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A randomized, double blind pilot study to assess the effects of losartan vs. atenolol on the biophysical properties of the aorta in patients with Marfan and Loeys–Dietz syndromes ☆

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ABSTRACT

Background: Patients with Marfan (MFS) and Loeys–Dietz (LDS) syndromes have been shown to have abnormal aortic biophysical properties. The purpose of this study was to compare the effects of 12-months of therapy with atenolol or losartan on vascular function in young patients with MFS and LDS.
Methods: Seventeen patients with MFS or LDS were recruited and randomized to treatment with atenolol, 25–50 mg, or losartan, 25 mg daily. Prior to treatment and following therapy, echocardiography for left ventricular size, function and aortic root size was performed. Pulse wave velocity (PWV), input (Zi, ZiF) and characteristic (Zc, ZcF) impedances, arterial stiffness (Ep and β-index), total arterial compliance (TAC), mean (Wm) and total (Wt) hydraulic power, efficiency, power cost per unit of forward flow (Wt/CI) and brachial artery flow-mediated dilation (FMD) were measured.
Results: The atenolol group consisted of 9 females (17.6 years) and the losartan group 7 males and 1 female (17.0 years). Their height, weight, BSA, BMI, systolic and diastolic blood pressures were similar. Baseline to 12-month changes for atenolol and losartan were PWV (20% vs −14%), Zi (−2% vs −27%), Zc (−20% vs −27%), Ep (1%, vs −13%), β-index (10% vs 14%), FMD (11% vs 20%), TAC (3% vs 42%), Wm (−24% vs 15%), Wt (−24% vs 17%), and Wt/CI (3% vs 21%). There was a trend for losartan to decrease PWV and stiffness indexes while atenolol decreased power and power/unit flow.
Conclusion: This pilot study suggests that atenolol and losartan may have different mechanisms of action on vascular function. A larger clinical trial is needed to confirm these effects.
Clinical trials registration NCT00593710 (ClinicalTrials.gov).

1. Introduction

Marfan syndrome (MFS) is an autosomal dominant, multisystem connective tissue disorder caused by a mutation in chromosome 15 affecting the fibrillin gene FBN1 [1–5]. Its effects are mediated by increased signaling of TGF -beta (TGF-β) due to decreased binding with the abnormal fibrillin-1 in elastic fibers and other tissues [6,7]. The syndrome is characterized by tall stature, skeletal changes, ectopia lentis and, most importantly, abnormal aortic elastic fibers leading to progressive aortic root dilation, dissection and possible rupture [1,3]. Recently, a closely related autosomal dominant connective tissue disorder caused by a TGF-β receptor abnormality was described by Loeys and Dietz (LDS) in which skeletal features and aortopathy are similar to that of MFS [8].

Beta blockers have been the standard treatment for MFS since the report by Shores et al. [9], but recently losartan, an angiotensin II receptor antagonist, has been introduced on the basis of experimental work with

Abbreviations: β-Index, stiffness index; BMI, body mass index; BPD, diastolic blood pressure; BPS, systolic blood pressure; BSA, body surface area; CI, cardiac index; EF, ejection fraction; Ep, elastic modulus; FMD, flow-mediated dilatation; HR, heart rate; IVSDs, interventricular septum dimension in systole; LDS, Loeys–Dietz syndrome; LVEDd, left ventricular end-diastolic dimension; LVEDs, left ventricular end-systolic dimension; LVMI, left ventricular mass indexed for body surface area; MBP, mean blood pressure; MFS, Marfan syndrome; MVCFc, mean velocity of circumferential fiber shortening, rate corrected; PP, pulse pressure; PWd, posterior wall dimension in diastole; PWs, posterior wall dimension in systole; PWV, pulse wave velocity; σPS, stress at peak systole; SF, shortening fraction; ST, sino-tubular; SVI, stroke volume index; TAC, total arterial compliance; Wm, mean hydraulic power; Wt, total hydraulic power; Wt/CI, power cost per unit of forward flow; Zc, characteristic impedance; ZcF, Fourier-derived characteristic impedance; Zi, input impedance; ZiF, Fourier-derived input impedance.

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the Marfan mouse model [10]. While losartan was found to be dramatically successful in preventing aortic disease in this model, there have been no reports of randomized trials in humans, although small case series on the use of losartan have been reported [11–13], and there is one very recent larger open-label study in older patients [14]. The results of a number of larger trials of beta blockers versus losartan or losartan versus placebo are underway, but the results of these are pending [15–19].

The aorta of patients with MFS has been shown to be stiff even in those in whom aortic dilation had not yet occurred [20,21]. In addition to the aortic disease caused by abnormal elastic fibers, endothelial and smooth muscle dysfunction has been described in humans and in animal models [22–24]. Endothelial dysfunction has been shown to contribute to aortic disease and all of these conditions combine to increase left ventricular afterload.

