Angiotensin Receptor Blockade and Exercise Capacity in Adults With Systemic Right Ventricles: A Multicenter, Randomized, Placebo-Controlled Clinical Trial

Annie Dore, Christine Houde, Kwan-Leung Chan, Anique Ducharme, Paul Khairy, Martin Juneau, François Marcotte and Lise-Andrée Mercier

Circulation 2005;112;2411-2416; originally published online Oct 10, 2005;
DOI: 10.1161/CIRCULATIONAHA.105.543470
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

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

A Multicenter, Randomized, Placebo-Controlled Clinical Trial

Annie Dore, MD; Christine Houde, MD; Kwan-Leung Chan, MD; Anique Ducharme, MD, MSc; Paul Khairy, MD, PhD; Martin Juneau, MD; François Marcotte, MD; Lise-Andrée Mercier, MD

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: $\dot{V}O_2$max, 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 $\dot{V}O_2$max (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,[8–12] 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.

Received February 16, 2005; revision received June 22, 2005; accepted July 29, 2005.

From the Department of Medicine, Montreal Heart Institute, Montreal (A.D., A.D., P.K., M.J., F.M., L.A.M.); Department of Pediatric Cardiology, Quebec Heart Institute, Quebec (C.H.); and Department of Cardiology, Ottawa Heart Institute, Ottawa (K.L.C.), Canada.

Correspondence to Annie Dore, MD, Adult Congenital Heart Center, Montreal Heart Institute, 5000 Belanger St E, Montreal, Quebec, Canada H1T 1C8. E-mail annie.dore@icm-mhi.org

Circulation **is available at http://www.circulationaha.org** **DOI: 10.1161/CIRCULATIONAHA.105.543470**

Study Design

A multicenter, randomized, double-blind, placebo-controlled, crossover 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 spiroergometry, 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 spiroergometry, 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 treadmill exercise testing using the same RAMP protocol and were encouraged to exercise to exhaustion. The RAMP protocol has been recommended by many authors[16,17] 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, Jaegger). Gas was sampled through a Rudolph mask. Recorded variables included maximal oxygen uptake ($\dot{V}O_2$max), oxygen pulse, metabolic units, exercise duration, minute ventilation, heart rate, respiratory rate, and blood pressure. The primary end point, $\dot{V}O_2$max, is the product of cardiac output and AV difference in oxygen content and was defined as the highest value recorded during the last minute of exercise. $\dot{V}O_2$ at the gas exchange anaerobic threshold was determined by means of the V-slope method. $\dot{V}O_2$ at peak exercise was expressed both as milliliters per kilogram per minute and as a percentage of the $\dot{V}O_2$max predicted for age, sex, weight, and height according to previously published normograms.[17]

Transthoracic Echocardiography

A standard 2D Doppler transthoracic echocardiogram was performed at baseline and after each treatment phase. RV dimensions were qualitatively assessed as normal, mildly dilated, or moderately to severely dilated. RV systolic function was assessed both qualitatively (ie, normal, mild, or moderately to severely impaired) and by calculation of an RV ejection fraction using the simplified Simpson method in an apical 4-chamber view.[18] Valvular stenosis and regurgitation were quantified by color and continuous-wave Doppler flow. Systemic and pulmonary venous inflows were evaluated by pulsed-wave Doppler. The presence of an intracardiac shunt was likewise systematically explored.

Neurohormone Levels

Levels of angiotensin II, epinephrine, norepinephrine, and N-terminal pro brain natriuretic peptide (NT-proBNP) were drawn at baseline and at the completion of each treatment phase. Peripheral venous blood samples were obtained in the morning after the subjects rested in a supine position in a dimly lit room for at least 30 minutes. All samples were centrifuged and frozen at −80°C until analysis. Analyses were performed in triplicate at the end of the study. Angiotensin II, epinephrine, and norepinephrine were measured by previously described techniques.[19–21] An angiotensin II level <5 pg/mL was considered normal.[22] Epinephrine and norepinephrine values for normal control subjects in our laboratory (mean±SD) were 40.6±24.3 and 291±111 pg/mL, respectively.[23] NT-proBNP levels were measured with the Elecsys NT-proBNP assay from Roche Diagnostics. A value of $P<125$ pg/mL was considered normal.[24]

Statistical Analysis

Sample size calculations were based on $\dot{V}O_2$max, the primary end point of interest. Assuming an SD of 7 mL · kg^{-1} · min^{-1} as reported by Musewe et al[6] and a conservative intraclass correlation coefficient of 0.3, a total of 26 patients (ie, 13 per treatment arm) were required to obtain 80% power to detect a 4.65-mL · kg^{-1} · min^{-1} difference between losartan and placebo with a 2-sided α of 0.05.

