Exercise Physiology

Angiotensin Receptor Blockade and Exercise Capacity in Adults With Systemic Right Ventricles

A Multicenter, Randomized, Placebo-Controlled Clinical Trial

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**Background**—Pharmacological blockade of the renin-angiotensin system improves exercise tolerance in patients with left ventricular dysfunction, yet its impact on patients with systemic right ventricles (RVs) remains unknown.

**Methods and Results**—A multicenter, randomized, double-blind, placebo-controlled, crossover clinical trial was performed to assess the effects of losartan on exercise capacity and neurohormonal levels in patients with systemic RVs. Of 29 patients studied (age, 30.3 ± 10.9 years), 21 had transposition of the great arteries with a Mustard baffle, and 8 had congenitally corrected transposition of the great arteries. Baseline values were as follows: \( V_{\text{O2max}} \), 29.8 ± 5.6 mL · kg \(^{-1} \) · min \(^{-1} \) (73.5 ± 12.9% predicted value); RV ejection fraction, 41.6 ± 9.3%; N-terminal pro brain natriuretic peptide (NT-proBNP), 257.7 ± 243.4 pg/mL (normal < 125 pg/mL); and angiotensin II, 5.7 ± 4.9 pg/mL (normal < 5.0 pg/mL). Comparing losartan to placebo showed no differences in \( V_{\text{O2max}} \) (29.9 ± 5.4 versus 29.4 ± 6.2 mL · kg \(^{-1} \) · min \(^{-1} \); \( P = 0.43 \)), exercise duration (632.3 ± 123.0 versus 629.9 ± 140.7 seconds; \( P = 0.76 \)), and NT-proBNP levels (201.2 ± 267.8 versus 229.7 ± 291.5 pg/mL; \( P = 0.10 \)), despite a trend toward increased angiotensin II levels (15.2 ± 13.8 versus 8.8 ± 12.5 pg/mL; \( P = 0.08 \)).

**Conclusions**—In adults with systemic RVs, losartan did not improve exercise capacity or reduce NT-proBNP levels. Minimal baseline activation of the renin-angiotensin system may explain this lack of benefit and imply an alternative pathophysiological mechanism for the progressive ventricular dysfunction and impaired exercise capacity observed in such patients. (Circulation. 2005;112:2411-2416.)

**Key Words:** angiotensin • exercise • transposition of great vessels

Patients with congenitally corrected transposition of the great arteries (L-TGA) or intra-atrial baffle repair for complete transposition of the great arteries (D-TGA) function with a morphological right ventricle (RV) supporting a systemic circulation. Overall, excellent long-term survival is reported, with most young adults remaining symptom free.1,2 However, long-term sequelae include progressive RV dilatation, systolic ventricular dysfunction,2–5 impaired exercise tolerance,6,7 arrhythmias,1,2,5 and sudden death,1 raising concern over the suboptimal capacity of the RV to endure against a systemic afterload.

In both symptomatic and asymptomatic patients with left ventricular (LV) dysfunction, pharmacological blockade of the renin-angiotensin system (RAS) improves LV filling pressures,8–10 cardiac index,8,9 exercise tolerance,5–12 and overall survival.13–15 Results of such studies are often extrapolated to patients with systemic RVs, and therapy frequently is empirically initiated. However, beneficial effects of inhibiting the RAS in patients with systemic RVs have not yet been demonstrated. This study therefore was designed to assess the effects of losartan on exercise capacity and neurohormonal levels in adults with systemic RVs.

**Methods**

**Study Population**
The study population was derived from patients having L-TGA or D-TGA with an intra-atrial Mustard baffle from participating centers. To be eligible for enrollment, patients had to be ≥18 years of age and on a stable medical regimen with no change in therapy or hospitalization in the preceding 3 months. Patients were excluded if they had severe symptomatic heart failure (New York Heart Association [NYHA] functional class III or IV), were unable to exercise, were pregnant, had a fixed-rate pacemaker, had a creatinine level > 250 mmol/L, or had a history of angioedema. Patients with any of the following hemodynamic criteria were likewise excluded: right-to-left shunting; substantial left-to-right shunting (Qp/Qs > 1.5); severe mitral, aortic, or pulmonary regurgitation; systemic or pulmonary inflow obstruction with a peak velocity > 1.5 m/s by transthoracic echocardiography; and severe outflow tract obstruction with a peak systolic gradient > 80 mm Hg.