One small trial comparing the ACE inhibitor perindopril with placebo reported the effects on vascular function; however, these patients were also taking beta blockers [25]. Another randomized, double-blind controlled trial reported the effects of atenolol, perindopril and verapamil on aspects of hemodynamic and vascular function in a small number of adult Marfan patients over a relatively short period of time [26]. Echo Doppler methods of assessing the vascular properties of the aorta have been established [20,27,28]. More recently, our laboratory has developed a method of measuring impedance, total arterial compliance, power and efficiency using hydraulic theory [29] that is similar to an invasive study performed on a small cohort of Marfan patients [30]. This type of information can provide insight into the mechanisms involved in the changes in vascular function. The purpose of this study was to perform a randomized blinded comparison of the effects of the beta blocker, atenolol, and the angiotensin II-receptor blocker, losartan, on the vascular properties of the aorta, hydraulic power and efficiency, and endothelial function in adolescents and young adults with MFS or LDS.

2. Methods

2.1. Patients

The databases of the British Columbia Children's Hospital (BCCH) and St. Paul's Hospital Pacific Adult Congenital Heart (PACH) clinics were searched for patients with MFS who had not had aortic root surgery. There were 48 patients who were eligible for enrolment in the study. Twenty-nine of these patients declined to participate; 19 were consented. One patient with severe aortic dilation and valvar insufficiency was not randomized, another patient who was randomized died in a motor vehicle accident. Seventeen eligible patients completed the trial. All patients were examined prior to enrolment to ensure that they met the diagnostic criteria for MFS based on the original Ghent nosology [31]. We used the results of the family history, echocardiographic, X-ray, ophthalmologic investigations and the results of genetic testing, if available, to make the diagnosis of MFS. During the course of the study, genetic information became available on some of the patients. One patient tested positive for both MFS and LDS. Among our cohort, 6 had their diagnosis made on clinical features plus a positive family history, 5 had the clinical features and positive genetic testing, and 3 patients met the criteria for MFS based on clinical findings alone. One patient with a first degree relative with MFS, had findings suggestive of LDS and is awaiting the results of genetic testing, and another patient, who met the Ghent criteria was gene positive for LDS.

The patients were randomized in blocks of four to either the atenolol or losartan therapeutic arm of the study. The physicans, nursing staff and echocardiography technicians were blinded to the assignment of study medications. The dose of losartan was 25 mg once daily and atenolol was 25 mg or 50 mg once daily according to the patient's size. Patients in the beta blocker arm of the study were initially prescribed half of their dose, and the study pharmacist increased the dose of their medication to the full dose according to the heart rate response. A decrease in heart rate of ≥20% after one week's therapy was considered to be an appropriate response to the medication. Only one patient, with a heart rate of 40 bpm, did not receive the full dose of atenolol and one patient's dose of atenolol was halved because of symptoms during the study. Patients were tested prior to randomization and at 12-months of treatment.

2.1.1. Echo Doppler

The techniques that we used to measure the vascular properties of the aorta have been described previously [20,32]. In brief, standard 2-dimensional, M-mode and Doppler echocardiography were performed on all patients. The ventricular ejection fraction was calculated from end-systolic and end-diastolic volumes estimated using a Simpson's rule algorithm. Aortic annulus was measured at the valve leaflets in systole from the parasternal long axis view. The aortic flow was calculated from the pulse wave Doppler waveform in the apical five-chamber view. From the standard suprasternal long-axis view of the aortic arch, pulse wave Doppler waveforms were obtained in the ascending and descending aorta respectively and on-line calipers were used to measure the length of the aortic arch. An M-mode recording of the ascending aorta was obtained from the high suprasternal view and the diameter measured at end-diastolic and maximum systolic dimensions.

For the measurement of indexes derived from hydraulic power and total arterial compliance, carotid pressure waveforms were recorded with applanation tonometry using a Millar pulse transducer (Model SPT-301, Millar Instruments Inc., Houston, TX) connected via a control box (Model SD-640, Millar Instruments Inc., Houston, TX) to a GE Vivid 7 Pro ultrasound machine (GE Healthcare, Wauwatosa, WI). The carotid pressure waveforms were obtained simultaneously with pulse wave Doppler waveforms in the ascending aorta and sphygmomanometric measurement of the left brachial artery blood pressure in the supine position. Three pressure waveforms were selected and averaged. In calibrating the tonometry pressure, diastolic and mean pressures were assumed to be the same at the carotid artery and at the brachial artery. Fourier analysis of the pressure and flow data derived from the aortic and carotid waveforms was used to calculate vascular impedances and left ventricular hydraulic power as described by Myers et al. [29].