Continuous normally distributed variables are expressed as mean±SD. Differences in outcome variables were compared by use of ANOVA models for repeated measures that accounted for assigned treatment arm (losartan versus placebo) and order of treatment phase (first 15 weeks versus second 15 weeks). Pearson correlation coefficients were used to assess bivariate associations. Two-tailed values of $P<0.05$ were considered statistically significant. Testing 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 dyspnea, fatigue, palpitations, 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 $\dot{V}O_2$max 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 $\dot{V}O_2$max, total exercise duration, anaerobic

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

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

DDDR indicates rate-adaptive DDD.

threshold, heart rate, systolic blood pressure, and oxygen saturation.

Echocardiographic Evaluation

Baseline echocardiographic characteristics are described in Table 1. RV size was abnormal in 95% of the patients. RV systolic function was qualitatively normal in 28%, mildly impaired in 69%, or moderately to severely impaired in 3%. It was possible to quantify the RV ejection fraction in 27 patients (range, 21% to 60%), with no statistically significant improvement in patients on losartan versus placebo (43.1±12.2% versus 40.5±9.9%; $P=0.24$). The degree of tricuspid regurgitation remains unaltered regardless of treatment modality.

Neurohormonal Levels

The mean baseline level of angiotensin II was nearly normal at 5.7±4.9 pg/mL (range, 0.4 to 24.1 pg/mL), with 48% of patients having values below the 5-pg/mL cutoff for normal. No significant correlations were detected between levels of angiotensin II and the baseline RV ejection fraction ($r=-0.18$, $P=0.36$) or $\dot{V}O_2$max ($r=-0.04$, $P=0.82$). The mean baseline level of epinephrine was 32.6±26.7 pg/mL, with 82% of patients having values below the mean normal 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 $\dot{V}O_2$max ($r=-0.26$, $P=0.16$). 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.[25–28] Moreover, they are sensitive markers for asymptomatic LV dysfunction[25] and correlate with impaired exercise capacity and lower LV ejection fraction.[26,27,29] NT-proBNP levels have been shown to increase proportionally with NYHA functional class.[29] In 105 patients with chronic heart failure in NYHA functional classes I, IIA, IIB, and III, NT-proBNP levels were 103.4±97.6, 622.2±472.7, 2241.0±1528.4, and 10 018.0±12 727.0 pg/mL, respectively.[29] 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 finding may be explained in part by an objectively decreased exercise capacity ($\dot{V}O_2$max 73.5% predicted), despite 27 of 29 patients reporting being in NYHA class I. This impaired exercise capacity has been consistently demonstrated in patients with systemic RVs.[6,7] In addition, discrepancies between NYHA class and cardiopulmonary exercise testing are not uncommon, with reports suggesting <50% concordance.[30]

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

	Losartan	Placebo	*P*	95% CI for the Difference (Losartan−Placebo)
Maximum oxygen consumption, mL · kg^{-1} · min^{-1}	29.9±5.4	29.4±6.2	0.43	−0.87–1.95
Exercise duration, s	632.3±123.0	629.9±140.7	0.76	−26.11–34.93
Anaerobic threshold, mL · kg^{-1} · min^{-1}	22.0±3.6	22.7±4.2	0.34	−2.23–0.79
METs, n	8.5±1.6	8.5±1.8	0.78	−0.36–0.47
Heart rate at rest, bpm	71.7±12.9	69.7±14.0	0.45	−3.23–7.09
Maximum heart rate, bpm	166.1±18.2	164.6±18.7	0.46	−2.75–5.87
Maximal predicted heart rate, %	86.6±8.5	86.3±8.7	0.83	−3.17–3.91
Systolic blood pressure at rest, mm Hg	121.6±13.2	122.6±11.5	0.66	−6.01–3.90
Maximum systolic blood pressure, mm Hg	144.6±19.4	148.2±28.5	0.49	−11.31–5.59
Oxygen saturation at rest, %	96.8±1.6	96.7±2.1	0.74	−0.59–0.82
Maximum oxygen saturation, %	93.1±3.8	92.3±4.9	0.27	−0.62–2.14
Respiratory exchange ratio	1.20±0.11	1.17±0.07	0.03	0.00–0.07

METs indicates metabolic equivalents.

