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Impact of Spironolactone on Endothelial Function in Patients with Single Ventricle Heart

William T. Mahle, MD^{*}, Alicia Wang, MD[†], Arshed A. Quyyumi, MD[‡], Michael E. McConnell, MD^{*}, and Wendy M. Book, MD[§]

^{*}Pediatrics, Emory University School of Medicine, Atlanta, Ga

[‡]Cardiology, Emory University School of Medicine, Atlanta, Ga

[§]Internal Medicine, Emory University School of Medicine, Atlanta, Ga

[†]Pediatrics, University of Connecticut School of Medicine, Conn, USA

Abstract

Background—Mid-term survivors of the Fontan procedure are at risk for progressive heart failure, and endothelial dysfunction is thought to contribute to this process. Aldosterone antagonism has been shown to improve survival in adults with heart failure and the effects are mediated in part by changes in endothelial function. In the present study, we sought to determine if a short course of spironolactone improves endothelial function and alters serum cytokine profiles in adolescents and adults with single ventricle heart.

Methods—Subjects had baseline assessment of flow-mediated dilation and cytokine profiles (C-reactive protein, interleukin-6, interleukin-1b, interleukin-10, tumor necrosis factor- α). They were started on spironolactone 25 mg once a day and uptitrated to 50 mg once daily. After 4 weeks, flow-mediated dilation and cytokine profiles were re-evaluated.

Results—Ten subjects (median age 28 years) were enrolled and completed the protocol. The median flow-mediated dilation at baseline was 9.1% and did not change significantly after 4 weeks of spironolactone 7.6%, $P = .46$. There was mild elevation in serum cytokine profiles and only interleukin-1b decreased significantly with therapy, 0.39 to 0.23 pg/mL, $P = .04$.

Conclusions—In this small study, a short course of spironolactone did not improve endothelial function or alter the majority of serum cytokine levels. Whether single ventricle patients might realize other potential benefits of aldosterone antagonism such as reduced cardiac fibrosis remains to be determined.

Keywords

Endothelial Function; Fontan; Inflammation

Introduction

While early surgical results for palliation of single ventricle lesions have improved dramatically, the risk of heart failure in the intermediate-term remains high.¹ A number of factors have been associated with the risk of developing progressive heart failure in this

population including atrioventricular valve insufficiency and residual obstructive lesions.² In recent years, investigators have demonstrated that impaired endothelial function and abnormal ventriculovascular coupling occur in the single ventricle population.^{3–6} Moreover, decreased endothelial function has been shown to correlate with poor exercise performance.⁴ As such, therapies directed at improving endothelial function have been proposed. Angiotension-converting enzyme (ACE) inhibitors are used in the majority of adolescents and adults with single ventricle.⁷

More recently, there has been interest in the potential benefits of aldosterone antagonists in the management of heart failure.⁸ Aldosterone antagonists such as spironolactone and eplerenone have been shown to improve survival in large congestive heart failure (CHF) trials in adults.⁹ The mechanism by which these agents improve survival is most likely multifactorial. Aldosterone antagonism is thought to reduce the development of cardiac fibrosis.¹⁰ In addition, spironolactone has been shown to improve endothelial function in adults with CHF. Spironolactone is thought to improve endothelial function in CHF primarily by increasing nitric oxide bioactivity, improving endothelial vasodilator dysfunction, and suppressing vascular angiotensin I/angiotensin II conversion.¹¹ As such, aldosterone antagonists are routinely administered to adults with CHF.¹²

It is not known, however, whether spironolactone should be administered routinely following the Fontan procedure. In the present study, we sought to determine whether the short-term administration of spironolactone improves endothelial function following the Fontan procedure and whether any changes are mediated by proinflammatory markers.

Methods

With the approval of the Institutional Review Board of Emory University, subjects were recruited from the Adult Congenital Heart Clinic at Emory University School of Medicine and Sibley Heart Center at Children's Healthcare of Atlanta. The study included patients with single ventricle heart lesions who had undergone the Fontan procedure and were 15 years of age and lived within 100 miles of the study center. Exclusion criteria included: (1) history of smoking; (2) diabetes mellitus; (3) renal failure (serum creatinine >2.5 mg/dL); (4) history of hyperkalemia (serum potassium >5.5 mEq/L); and (5) listed for heart transplantation. Subjects already receiving spironolactone for maintenance therapy were not eligible for enrollment.

Patients were screened for eligibility and informed written consent was obtained. Baseline serum chemistry was obtained along with a cytokine panel. The cytokine panel consisted of C-reactive protein, interleukin-6, interleukin-1b, interleukin-10, and tumor necrosis factor- α .

