The systemic right ventricle
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Rationale and Design of a Trial on the Effect of Angiotensin II Receptor Blockers on the Function of the Systemic Right Ventricle


American Heart Journal. Accepted for publication.
**ABSTRACT**

**Background:** Angiotensin II receptor blockers (ARB’s) have been proven beneficial in left ventricular failure. In patients with a morphologic right ventricle supporting the systemic circulation, its efficacy has not yet been established.

**Methods:** We designed a multicenter, prospective, randomized, double-blind, placebo-controlled trial studying the effect of valsartan in patients with a systemic right ventricle due to a congenitally or surgically corrected transposition of the great arteries. The primary endpoint is the change in right ventricular ejection-fraction as measured by Cardiovascular Magnetic Resonance (CMR) or multidetector row cardiac computed tomography (MDCT) in case of pacemaker patients.

**Conclusion:** This large prospective, double blind randomized placebo controlled trial will establish the role of ARBs (valsartan) in the treatment of patients with a systemic right ventricle.
BACKGROUND

Patients with complete transposition of the great arteries (TGA) who were treated with an atrial switch operation as well as patients with a congenitally corrected transposition (ccTGA) of the great arteries function with a systemic right ventricle (RV).\textsuperscript{1, 2} Although midterm survival is favorable, deterioration of RV function usually starts early in life.\textsuperscript{3-8} In addition, both ventricular and supraventricular arrhythmias are relatively common.\textsuperscript{9} Both progressive RV dysfunction and arrhythmias are important contributors to morbidity and mortality in patients with a systemic RV.\textsuperscript{10} These late complications led to a shift towards the application of the arterial switch procedure, in which the morphological left ventricle becomes the systemic ventricle. This is currently the standard treatment for newborns with complete transposition.\textsuperscript{11}

However, most TGA-patients now seen at the adult cardiology department have undergone an atrial switch procedure. Unfortunately, the use of pharmacological agents aiming to slow down deterioration of systemic right ventricular function, though widely applied empirically, is not underpinned by literature.\textsuperscript{12} This is caused by the small size and heterogeneity of this patient group, which complicates prospective and sufficiently powered research. At present, there is no evidence-based foundation for the use of pharmacological agents in the attenuation of RV deterioration in adults with congenital heart disease. In patients with LV failure the role of Angiotensin Converting Enzyme (ACE) inhibitors and Angiotensin II Receptor Antagonists (ARBs) is well established, and is known to decrease both mortality and morbidity.\textsuperscript{13, 14} As the renin-angiotensin system is activated in all patients with cardiac failure, regardless of the affected ventricle, one would expect a similar beneficial effect in patients with a systemic RV.\textsuperscript{15} To date, only few small studies have been performed on the effect of ACE inhibitors and ARBs in patients with a systemic RV.\textsuperscript{16-20} These studies suffered from short follow-up, a small number of patients, inaccurate endpoints or retrospective study design. Moreover, results are contradictory. Therefore, a large prospective sufficiently powered trial, with a long follow-up, evaluating the use of ARBs in
patients with a morphologic right ventricle supporting the systemic circulation is warranted.

**STUDY OVERVIEW**

We designed a prospective multicenter, double blind, randomized placebo-controlled trial to evaluate the effect of ARBs (valsartan) on RV ejection fraction (EF). Primary hypothesis of this study is that ARBs improve systemic RV EF as measured by CMR or MDCT. Secondary hypotheses are that ARBs decrease systemic RV volumes, the incidence of (supra-) ventricular arrhythmias, serum neurohormone levels, and improve maximal exercise capacity and quality of life. The study is being conducted in six tertiary referral centers in the Netherlands, of which three were added one year after study initiation to augment the enrollment rate. The protocol has been approved by the institutional ethics committees of each participating center. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents. The study is supported by an unrestricted grant from Novartis Pharma, the Netherlands. The trial is registered at http://www.controlled-trials.com/ISRCTN52352170/52352170. A flow chart of the study design is shown in figure 1.

**Subject selection**

Patients of 18 years and over with systemic RV due to ccTGA or surgically corrected TGA, treated in one of the participating centers (Academic Medical Center Amsterdam, University Medical Center Utrecht, Radboud University Nijmegen Medical Centre, University Medical Center Groningen, Erasmus Medical Center Rotterdam, and Leiden University Medical Center) were eligible to participate in the study. Inclusion and exclusion criteria are detailed in Table 1. Potential candidates were identified via the CONCOR database, a national database and DNA bank of adult patients with congenital heart disease.21 If a patient met all inclusion, and none of the exclusion criteria, the patient was invited to the
outpatient clinic for a detailed explanation of the study and asked for informed consent.