The detrimental effects of an overactive RAS in LV dysfunction[31] 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 $\dot{V}O_2$max increased from 12.9±2.3 to 15±1.8 mL · kg^{-1} · min^{-1} after 3 months of therapy with captopril in patients with NYHA class II to IV symptoms and an LV ejection fraction <25%. Sharpe et al[9] also observed an increase in exercise duration in NYHA class II and III patients, from 9.3±5.7 to 17.6±5.6 minutes after 3 months of treatment with enalapril. When an angiotensin II receptor inhibitor, losartan 50 mg daily, was compared with enalapril 20 mg daily in a 12-week randomized parallel trial of 116 patients in NYHA class II to IV with an LV ejection fraction <45%, equivalent benefits in exercise duration, 6-minute walk test, and LV ejection fraction were found.[32]

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 $\dot{V}O_2$max, 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 3. Neurohormone Levels After 15 Weeks of Losartan Versus 15 Weeks of Placebo

Neurohormones	Normal Values, pg/mL	Losartan, pg/mL	Placebo, pg/mL	*P*	95% CI for the Difference (Losartan−Placebo)
Epinephrine	<41	39.1±41.9	49.3±66.1	0.53	−44.81–24.08
Norepinephrine	<291	256.6±114.7	225.1±86.6	0.18	−18.68–89.30
Angiotensin II	<5	15.2±13.8	8.8±12.5	0.08	−0.88–13.26
NT-proBNP	<125	201.2±267.8	229.7±291.5	0.10	−54.85–5.64

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[39] 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 LV and RV 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 $\dot{V}O_2$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, β-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 equivalency with placebo. Given that no statistical difference in $\dot{V}O_2$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 $\cdot$ kg^{-1} $\cdot$ min^{-1}) was substantially lower than predicted (ie, 7 mL $\cdot$ kg^{-1} $\cdot$ 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 $\cdot$ kg^{-1} $\cdot$ min^{-1}, indicating a <1% risk of a type II error. Indeed, the study had >80% power to detect a difference in $\dot{V}O_2$max of as little as 2.0 mL $\cdot$ kg^{-1} $\cdot$ 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.

Acknowledgments

Losartan and placebos were provided by Merck-Frosst Canada. The Réseau en santé cardiovasculaire du Fonds de la recherche en santé du Québec provided funding for the nurse coordinator. Dr Ducharme is supported by the Fonds de la recherche en santé du Québec; Dr Khairy, by a Canada Research Chair in Adult Congenital Heart Disease and Electrophysiology. We wish to acknowledge the support of Maude Bergeron, RN, who helped with the randomization process, test coordination, and data collection, and Dr Angelo Calderone for his expert laboratory support.

References

1. Myridakis DJ, Ehlers KH, Engle MA. Late follow-up after venous switch operation (Mustard procedure) for simple and complex transposition of the great arteries. *Am J Cardiol*. 1994;74:1030–1036.
2. Connelly MS, Liu PP, Williams WG, Webb GD, Robertson P, McLaughlin PR. Congenitally corrected transposition of the great arteries in the adult: functional status and complications. *J Am Coll Cardiol*. 1996;27:1238–1243.
3. Ramsay JM, Venables AW, Kelly MJ, Kalff V. Right and left ventricular function at rest and with exercise after the Mustard operation for transposition of the great arteries. *Br Heart J*. 1984;51:364–370.
4. Hurwitz RA, Caldwell RL, Girod DA, Brown J. Right ventricular systolic function in adolescents and young adults after Mustard operation for transposition of the great arteries. *Am J Cardiol*. 1996;77:294–297.
5. Piran S, Veldtman G, Siu S, Webb GD, Liu PP. Heart failure and ventricular dysfunction in patients with single or systemic right ventricles. *Circulation*. 2002;105:1189–1194.
6. Musewe NN, Reisman J, Benson LN, Wilkes D, Levison H, Freedom RM, Trusler GA, canny GJ. Cardiopulmonary adaptation at rest and during exercise 10 years after Mustard atrial repair for transposition of the great arteries. *Circulation.* 1988;77:1055–1061.
7. Fredriksen PM, Veldtman G, Hechter S, Therrien J, Chen A, Warsi MA, Freeman M, Liu P, Siu S, Thaulow E, Webb G. Aerobic capacity in adults with various congenital heart diseases. *Am J Cardiol*. 2001;87:310–314.
8. Kramer BL, Massie BM, Topic RN. Controlled trial of captopril in chronic heart failure: a rest and exercise hemodynamic study. *Circulation*. 1983;67:807–816.
9. Sharpe DN, Murphy J, Coxon R, Hannan SF. Enalapril in patients with chronic heart failure: a placebo-controlled, randomized, double-blind study. *Circulation*. 1984;70:271–278.