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Study Design
A multicenter, randomized, double-blind, placebo-controlled, cross-over trial was performed. Patients already receiving ACE inhibitors or angiotensin receptor blockers were required to discontinue therapy 4 weeks before their preliminary assessment. All other medications were continued at the same doses.

One week before randomization, all patients were preliminarily assessed with standard exercise treadmill tests using a RAMP protocol. On the day of randomization, baseline testing consisted of a transthoracic echocardiogram, maximal symptom-limited exercise treadmill test with spirometry, and laboratory testing that included creatinine, potassium, and neurohormonal levels. For a patient to be eligible for randomization, differences in exercise duration between preliminary and baseline tests could not exceed 15% or 60 seconds. After providing informed consent, qualifying patients were then randomized to therapy with losartan or placebo in a double-blinded fashion. Treatment was continued for 15 weeks (phase 1), after which crossover to the second treatment arm was performed for an additional 15 weeks (phase 2).

On initial randomization, patients received losartan 50 mg or placebo once a day for the first 4 weeks. At 14 days, potential side effects were assessed by telephone interviews. If therapy was well tolerated, the dose was doubled at 28 days (ie, losartan 50 mg or placebo twice daily). Once again, patients were contacted 14 days after the dosage increase to reassess side effects. At the conclusion of each phase, repeated testing was performed with a transthoracic echocardiogram, exercise treadmill spirometry, and blood tests, including neurohormonal levels. The study protocol was approved by all local institutional review boards and ethics committees.

Cardiopulmonary Testing
At baseline and after each treatment phase, patients underwent symptom-limited exercise treadmill testing using the same RAMP protocol and were encouraged to exercise to exhaustion. The RAMP protocol has been recommended by many authors because it allows the increase in work to be individualized. The speed and incline are increased at fixed intervals of 6 to 10 seconds, permitting a constant and continuous increase in external work. Gas exchange was assessed during each exercise test with a computerized metabolic cart (Oxycon Alpha, Jaeger). Gas was sampled through a face mask and analyzed with a computerized metabolic cart. Heart rate, respiratory rate, and blood pressure were recorded at the end of each exercise test.

Neurohormone Levels
Levels of angiotensin II, epinephrine, norepinephrine, and N-terminal pro brain natriuretic peptide (NT-proBNP) were determined with standard assay methods from Roche Diagnostics. A value of P<0.05 was considered statistically significant. The study was performed with SAS software, version 8 (SAS Institute).

Results
Baseline Characteristics
A total of 35 patients from 3 participating centers were randomized (Table 1). Six were excluded from final analyses because of noncompliance with follow-up visits (n=5) and inability to swallow assigned pills (n=1). Thus, 29 patients (age, 18.5 to 60.9 years) completed the study. Twenty-two patients had prior cardiac surgery: All patients with D-TGA had prior Mustard intra-atrial baffle repair at a mean age of 2.5±1.6 years, and 1 patient with L-TGA had closure of a ventricular septal defect and pulmonary commissurotomy at 10 years of age.

Clinical Follow-Up
Mean treatment duration was 106.1±6.1 and 108.6±8.6 days for losartan and placebo, respectively (P=NS). Twenty-five patients (86%) reached the target dose of losartan 50 mg twice daily, whereas 4 remained at 50 mg once a day throughout the study. Mild side effects were equally distributed between the losartan and placebo groups and included dizziness, diarrhea, cough, and muscular pain. No patient experienced a change in functional class during the course of study.

Cardiopulmonary Testing
At baseline, the mean VO2max was 29.8±5.6 mL·kg⁻¹·min⁻¹ (range, 18.5 to 38.6 mL·kg⁻¹·min⁻¹), equivalent to 73.5±12.9% of the predicted value (Table 2). All subjects exercised to the point of exhaustion. No patient reached 100% of the predicted value. The maximum heart rate achieved was ≥85% predicted in 20 patients, between 80% and 84% in 3, and <80% in 6. Comparing losartan to placebo showed no differences in VO2max, total exercise duration, anaerobic...
value of 41 pg/mL for healthy subjects. The mean level of norepinephrine was 204.3 ± 57.7 pg/mL, with 89% of patients having values below the mean 291 pg/mL cutoff for normal subjects.