**Randomization and masking**

Subjects were randomly assigned in 1:1 ratio to the valsartan or placebo treatment groups, using randomly permuted blocks of 6 or 4, stratified by site. Randomization was performed by the hospital pharmacy of the Academic Medical Center in Amsterdam, which acted as a third party. Consequently, both patients and study personnel are blinded to the treatment.

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**Table 1.**

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>All adult patients with a systemic right ventricle due to a congenitally or surgically</td>
</tr>
</tbody>
</table>

**Inclusion criteria**

- Incapability of giving informed consent
- Hypersensitivity to valsartan or any of its help substances
- Hypersensitivity to intravenous contrast agents
- Known bilateral renal artery stenosis
- Myocardial infarction, stroke or open heart surgery in the previous four weeks
- Previous heart transplant, or expected heart transplant within the next six months
- Plasma creatinine level > 205 μmol/L
- Plasma potassium level > 5.5 mmol/L
- Current treatment of hypertension with an ACE-inhibitor or an Angiotensin II Receptor Blocker, which cannot be discontinued
- Pregnant or nursing women (a pregnancy test is offered to every female patient within fertile age)
- Desire to have children during follow-up
**Figure 1:** Flow diagram for the trial

*CPET* Cardiopulmonary exercise testing; *QoL* Quality of life questionnaires; *CMR* Cardiovascular magnetic resonance; *MDCT* multidetector row cardiac computed tomography, CONCOR national database and DNA bank of adult patients with congenital heart disease.

- **CONCOR**
  - Patients with systemic right ventricle due to a congenitally or surgically corrected transposition of the great arteries
  - Screening eligibility/consent
  - Baseline measurements:
    - ECG, Holter, Echocardiography, CPET, QoL, CMR/MDCT, blood analysis, Neurohormones
  - Randomization
    - Valsartan
    - Placebo
  - Two weeks follow up:
    - ECG, blood analysis
    - Double study medication
  - Four weeks follow up:
    - ECG, blood analysis
  - 1 year follow up:
    - ECG, blood analysis, echocardiogram
  - 2 year follow up:
    - ECG, blood analysis, echocardiogram
  - 3 year follow up:
    - ECG, Holter, Echocardiography, CPET, QoL, CMR/MDCT, blood analysis, Neurohormones
**Study medication**

Patients in the valsartan group started on 160mg once daily. After two weeks the dose was increased to 160 mg twice daily if renal function remained normal. Patients in the placebo group were given a similar regimen. Patients who were already on ACE inhibitors or ARBs discontinued these at least four weeks prior to commencing with the trial medication. Other medication was noted, but continued. There is no data on the appropriate dose of valsartan in the treatment of the systemic right ventricle. Consequently, the dose was chosen for its hemodynamic and hormonal effects in the left ventricle, which have been reported by Latif and Baruch. 22, 23

**OUTCOME MEASURES**

Study measures (i.e. extensive history-taking, physical examination, CMR or MDCT, (24-hours ambulatory) electrocardiography, echocardiography, blood analysis, cardiopulmonary exercise testing and quality of life questionnaires) were obtained in all participating patients at baseline. They will be repeated after a three year follow-up period. Echocardiography is performed yearly (Figure 1).

**Clinical data and definitions:**

*Cardiovascular Magnetic Resonance*

CMR was performed in all patients at baseline and will be repeated at three year follow-up to establish the primary endpoint. CMR imaging acquisition was performed with a 1.5 Tesla scanner using a standardized protocol to diminish inter-observer variability between the different centers.24-27

After determining the long and short axis, a steady state free procession sequence (SSFP) with retrospective electrocardiographic triggering was acquired to visualize 2-, 3- and 4-chamber views. These views were used to obtain multi-phase contiguous 8 mm short axis slices perpendicular to the ventricular septum encompassing the total heart. These sequences were individually adjusted to acquire short axis slices with optimal spatial and temporal resolution. Typical
parameters were: flip angle: 50-70 degrees; repetition time: 3-4 msec; echo time: 1-2 msec; temporal resolution: 40 msec, 1-2 X 1-2 mm / pixel in-plane spatial resolution, 8 mm slice thickness, and 1 mm interslice gap. This resulted in 9 to 15 slices to cover the whole heart. CMR images were acquired during repeated end-expiratory breath holds.