10. Pfeffer MA, Lamas GA, Vaughan DE, Parisi AF, Braunwald E. Effect of captopril on progressive ventricular dilatation after anterior myocardial infarction. *N Engl J Med*. 1988;319:80–86.
11. Cleland JGF, Shah D, Krickler S, Dritsas A, Nihoyannopoulos P, Frost G, Oakley CM. Effects of lisinopril on cardiorespiratory, neuroendocrine, and renal function in patients with asymptomatic left ventricular dysfunction. *Br Heart J*. 1993;69:512–515.
12. Riegger GAJ, Bouzo H, Petr P, Münz J, Spacek R, Pethig H, von Behren V, George M, Arens HJ. Improvement in exercise tolerance and symptoms of congestive heart failure during treatment with candesartan cilexitil. *Circulation*. 1999;100:2224–2230.
13. SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fraction. *N Engl J Med.* 1992;327:685–691.
14. Pfeffer MA, Braunwald E, Moyé LA, Basta L, Brown EJ, Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC, Klein M, Lamas GA, Packer M, Rouleau J, Rouleau JL, Rutherford J, Wertheimer JH, Hawkins CM. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 1992; 327:669–677.
15. SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med.* 1991;325:292–302.
16. Myers J, Froelicher VF. Optimizing the exercise test for pharmacological investigations. *Circulation*. 1990;82:1839–1846.
17. Froelicher VF, Myers J, Follansbee WP. *Exercise and the Heart*. 3rd ed. St Louis, Mo: Mosby; 1993.
18. Ninomiya K, Duncan WJ, Cook DH, Olley PM, Rowe RD. Right ventricular ejection fraction and volumes after Mustard repair: correlation of two dimensional echocardiograms and cineangiograms. *Am J Cardiol*. 1981;48:317–324.
19. Mettauer B, Rouleau JL, Bichet D, Kortas C, Manzini C, Tremblay G, Chatterjee K. Differential long-term intrarenal and neurohormonal effects of captopril and prazosin in patients with chronic congestive heart failure: importance of initial plasma renin activity. *Circulation*. 1986;73: 492–502.
20. Passon PG, Peuler JD. A simplified radiometric assay for plasma norepinephrine and epinephrine. *Anal Biochem*. 1973;51:618–631.
21. de Champlain J, Karas M, Nguyen P, Cartier P, Wistaff R, Toal CB, Nadeau R, Larochelle P. Different effects of nifedipine and amlodipine on circulating catecholamine levels in essential hypertensive patients. *J Hypertens*. 1998;16:1357–1369.
22. Bragat AC, Blumenfeld J, Sealy JE. Effect of high-performance liquid chromatography on plasma angiotensin, II: measurements in treated and untreated normotensive and hypertensive patients. *J Hypertens*. 1997;15: 459–465.
23. White M, Rouleau JL, Hall C, Arnold M, Harel F, Sirois P, Greaves S, Solomon S, Ajani U, Glynn R, Hennekens C, Pfeffer M. Changes in vasoconstrictive hormones, natriuretic peptides, and left ventricular remodeling soon after anterior myocardial infarction. *Am Heart J*. 2001; 142:1056–1064.
24. McDonagh TA, Holmer S, Raymond I, Luchner A, Hildebrant P, Dargie HJ. NT-proBNP and the diagnosis of heart failure: a pooled analysis of three European epidemiological studies. *Eur J Heart Fail*. 2004;6: 269–273.
25. McDonagh TA, Robb SD, Murdoch DR, Morton JJ, Ford I, Morrison CE, Tunstall-Pedoe H, McMurray JJV, Dargie HJ. Biochemical detection of left-ventricular dysfunction. *The Lancet*. 1998;351:9–13.
26. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, Omland T, Storrow AB, Abraham WT, Wu AHB, Clopton P, Steg PG, Westheim A, Wold Knudsen C, Perez A, Kazanegra R, Herrmann HC, McCullough PA. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med*. 2002;347:161–167.