Endothelium-dependent brachial artery flow-mediated dilation (FMD) was determined as previously described after a blood sample for biomarker evaluation was obtained.¹³ Briefly, ultrasound images were obtained at baseline under standardized conditions and 60 seconds after induction of reactive hyperemia by 5-minute cuff occlusion of the forearm. Images were digitized online, and arterial diameters were measured with customized software. FMD was expressed as the percentage increase in diameter from baseline.

Spironolactone

The starting dose of spironolactone was 25 mg daily. After 2 weeks, this dose was doubled to a maximum dose of 50 mg daily. Measurement of serum electrolytes was undertaken at baseline and at 2 weeks.

Follow Up

After 4 weeks of spironolactone, subjects returned for repeat assessment of FMD and serum cytokines. At study completion, continuation of spironolactone was left to the discretion of the attending cardiologist.

Statistical Considerations

Comparison between enrolled subjects and ineligible subjects was performed with Fisher's exact test and chi-square for trend. The McNemar test was employed to analyze New York Heart Association class. The Mann–Whitney *U* test was performed to determine changes in FMD from baseline to follow up and to assess changes in cytokine levels. Correlation between baseline FMD and patient variables and baseline serum cytokine levels was performed with stepwise linear regression. Analysis was performed with STATA 6.0 (Stata Corp., College Station, Tex).

Results

There were 33 age-appropriate patients who had undergone the Fontan procedure who were identified through the clinic database. Fourteen subjects were already receiving spironolactone as part of routine therapy. Seven subjects refused consent. Therefore, 12 subjects were enrolled in the study, 10 of whom completed 4 weeks of spironolactone therapy and underwent reevaluation. Comparison between the subjects who were enrolled to those ineligible because of exclusion criteria is shown in Table 1. The median age of study subjects was 28 years, range 15–42 years. The anatomic defects of the 10 subjects initially enrolled included tricuspid atresia ($n = 3$), pulmonary atresia with intact ventricular septum, double outlet right ventricle ($n = 2$), hypoplastic left heart syndrome ($n = 1$), unbalanced atrioventricular canal ($n = 1$), and other ($n = 1$). The summary of baseline medications is shown in Table 2.

At baseline, the median FMD was 9.1%. There was no significant association between age and previous history of aortic arch anomaly and the measured FMD at baseline.

In our study, administration of spironolactone was well tolerated and no subject needed to discontinue medication. Administration of spironolactone was associated with a significant reduction in interleukin-1b, but all other cytokine measures remained unchanged (Table 3). There was no significant change in FMD with the administration of spironolactone. The median FMD at follow up was 7.6% as compared with 9.1% at baseline (Figure 1).

Discussion

In the present study, a 4-week trial of spironolactone did not significantly alter endothelial function as measured by FMD. The majority of cytokines also appeared unchanged by addition of an aldosterone antagonist to routine medical management. It is unclear what role spironolactone has in the management of adolescents and adults with functional single ventricle.

We and others have previously demonstrated that school-age children with Fontan-type physiology have impaired endothelial function. Endothelial dysfunction plays an important role in the pathogenesis of heart failure. We also studied the relationship between asymmetric dimethylarginine, an endogenous inhibitor of nitric oxide synthase, or symmetric dimethylarginine, which competes with arginine for cellular uptake, and endothelial function. In that study, the median FMD was significantly lower in the Fontan patients vs. controls, 4.2% vs. 7.9%, ($P = .007$). The FMD in Fontan patients in the present series was significantly higher than the previous report. It is important to note that while

these studies were performed at the same institution, they were also carried out in different vascular laboratories, and FMD data are generally thought not to be generalizable across laboratories. Another explanation for this difference is that the present study enrolled the “least sick” patients because subjects already on spironolactone or listed for transplantation were not included.

A number of interventions have been shown to improve endothelial function in adults with CHF. These interventions include regular exercise training and use of ACE inhibitors among others. The suppression of aldosterone by ACE inhibitors in CHF, however, is not sustained and both angiotensin II and aldosterone levels are reactivated in many patients with CHF during long-term ACE inhibition. This process has been called “aldosterone escape.” Aldosterone escape results in sodium retention, hypokalemia, sympathetic activation, parasympathetic inhibition, myocardial fibrosis, and endothelial dysfunction.¹¹ Experimental evidence suggests that aldosterone inhibits nitric oxide activity, and the addition of spironolactone to ACE inhibitors in CHF rat models normalizes nitric oxide-mediated relaxation.¹⁴ In patients with CHF on ACE inhibitors, the addition of spironolactone increases nitric oxide bioavailability, suggesting a major role for improved endothelial function through nitric oxide release. Cumulatively, these effects accounted for the significant 30% survival advantage in the Randomized Aldactone Evaluation Study in patients receiving spironolactone in addition to standard therapy for CHF, including diuretics and ACE inhibition.¹⁵

