment duration of the studies is often relatively short e.g. 12 months or less [27,28,30,31,38,39]. The main benefit of RAAS inhibition is expected to be a result of long-term neurohormonal blockade and not short-term hemodynamic effects, and consequently beneficial effects may not be detectable if the follow-up period is too short. However, in severe left heart failure, enalapril improved NYHA

**Table 3**
Clinical studies investigating the effects of aldosterone receptor blockers in adult congenital heart disease.

| Reference | Design | Treatment | Duration | Population | N | Findings |
|---|---|---|---|---|---|---|
| Mahle, 2009 [38] | Prospective cohort study | Spironolactone (50 mg/day) | 4 weeks | Fontan patients<br>Mean age: 28 years<br>NYHA class: I–II | 10 | Treatment with spironolactone caused:<br>– No effects on endothelial function measured by flow mediated dilation<br>– No effects on serum cytokine levels |
| Dos, 2013 [39] | Randomized, double blind, placebo-controlled trial | Eplerenone (50 mg/day) | 12 months | Patients with systemic RV after atrial switch repair of TGA<br>Mean age: 26.4 years<br>NYHA class: I–II | 25 | Compared to placebo treatment with eplerenone caused:<br>– No effects on RV mass or RVEF<br>– No effects on neurohormonal or collagen turnover biomarker levels |

NYHA: New York Heart Association; TGA: transposition of the great arteries; RV: right ventricle; TGA: transposition of the great arteries; RVEF: right ventricular ejection fraction.

class and exercise tolerance after two months of treatment [40], and in asymptomatic patients with reduced ejection fraction (LVEF < 35%) the incidence of development of heart failure was lower in the enalapril group compared to the placebo group after three months of treatment [41].

Thirdly, as a consequence of the low number of included patients and short follow-up periods, the randomized trials often evaluate surrogate endpoints (RV function, reported symptoms or level of NT-pro-BNP) instead of hard clinical endpoints (hospitalization or mortality) [27,30,31,34,35]. Evaluation of RV function in adults with CHD implies a number of challenges. In adults with acquired left heart failure clear definitions of normal vs. abnormal function assessed by different imaging modalities are available, but in adults with CHD and right heart failure this is not the case. The complex shape of the RV makes it difficult to evaluate, and defining normal values of RV function, e.g. when the RV performs as the systemic ventricle, is complicated [42].

Furthermore, adults with CHD in general do not recognize or report symptoms of for example exercise intolerance, and often there is a high discrepancy between the patients' own assessments of their functional capacity and objective measures of RV function and exercise variables [26,27,33,34]. This limits the use of self-reported symptoms in clinical studies with this patient group.

Enrolling a sufficient number of patients to evaluate clinical endpoints in studies of adults with CHD may, however, be very difficult considering the low number and the heterogeneity of the patient group. Consequently, prior identification and validation of suitable surrogate endpoints is essential for evaluation of safety and efficacy of heart failure therapies in adults with CHD in future studies [43].

### *3.2. The role of the renin–angiotensin–aldosterone-system in the development of right heart failure*

The lack of demonstrated effects of RAAS inhibitory treatments in CHD and right heart failure in clinical trials may be explained by study limitations, but more intrinsic reasons ought to be considered too. The metabolic inactivation of ACE-inhibitory drugs is much more effective in the RV compared to the LV [44], and the use of ACE inhibitors did not affect neurohormone levels in adult patients with CHD [25]. The intracellular angiotensin signaling pathway is down regulated in the failing RV compared to the failing LV of children with CHD and RV or LV outflow obstructions, respectively [6]. In adults with an overloaded RV due to CHD, natriuretic peptides, endothelin-1, norepinephrine and epinephrine correlate closely with each other and with the dysfunction of the RV, while renin and aldosterone levels relate only to one another [25]. Thus, the RAAS may be a less important pathophysiological factor in the development of right heart failure compared to left heart failure.

Baseline levels of angiotensin II are only slightly elevated in patients with systemic RV [34], and in a larger group of patients with CHD (systemic RV, tetralogy of Fallot and single ventricle), RAAS was only activated in symptomatic patients contrary to other neurohormones, which were increased in both asymptomatic and symptomatic patients [25]. Also, aldosterone levels are significantly lower in asymptomatic patients with systemic RV compared to symptomatic patients. Accordingly, the RAAS does not seem to be an important factor in early asymptomatic stages of CHD. On the contrary, RAAS inhibition prevents RV hypertrophy and deterioration of RV function [36] and causes a decrease in NT-pro-BNP [37] in symptomatic patients.