27. Tsutamoto T, Wada A, Maeda K, Hisanaga T, Maeda Y, Fukai D, Ohnishi M, Sugimoto Y, Kinoshita M. Attenuation of compensation of endogenous cardiac natriuretic peptide system in chronic heart failure. *Circulation*. 1997;96:509–516.
28. Groenning BA, Nilsson JC, Sondergaard L, Pedersen F, Tonwinski J, Baumann M, Larsson HBW, Hihlebrandt PR. Detection of left ventricular enlargement and impaired systolic function with plasma N-terminal pro brain natriuretic peptide concentrations. *Am Heart J*. 2002;143:923–929.
29. Seino Y, Ogawa A, Yamashita T, Fukushima M, Ogata K, Fukumoto H, Takano T. Application of NT-proBNP and BNP measurements in cardiac care: a more discerning marker for the detection and evaluation of heart failure. *Eur J Heart Fail*. 2004;6:295–300.
30. Rostagno C, Galanti G, Comeglio M, Boddi V, Olivo G, Gastone Neri Serneri G. Comparison of different methods of functional evaluation in patients with chronic heart failure. *Eur J Heart Fail*. 2000;2:273–280.
31. Francis GS, Benedict C, Johnstone DE, Kirlin PC, Nicklas J, Liang CS, Kubo SH, Rudin-Toretsky E, Yusuf S. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure: a substudy of the Studies of Left Ventricular Dysfunction (SOLVD). *Circulation*. 1990;82:1724–1729.
32. Lang RM, Elkayam U, Yellen LG, Krauss D, McKelvie RS, Vaughan DE, Ney DE, Makris L, Chang PI. Comparative effects of losartan and enalapril on exercise capacity and clinical status in patients with heart failure. *J Am Coll Cardiol*. 1997;30:983–991.
33. Lester SJ, McElhinney DB, Viloria E, Reddy GP, Ryan E, Tworetzky W, Schiller NB, Foster E. Effects of losartan in patients with a systemically functioning morphologic right ventricle after atrial repair of transposition of the great arteries. *Am J Cardiol*. 2001;88:1314–1316.
34. Robinson B, Heise CT, Moore JW, Anella J, Sokoloski M, Eshaghpour E. Afterload reduction therapy in patients following intraatrial baffle operation for transposition of the great arteries. *Pediatr Cardiol*. 2002; 23:618–623.
35. Koide M, Carabello BA, Conrad CC, Buckley JM, DeFreyte G, Barnes M, Tomanek RJ, Wei CC, Dell'Italia LJ, Cooper IVG, Zile MR. Hypertrophic response to hemodynamic overload: role of load vs renin-angiotensin system activation. *Am J Physiol*. 1999;276:H350–H358.
36. Bolger AP, Sharma R, Wei L, Leenarts M, Kalra PR, Kemp M, Coats AJS, Anker SD, Gatzoulis MA. Neurohormonal activation and the chronic heart failure syndrome in adults with congenital heart disease. *Circulation*. 2002;106:92–99.
37. Paridon SM, Humes RA, Pinsky WW. The role of chronotropic impairment during exercise after the Mustard operation. *J Am Coll Cardiol*. 1991;17:729–732.
38. Millane T, Bernard EJ, Jaeggi E, Hawman-Giles RB, Uren RF, Gartmill TB, Hawker RE, Celermajer DS. Role of ischemia and infarction in late right ventricular dysfunction after atrial repair of transposition of the great arteries. *J Am Coll Cardiol*. 2000;35:161–168.
39. Reich O, Voriskova M, Ruth C, Krejcir M, Marek J, Skovranek J, Hucin B, Samanek M. Long term ventricular performance after intra-atrial correction of transposition: left ventricular filling is the major limitation. *Heart*. 1997;78:376–381.
40. Derrick GP, Narang I, White PA, Kelleher A, Bush A, Penny DJ, Redington AN. Failure of stroke volume augmentation during exercise and dobutamine stress is unrelated to load-independent indexes of right ventricular performance after the Mustard operation. *Circulation.* 2000; 102(suppl III):III-154–III-159.