At baseline, the mean level of NT-proBNP was mildly increased at 257.7 ± 243.4 pg/mL (range, 33.2 to 1048.0 pg/mL), with 44% of patients having lower than the 125-pg/mL cutoff. Patients with lower RV ejection fractions had significantly higher NT-proBNP levels ($r = -0.42, P = 0.02$), but no correlation was found between NT-proBNP levels and baseline $V_{Omax}$ ($r = -0.26, P = 0.16$). Comparing losartan and placebo showed no significant differences in levels of epinephrine, norepinephrine, and NT-proBNP, but an expected increase in angiotensin II, indicating inhibition of the AT1 receptor, was noted (Table 3).

**Discussion**

Over the past 2 decades, advances in pharmacological therapies that target neurohormonal activation have permitted substantial improvements in the prognosis of patients with LV systolic dysfunction. In complex congenital heart disease, however, the morphological RV may be systemically positioned. Faced with an increased afterload, the systemic RV may fatigue over time, resulting in progressive dilatation, systolic dysfunction, and/or decreased exercise tolerance. There is a paucity of data on pathophysiological mechanisms for functional impairment and therapeutic options to support such a failing systemic RV. In particular, it is not known whether patients with systemic RVs may derive similar benefits from treatments validated for systemic LV dysfunction. In this first randomized trial of an angiotensin receptor antagonist in the adult with a systemic RV, no benefit on exercise capacity or NT-proBNP levels was found.

It is well known that LV dysfunction is characterized by increased circulating levels of neurohormones. BNP is secreted by the heart in response to pressure or volume overload and is produced as a prohormone, pro-BNP, that is enzymatically cleaved into BNP and an amino-terminal portion, NT-proBNP. Plasma BNP and NT-proBNP levels are clinically useful in the diagnosis, management, and risk stratification of adults with LV congestive heart failure. Moreover, they are sensitive markers for asymptomatic LV dysfunction and correlate with impaired exercise capacity and lower LV ejection fraction. NT-proBNP levels have been shown to increase proportionally with NYHA functional class. In 105 patients with chronic heart failure in NYHA functional classes I, IIA, IIB, and III, NT-proBNP levels were 103 ± 97.6, 622 ± 472.7, 2241.0 ± 1528.4, and 10 018.0 ± 12 727.0 pg/mL, respectively. Comparatively, our patients had mildly higher levels of NT-proBNP (257 ± 243 pg/mL) than NYHA class I patients but lower levels than NYHA class IIA patients. This impaired exercise capacity has been consistently demonstrated in patients with systemic RVs. In addition, discrepancies between NYHA class and cardiopulmonary exercise testing are not uncommon, with reports suggesting <50% concordance.

**TABLE 1. Baseline Characteristics of the 29 Patients Who Completed the Study**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD age, y</td>
<td>30.3 ± 10.9</td>
</tr>
<tr>
<td>Male, %</td>
<td>83</td>
</tr>
<tr>
<td>Diagnosis, %</td>
<td></td>
</tr>
<tr>
<td>D-TGA after Mustard</td>
<td>72</td>
</tr>
<tr>
<td>L-TGA</td>
<td>28</td>
</tr>
<tr>
<td>Pacemaker (all DDDR), %</td>
<td>34</td>
</tr>
<tr>
<td>Background therapy, %</td>
<td>62</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>24</td>
</tr>
<tr>
<td>Digoxin</td>
<td>14</td>
</tr>
<tr>
<td>Diuretics</td>
<td>7</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>7</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>7</td>
</tr>
<tr>
<td>Propafenone</td>
<td>7</td>
</tr>
<tr>
<td>Sotalol</td>
<td>3</td>
</tr>
<tr>
<td>Warfarin</td>
<td>3</td>
</tr>
<tr>
<td>NYHA class, %</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>93</td>
</tr>
<tr>
<td>II</td>
<td>7</td>
</tr>
<tr>
<td>RV dilatation, %</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>3</td>
</tr>
<tr>
<td>Mild</td>
<td>45</td>
</tr>
<tr>
<td>Moderate to severe</td>
<td>52</td>
</tr>
<tr>
<td>RV ejection fraction (mean ± SD), %</td>
<td>41.6 ± 9.3</td>
</tr>
<tr>
<td>Degree of tricuspid regurgitation, %</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>28</td>
</tr>
<tr>
<td>Mild</td>
<td>52</td>
</tr>
<tr>
<td>Moderate</td>
<td>20</td>
</tr>
</tbody>
</table>