**Multi-row Detector Computed Tomography**

MDCT was performed in all patients with contraindications for CMR at baseline and will be repeated at three year follow-up to establish the primary endpoint. A Brilliance-64 CT-scanner (120 kVolt; average 500mAs) was used for cardiac images. Data were obtained by contrast enhanced, ECG-gated cardiac MDCT in craniocaudal direction, during inspiratory breath-hold. Patients received 90 mL of a contrast medium (70 mL at a flow rate of 5.0 mL/s, followed by a 20 mL bolus at a flow rate of 3.5 mL/s, and a 40 mL bolus of saline at a flow rate of 3.5 mL/s) containing 300 mg of iodine (Iomeron 300, Bracco Imaging SpA, Milan, Italy). Axial images of 10 cardiac phases were acquired in steps of 10% of the RR-interval. To depict the entire heart 60 to 80 slices were made each with 2mm thickness and no interslice gap. From these 12-15 short-axis reconstructions are created, which were used for functional analysis.

**CMR and MDCT image analysis**

For MDCT and CMR image analysis we used MASS Analytical Software System (Medis, Leiden, the Netherlands). Cine loops were used to choose end-diastole and end-systole. End diastole was defined as the phase with the largest RV (and LV) volume and end systole as the phase with the smallest RV (and LV) volume. The slices at the base of the heart were considered to be in the ventricle if the blood was at least half surrounded by ventricular myocardium. To optimize differentiation between ventricle and atria and vessels in the basal slices, 4-chamber views in phase with short-axis views were available in the CMR group. Trabeculations and papillary muscles were considered part of the ventricular cavity. The sums of the
traced contours in end diastole and end systole were used to calculate end diastolic volume and end systolic volume using a disc summation technique. End diastolic volumes and end systolic volumes were used to calculate stroke volume and ejection fraction. Stroke volume was defined as end diastolic volume – end systolic volume, and EF as \[ \frac{(\text{end diastolic volume} - \text{end systolic volume})}{\text{end diastolic volume}} \times 100\% \].

Electrocardiography:
A 12 lead electrocardiogram (ECG) was registered in all patients at each visit.

24-hour ambulatory electrocardiography:
24-hour ambulatory ECG was performed at baseline and will be repeated at three years follow-up. A 24-hour ambulatory ECG was acquired with a 3 channel Holter-monitor during normal out-of-hospital activities. The ECG-registration was analyzed for the presence of (supra-) ventricular arrhythmias. Any complaints during the ambulatory ECG were noted and compared to the registration.

Echocardiography
All patients underwent transthoracic echocardiographic examination (Vivid 7, GE Medical Systems, Horten, Norway; Sonos 7500, Philips, Best, The Netherlands) at baseline and at one year intervals throughout the study period to evaluate systolic and diastolic function. Parasternal and apical views were obtained according to the recommendations of the American Society of Echocardiography. Echocardiography was performed for qualitative and quantitative assessment of systolic function of the systemic RV and the subpulmonary LV. Tricuspid and mitral annular plane systolic excursion (TAPSE / MAPSE) were measured by M-mode, Tissue Doppler Imaging (TDI) were obtained to measure peak systolic myocardial velocities at the tricuspid and mitral annuli. Diastolic function of the systemic RV and the subpulmonary LV was determined using an apical 4-chamber view, with trans-tricuspid, and trans-mitral pulsed wave Doppler curves, and pulsed wave TDI.
curves. The severity of tricuspid regurgitation was quantified according to recommendations of American Society of Echocardiography’s Nomenclature and Standards Committee and The Task Force on Valvular Regurgitation. Systemic and pulmonary venous inflow was measured using color and pulsed wave Doppler. Flow velocity in the baffle was evaluated using Doppler flow patterns.

Cardiopulmonary exercise testing:
Cardiopulmonary exercise testing (CPET) was performed in all patients at baseline and will be repeated at three years follow-up. Before exercise respiratory flow volume loops were acquired and maximal breathing capacity was determined. CPET was performed to assess maximal exercise capacity, and maximal heart rate, according to the guidelines of the American Thoracic Society. Patients were placed on a cycle ergometer to perform continuous measurements of minute ventilation, oxygen consumption (V'O2), carbon dioxide production (V'CO2), heart rate, blood pressure and electrocardiography (Jaeger Oxycon pro, Wuerzburg, Germany). Work load was increased by 5 to 15 Watt in a stepwise manner, depending on the individually predicted maximum exercise capacity and in such a way that calculated maximal effort was attained in approximately 10-15 minutes. All patients were exercised to their maximum exercise capability.