The effects of RAAS inhibition also vary with the etiology of heart failure. In acquired left heart failure with preserved ejection fraction (diastolic heart failure), the effects of RAAS inhibition are less pronounced compared to heart failure with reduced ejection fraction (systolic heart failure) [45], and RAAS inhibitory therapies are in general not recommended in valvular heart disease [46]. Adults with CHD more often present with diastolic dysfunction and/or valvular defects than systolic dysfunction, which may reduce the potential effects of RAAS inhibition in this patient group.

Also, beneficial treatment strategies of one condition of CHD with right heart failure may not apply to other conditions. Theoretically, the vasodilatation induced by RAAS inhibition may be beneficial in conditions with a septal defect where decreased systemic vascular resistance may reduce the magnitude of the shunt [47], but detrimental in patients after the Fontan procedure where venous vasodilatation may reduce the ability to mobilize blood from the venous reserve during exercise [27].

### *3.3. Current recommendations and clinical practice*

With no effective right heart failure treatments available, the dilemma of extrapolating recommendations from the treatment guidelines for acquired left heart failure persists. But despite some parallels in the remodeling processes and neurohormonal activation in heart failure regardless of the etiology, the differences between acquired left heart failure and right heart failure associated with CHD are considerable (Fig. 1). Recently, the American Heart Association have stated that older adults with CHD (age > 40) should only be treated at specialized centers, as they cannot be directly compared to patients with acquired heart failure [48].

Today's treatment guidelines in general include very few recommendations for medical treatment of heart failure in adults with CHD. According to the ACC/AHA 2008 Guidelines for the Management of Adults With Congenital Heart Disease [49], the use of ACE inhibitors are restricted to 1) patients with atrioventricular septal defects and symptoms of chronic heart failure and 2) Fontan patients with dysfunction of the systemic ventricle. Aldosterone antagonism may improve the protein losing enteropathy syndrome of Fontan patients, although the effects have only been reported by case reports. Diuretics in general are only recommended in patients with signs of congestion.


| | CHD related heart failure | Acquired heart failure |
|---|---|---|
| The patient | Younger<br>Cardiovascular risk factors ↑ | Older<br>Cardiovascular risk factors↑ ↑ |
| The heart | RV failure<br>Anatomically abnormal heart<br>Other possible cardiac characteristics:<br>- Systemic RV<br>- Univentricular heart<br>- Valve regurgitation<br>- RVOT obstruction<br>- Atrial and/or ventricular septal defect | LV failure<br>Anatomically normal heart<br>Other possible cardiac characteristics:<br>- Ischemia<br>- Atrial fibrillation<br>- Acquired valve disease<br>- Post myocardial infarction scar tissue |
| The RAAS | RAAS activation mainly in symptomatic patients<br>Metabolic inactivation of ACE inhibitors↑<br>Angiotensin signaling pathway↓ | Hyperactivation of RAAS<br>RAAS inhibition leads to:<br>- Improved LV function<br>- Reduced morbidity and mortality |

**Fig. 1.** Differences between CHD related heart failure and acquired heart failure. CHD: congenital heart disease; RV: right ventricle; LV: left ventricle; RVOT: right ventricular outflow tract; RAAS: renin–angiotensin–aldosterone-system; ACE: angiotensin converting enzyme.

Despite the fact that the guidelines for the management of adults with CHD in general advise against the use of traditional left heart failure therapies in CHD, treatment with ACE inhibitors, angiotensin II receptor blockers and aldosterone antagonists is often initiated nonetheless. Data from clinical studies reveal that patients with CHD are often empirically treated with RAAS inhibitory drugs [32,34,35,39]. Of the 53 patients with CHD evaluated by Bolger et al., 14 were taking ACE inhibitors, 3 were treated with angiotensin II receptor blockers, and 6 were treated with spironolactone [25]. In a more recent study, only 1 of 104 adult patients with CHD and RV dysfunction were treated with an angiotensin II receptor blocker [26], indicating that treatment practices may have changed during the past years. A retrospective evaluation of patients with systemic RV after atrial switch repair of TGA revealed that in the majority treatment with ACE inhibitor was initiated based solely on the belief that the therapy might be helpful. Only a few were treated because of dyspnea or high blood pressures [32].

## 4. Conclusion

Adults with CHD constitute a growing patient group often presenting with dysfunction and eventually failure of the RV. Traditionally, they have been excluded from the large heart failure trials, and consequently no clear evidence of effective medical heart failure therapies are available for these patients. Clinical studies investigating heart failure therapies, including RAAS inhibitory treatments, specifically in adults with CHD have failed to demonstrate beneficial effects, but may have been underpowered. Therefore, current clinical practice regarding these patients is primarily based on empirical extrapolations and expert opinions. This may include initiation of treatment with ACE inhibitors, angiotensin II receptor blockers and aldosterone antagonists despite the lack of clinical evidence to support this strategy. Thus, there is an urgent need for well-designed trials including higher numbers of patients and validated endpoints to optimize and guide future treatment of adults with CHD.

## Conflicts of interest

None.

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