DDDR indicates rate-adaptive DDD.
The detrimental effects of an overactive RAS in LV dysfunction and benefits of pharmacological blockade on exercise tolerance have been repeatedly demonstrated over the past 20 years. In 1983, Kramer et al.8 reported that V˙O₂max exercise tolerance have been repeatedly demonstrated over the past 20 years. In 1983, Kramer et al.8 reported that V˙O₂max, exercise duration, and cardiac index compared with control subjects achieved. Intriguingly, the baseline circulating angiotensin II level was only mildly elevated, with nearly half the patients having normal levels. This provocative finding, combined with the observed lack of clinical benefit, raises the possibility that, unlike patients with LV dysfunction, activation of the RAS is not a dominant pathophysiological contributor to impaired exercise tolerance observed in patients with a systemic RV.

Unfortunately, the situation is less clear when the RV is systemic because prior data were limited to nonrandomized studies involving few patients. In 7 patients >13 years of age with a systemic RV, Lester et al.33 found a small but statistically significant increase in exercise duration after 8 weeks of losartan therapy. The results of our trial, however, are consistent with a subsequent nonrandomized and unblinded study of 8 young patients (mean age, 13.8 years) with D-TGA, a Mustard baffle, and qualitatively depressed RV function that found baseline reductions in V˙O₂max, exercise duration, and cardiac index compared with control subjects with a systemic LV, but no improvements occurred after 12 months of enalapril.34

It is important to note that the lack of benefit observed in our patients occurred despite most having a baseline dilated RV, depressed RV systolic function, decreased exercise tolerance, and an increase angiotensin II level on losartan, indicating that the desired pharmacokinetic response was achieved. Intriguingly, the baseline circulating angiotensin II level was only mildly elevated, with nearly half the patients having normal levels. This provocative finding, combined with the observed lack of clinical benefit, raises the possibility that, unlike patients with LV dysfunction, activation of the RAS is not a dominant pathophysiological contributor to impaired exercise tolerance observed in patients with a systemic RV.

In fact, animal models suggest that activation of the RAS is not implicated in an RV hypertrophy response to pressure overload.35 When pulmonary artery–banded cats were compared with controls, similar levels of angiotensin II were found, prompting the authors to conclude that RV pressure-overload hypertrophy can occur without RAS activation. Moreover, pharmacological modulation of the RAS with losartan and captopril did not alter the extent of hemodynamic overload or hypertrophic response. A clinical study in 53 adults with a variety of congenital heart defects further supports these findings.36 Asymptomatic patients and control subjects had no evidence of RAS activation, unlike those with symptoms.

<table>
<thead>
<tr>
<th>Neurohormones</th>
<th>Normal Values, pg/mL</th>
<th>Losartan, pg/mL</th>
<th>Placebo, pg/mL</th>
<th>P</th>
<th>95% CI for the Difference (Losartan – Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>&lt;41</td>
<td>39.1±41.9</td>
<td>49.3±66.1</td>
<td>0.53</td>
<td>–44.81–24.08</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>&lt;291</td>
<td>256.6±114.7</td>
<td>225.1±86.6</td>
<td>0.18</td>
<td>–18.68–89.30</td>
</tr>
<tr>
<td>Angiotensin II</td>
<td>&lt;5</td>
<td>15.2±13.8</td>
<td>8.8±12.5</td>
<td>0.08</td>
<td>–0.86–13.26</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>&lt;125</td>
<td>201.2±267.8</td>
<td>229.7±291.5</td>
<td>0.10</td>
<td>–54.85–5.64</td>
</tr>
</tbody>
</table>