Abiose et al. have shown that the addition of spironolactone to standard heart failure therapy improves endothelial function in adults with CHF.¹⁶ FMD improved from a mean baseline value of $5.5 \pm 2.1\%$ to $9.3 \pm 4.0\%$ after 4 weeks of spironolactone treatment ($P = .017$) and to $9.0 \pm 3.4\%$ after 8 weeks ($P = .018$). On multivariate analysis, changes in FMD were not significantly correlated or predicted by variables such as gender, ejection fraction, diabetes mellitus, coronary artery disease, or treatment for hyperlipidemia.

There are several possible explanations for the lack of benefit of spironolactone in our study population. Admittedly, the overall study size is small. Hence, we cannot exclude a type II error. As mentioned previously, approximately 50% of the subjects followed in our clinic were already receiving spironolactone. These patients tended to be on more cardiac medications, especially diuretics, and were clinically more symptomatic. We did not feel that it was appropriate to withdraw medications in this population for the purposes of enrollment, and hence, the study enrolled primarily mildly symptomatic patients. Therefore, we may have been evaluating the impact of spironolactone in the healthiest subset of Fontan patients. This notion is supported by the fact that the degree of elevation of cytokines was really quite mild in our study population. The median C-reactive protein level was 1.10. Most studies of adults with CHF from ischemic and nonischemic cardiomyopathy have reported mean C-reactive protein levels that are 2–3-fold higher.¹⁷ Lastly, it should be recognized that not all populations appear to respond equally to aldosterone antagonism. Studies in adults with diabetes have suggested that spironolactone worsens endothelial function.¹⁸ In addition, the American Heart Association/American College of Cardiology consensus guidelines suggest that aldosterone antagonism should be considered only in those patients with low ejection fraction.¹² It is unknown if the beneficial effects exist to a similar degree in primary diastolic heart failure.¹⁹

It is also important to consider that spironolactone is thought to have numerous other benefits in addition to modulating endothelial function. Aldosterone antagonism is thought to slow or prevent cardiac fibrosis.¹⁰ It is known that the most common form of heart failure in adults with Fontan circulation is impaired diastolic function with elevation in atrial pressure, and ultimately, elevation in systemic venous pressure. It is possible that

spironolactone can act favorably in the single ventricle population through this mechanism but a short 4-week course of therapy is unlikely to have a major impact on this chronic process.

In summary, in a small cohort of adults and adolescents who had undergone the Fontan procedure for single ventricle heart lesions, a short course of spironolactone did not improve endothelial function or alter most inflammatory cytokines.

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Figure 1. Box and whisker plot of flow-mediated dilation (FMD) at baseline and after 4 weeks of spironolactone therapy.

Table 1

Patient Data Enrolled and Ineligible Subjects

	Enrolled n = 10	Ineligible n = 14	P
Median age in years (range)	28 (15–42)	29 (15–46)	.89
Single right ventricle morphology	2 (20%)	2 (14%)	.86
NYHA class			.17
I	5 (50%)	3 (21%)	
II	5 (50%)	6 (43%)	
III	0	4 (29%)	
IV	0	1 (7%)	
Protein-losing enteropathy	0	3 (21%)	.35
AV valve regurgitation moderate	3 (30%)	7 (50%)	.58

AV, atrioventricular; NYHA, New York Heart Association.

Table 2

Cardiac Medication Usage at Baseline

Medication	n (%)
ACE inhibitor	8 (80)
Digoxin	6 (60)
Aspirin	4 (40)
Loop diuretic	3 (30)
Carvedilol	1 (10)
Amiodarone	1 (10)
Atenolol	1 (10)

ACE, angiotension-converting enzyme.

Table 3

Cytokine Levels at Baseline and after Spironolactone Therapy

	Baseline	4-Week Follow Up	<i>P</i>
CRP	1.10 (0.15–21.4)	1.10 (0.17–19.95)	.75
IL-6	1.96 (1.18–14.78)	1.54 (1.29–5.29)	.48
IL1b	0.38 (0.23–0.53)	0.23 (0.08–0.48)	.04
IL10	0.26 (<0.10–0.36)	0.13 (<0.10–0.70)	.39
TNF-a	2.20 (1.17–5.72)	2.42 (1.54–5.94)	.54

CRP, C-reactive protein; IL, interleukin; TNF-a, tumor necrosis factor-alpha.