Neurohormone levels:
At baseline concentrations of the neurohormones norepinephrine, epinephrine, angiotensin converting enzyme, aldosterone and N-terminal pro brain natriuretic peptide (NT-proBNP) were measured. After three years follow-up the measurements will be repeated.

Statistical considerations
Sample size calculation was based on change in right ventricular ejection fraction as measured by CMR; the primary outcome variable. Assuming a standard deviation of 10%, 102 patients are required to obtain an 80% power to detect a
5.6% difference in ejection-fraction between the two treatment groups with a two-sided alpha of 0.05. Considering a possible drop-out of 20%, at least 128 patients need to be included. The difference of 5.6% was chosen as differences between baseline and follow-up were expected to be to be subtle and, in contrast to the small studies to date, we aimed for a study with a substantial population.

For statistical analyses SPSS 16.0 (SPSS Inc., Chicago, Illinois) for Windows is used. A 2-tailed probability value of < 0.05 is used as a criterion for statistical significance. Descriptive data will be presented as numbers with percentage, or as mean with standard deviation, or median with range, as appropriate. The primary analysis will be according to the intention-to-treat principle. Chi square for qualitative data and independent t-tests for quantitative data will be applied to detect differences between the valsartan group and placebo group at baseline. If there are significant differences between groups on parameters that could influence study outcome, we will perform covariate-adjusted comparisons as a secondary analysis. Differences between baseline and follow-up within groups will be assessed using a paired t test. To detect differences in the endpoints between the valsartan and placebo group, again chi square and independent t-test will be applied.

Covariate by treatment group interaction tests will be performed to analyze whether there are differences in treatment effects between subgroups. Predefined subgroups are 1). patients with an atrially switched TGA versus ccTGA, 2). patients with isolated TGA (simple TGA) versus patients with TGA in conjunction with other cardiac lesions (complex TGA) 3). patients who have undergone a Mustard versus a Senning operation, 4)

TIME LINE AND STUDY ENROLEMENT
Patients were enrolled in the study from October 2006 until April 2009 (Figure 2). Of 277 eligible patients 88 (32%) gave informed consent. There were no significant differences between eligible patients that consented and eligible patients that refused participation (table 2). Of all consenting patients 19 (22%)
discontinued their involvement before the end of the study at three year follow-up. Of these 19 patients 13 refused exclusion examinations and were consequently lost to follow-up. Reasons for discontinuation included symptomatic hypotension, fatigue, pregnancy-wish, and malaise. One patient developed elevated liver enzymes and was afraid to continue study medication. Since inclusion, one patient has died. The primary cause of death was pulmonary (respiratory complications caused by bronchiectasis). Table 3 summarizes the baseline characteristic of the study population.

**Table 2. Baseline comparison between participating and non-participating patients**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Consent (n=88)</th>
<th>No Consent (n=189)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>35.7 ± 9.8</td>
<td>33.7 ± 8.2</td>
<td>0.077</td>
</tr>
<tr>
<td>Male</td>
<td>35.0 ± 8.9</td>
<td>32.6 ± 7.7</td>
<td>0.068</td>
</tr>
<tr>
<td>Female</td>
<td>36.9 ± 11.3</td>
<td>35.8 ± 8.9</td>
<td>0.584</td>
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<tr>
<td>Male</td>
<td>57 (64.8%)</td>
<td>134 (67.5)</td>
<td>0.654</td>
</tr>
<tr>
<td>Transposition</td>
<td></td>
<td></td>
<td>0.768</td>
</tr>
<tr>
<td>ccTGA</td>
<td>25 (28.4%)</td>
<td>48 (25.4%)</td>
<td></td>
</tr>
<tr>
<td>Simple TGA</td>
<td>39 (44.3%)</td>
<td>92 (48.7%)</td>
<td></td>
</tr>
<tr>
<td>Complex TGA</td>
<td>24 (27.3%)</td>
<td>49 (25.9%)</td>
<td></td>
</tr>
</tbody>
</table>

Data are number of patients (percentage) or mean ± standard deviation; * test of significance for differences between eligible patients that consented and eligible patients that refused participation. Chi square test for categorial variables and independent t-tests for continuous variables. ccTGA = congenitally corrected transposition of the great arteries; TGA = transposition of the great arteries.