**TABLE 2.** Results of Cardiopulmonary Testing After 15 Weeks of Losartan Versus 15 Weeks of Placebo

**TABLE 3.** Neurohormone Levels After 15 Weeks of Losartan Versus 15 Weeks of Placebo
If RAS activation is not the primary mechanism implicated in the almost universal findings of decreased exercise capacity, RV dilatation, and RV systolic dysfunction in patients with intra-atrial baffle redirection surgery, other hypotheses merit consideration. Chronotropic incompetence, ischemia, and diastolic dysfunction have been previously proposed. As a result of extensive intra-atrial surgery, sinus node dysfunction is indeed prevalent in this patient population and may contribute to decreased exercise tolerance.\(^1,6,37\) Chronotropic incompetence, however, could not be confirmed in our study because 80% of patients achieved >80% of their maximum predicted heart rate, albeit with some help from implanted pacemakers. Second, reversible and fixed perfusion defects with concordant regional wall motion abnormalities have indeed been documented.\(^38\) Although this may play a role, if ischemic RV cardiomyopathy was primarily responsible for the impaired exercise capacity, some benefit may be expected from afterload reduction with losartan.

Finally, both systolic function and diastolic function have been previously assessed in patients with Mustard and Senning procedures. Reich et al\(^9\) studied 153 children with radionuclide ventriculography and found that, although RV and LV ejection fractions were usually normal 4.4 years postoperatively, the LV peak filling rate was significantly depressed with a marked increase in filling fraction resulting from atrial systole. LV diastolic abnormalities progressed in a subset of 99 patients studied 8.8 years later, despite unaltered RV and LV ejection fractions. Inversely, RV peak filling rate was higher than normal, with a prolonged right atrial contraction time at the expense of shorter RV rapid and slow filling times. The authors surmised that abnormal filling patterns resulted from decreased capacity of the systemic venous atrium and diminished ability of atrial contraction to boost LV filling. In 14 older patients, Derrick et al\(^40\) reported reductions in \(\dot{V}O_2\text{max}\) (77% predicted) despite appropriate responses of load-independent indexes of contraction and relaxation. This finding was attributed to a failure to augment RV filling rates during tachycardia, presumably resulting from AV transport impaired by abnormal intra-atrial pathways.

On the whole, these studies suggest that the main factor limiting an appropriate increase in stroke volume during exertion is decreased preload, which accompanies the exercise-induced tachycardia response. If this were borne out in further studies, \(\beta\)-blockers may prove to be a sounder approach to this therapeutic conundrum than treatment aimed at inhibiting the RAS.

**Study Limitations**

Given the complexity of the patient population, some potential confounding variables such as technical surgical variations, type of palliative surgery before intra-atrial repair, perioperative support, and form of myocardial protection are difficult to quantify and adjust for in analyses. Nevertheless, the randomized and crossover nature of the study design offers some protection over confounding by immeasurable variables. All subjects who participated in this study were in NYHA functional class I or II. Therefore, results may not be applicable to more symptomatic patients. Finally, our study was designed to assess the superiority of losartan versus placebo and is likely underpowered to determine equivalence with placebo. Given that no statistical difference in \(\dot{V}O_2\text{max}\) between the losartan and placebo groups was noted, it is important to consider the risk of a type II error (ie, failing to reject the null hypothesis when a true difference actually exists). Because the observed SD (ie, 3.7 mL · kg\(^{-1}\) · min\(^{-1}\)) was substantially lower than predicted (ie, 7 mL · kg\(^{-1}\) · min\(^{-1}\)) and more patients were enrolled than sample size calculations required, >99% study power was obtained to detect the hypothesized difference of 4.65 mL · kg\(^{-1}\) · min\(^{-1}\), indicating a <1% risk of a type II error. Indeed, the study had >80% power to detect a difference in \(\dot{V}O_2\text{max}\) of as little as 2.0 mL · kg\(^{-1}\) · min\(^{-1}\). It is therefore highly improbable that the lack of improvement in exercise capacity from losartan therapy resulted from insufficient statistical power.

**Conclusions**

Despite impairments in baseline functional testing, adult patients with a systemic RV did not have improved exercise capacity with losartan therapy. Minimal baseline activation of the RAS may explain this lack of benefit. Caution is warranted when results from studies assessing the effects of inhibition of the RAS on the failing LV are extrapolated without independent validation on the systemic RV.

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