**DISCUSSION**

This is the first large multi-center, randomized, double blind, placebo-controlled trail that evaluates the long term effect of ARBs on the function of the systemic RV and hopes to establish its purpose in patients with a systemic RV. In 2005 Dore et al. performed a multi-center, randomized, double blind, placebo-controlled,
crossover trial, which did not show improvement of exercise capacity in 29 patients with a systemic RV treated with losartan for 15 weeks. However, the long term effect of RAS inhibition on the deteriorating RV was not studied, as the follow-up period was relatively short.

**Figure 2**: Flow diagram of patient enrolment
*These patients discontinued their participation during the trial and refused exclusion examinations and are consequently lost to follow-up. CONCOR national database and DNA bank of adult patients with congenital heart disease; RV right ventricle
In patients with a systemic RV late complications are common and often relate to RV dysfunction. The mechanisms behind systemic RV deterioration seem to be multifactorial. Surgical interventions, morphological aspects of the RV and physiological processes are all known to contribute to the deterioration of the systemic RV. Treatment regimens for patients with LV failure have been well established. Inhibition of the RAS system has been shown to diminish ventricular remodeling and improve morbidity and mortality.\textsuperscript{13, 14} However, the role of ACE inhibitors and ARBs in the treatment of patients with a failing RV, whether systemic of subpulmonary, remains unclear. Although some of the pathophysiological mechanisms of RV dysfunction differ from those in LV failure, the RAS-system is activated in both left and right ventricular failure and angiotensin II receptor density is similar in right and left ventricles.\textsuperscript{15, 32} Consequently, in theory patients with a failing RV are likely to benefit from ACE-inhibitors or ARBs. Until today, only few small trials with short follow-up have been performed with equivocal results.\textsuperscript{16-20}

Major cardiac events, cardiac transplantation, and (cardiac) death could be considered superior endpoints, compared to RV ejection fraction. However, these events are relatively rare, even though complications are quite common in this population. Performing a placebo-controlled trial that assesses differences in hard clinical endpoints seems unrealistic in these patients, as it would involve very large patient numbers and very long follow-up period.

Although the sample size calculation for this study indicates that 128 patients need to be included, only 88 patients consented. The sample size calculation that aimed at detecting a small difference of 5.6% is based on an estimation of 10% for the standard deviation for the difference in RV ejection fraction at baseline and at three year follow-up as measured by CMR. The analysis of the 75 patients who have undergone or will undergo exclusion examinations will still have an 80% power to detect a 7% difference in RV ejection fraction.

Patients with a congenitally or surgically corrected TGA display a wide range of symptoms, both in variety and severity. Many patients remain
asymptomatic for a very long period, have no complications and do not use cardiac medication. These patients might be less inclined to participate in a study, as they feel that they have little to gain. Conversely, symptomatic patients might hope to improve as a result of the study-medication, and could be more likely to participate. This might create an inclusion bias, favoring symptomatic patients. However, a comparison between patients who were included and those that refused participation did not show significant differences, although in particular male subjects tended to be slightly older (table 3).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Consent (n=88)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at inclusion (years)</td>
<td>35.7 ± 9.8</td>
</tr>
<tr>
<td>Male</td>
<td>57 (64.8%)</td>
</tr>
<tr>
<td>Transposition</td>
<td></td>
</tr>
<tr>
<td>ccTGA</td>
<td>25 (28.4%)</td>
</tr>
<tr>
<td>Simple TGA</td>
<td>39 (44.3%)</td>
</tr>
<tr>
<td>Complex TGA</td>
<td>24 (27.3%)</td>
</tr>
<tr>
<td>RVEF (%)</td>
<td>40.1 ± 9.51</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>52.3 ± 10.6</td>
</tr>
<tr>
<td>NYHA III/IV</td>
<td>8 (9%)</td>
</tr>
<tr>
<td>V'O2peak (% of predicted)</td>
<td>78.1 ± 20.8</td>
</tr>
</tbody>
</table>

Data are number of patients (percentage) or mean ± standard deviation. ccTGA = congenitally corrected transposition of the great arteries; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association class; RVEF = right ventricular ejection fraction; TGA = transposition of the great arteries; V'O2peak = maximal exercise capacity.

CONCLUSIONS
This prospective multicenter, double blind, randomized placebo-controlled trial may establish the role of ARBs (valsartan) in the treatment of patients with a systemic RV, and might provide these patients with a long-term and evidence based treatment option.
Reference List


29. Lang RM. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. 2005.