2.2. Data analysis

The following calculations were made: transit time was the difference in time between the onset of the QRS and the onset of flow in the ascending aorta and descending aorta respectively, as previously described [20,28]. Pulse wave velocity, PWV = aortic length / transit time ($cm \cdot s^{-1}$); pulse pressure = systolic blood pressure − diastolic blood pressure (mm Hg); peak aortic flow, PAoQ = peak aortic velocity × aortic annulus cross-sectional area ($cm^3 \cdot s^{-1}$); elastic modulus, Ep = pulse pressure/[(maximum systolic ascending aortic diameter − end-diastolic ascending aortic diameter) / end-diastolic ascending aortic diameter] (mm Hg); stiffness index, ß = ln(systolic blood pressure / diastolic blood pressure) / [(maximum systolic ascending aortic diameter − end-diastolic ascending aortic diameter) / end-diastolic ascending aortic diameter]; input impedance, Zi = pulse pressure / peak aortic flow ($dyn \cdot s \cdot cm^{-5} \cdot m^2$, 1 mm Hg = 1333 $dyn \cdot cm^{-2}$); and characteristic impedance, Zc = PWV × ρ / aortic annulus cross-sectional area ($dyn \cdot s \cdot cm^{-5} \cdot m^2$, ρ = blood density = 1.06 $g \cdot cm^{-3}$). The variability of this method has been established in earlier studies [20,32]. The ventricular ejection fraction was calculated using echocardiography with end-systolic and end-diastolic volumes estimated using a Simpson's rule algorithm.

Mean brachial artery pressure (MBP) was calculated as: MBP = DBP + [(SBP − DBP) / 3], where SBP is the systolic brachial artery pressure and DBP is the diastolic brachial artery pressure. It was assumed that MBP and DBP pressure stay constant throughout the large arterial tree. The carotid pressure waveform was assigned the same mean and diastolic pressures as the brachial artery [33–35]. Total arterial compliance (TAC) was calculated using the area method [36]; $TAC = A_d / R(P_1 - P_2)$ where P_1 was the end-systolic pressure, P_2 was the end-diastolic pressure, A_d was the area under the pressure waveform enclosed by P_1 and P_2, and R was the peripheral resistance which was given by mean pressure divided by mean flow.

The aortic flow waveform was calculated by multiplying the aortic blood velocity spectrum envelope by the aortic cross-sectional area. Aortic cross-sectional area was calculated from the aortic annular diameter, assuming a circular orifice. Since the pressure and flow waves were recorded at different locations, there was a time lag between them. This was corrected by aligning the foot of the pressure wave to the onset of flow [37]. The aortic impedance spectrum Zin(i) was calculated as P(i) / Q(i), where P(i) and Q(i) are the Fourier transforms of pressure and flow at harmonic i respectively. ZiF was the aortic impedance at the first harmonic, which was calculated as ZiF = Zin. ZcF was the characteristic impedance, which was calculated as the average of the input impedance spectrum at frequency 2 to 12. ZcF = Zin(f) / 12 − 2, f = 2, …, 12 where the harmonic is 1/cardiac cycle and frequency is 1/s. Instantaneous aortic pressure (P(t)) and flow (Q(t)) were used to calculate mean (Wm) and total (Wt) hydraulic power [35]. Total power, $Wt = \frac{1}{T}\int_0^T P(t)Q(t)\,dt$, where T is the cardiac cycle duration, P and Q are the instantaneous pressure and flow respectively. Mean power, Wm = mean pressure × mean flow. Efficiency (Wm/Wt) was calculated as the mean power (Wm) divided by the total power (Wt). The power cost per unit of forward flow, Wt/CI, was calculated as the total power (Wt) divided by the cardiac index (CI).

2.3. Measurement of endothelial function

All subjects refrained from vasoactive substances (alcohol, tobacco, caffeine, etc.) for 12 h, vasoactive medications (apart from the study medications) for 5 half-lives, vigorous exertion for 4 h, and fasted for 4 h prior to testing. The patients rested on the stretcher for at least 10 min prior to testing. The study protocol that we used is as follows [38]. An appropriately-sized blood pressure cuff was placed on the right fore-arm and the arm extended at least 80–90° from the thorax and rested on a board with the thumb pointed towards the ceiling. The portion of the brachial artery under the biceps muscle was located and imaged with a high frequency linear probe, the image optimized and the transducer's position marked on the arm. The baseline B-mode and pulsed Doppler images were acquired. The pulsed Doppler sample volume was placed in the center of the artery pointing towards the direction of flow at 60°. The blood pressure cuff was inflated to 40–50 mm Hg above systolic pressure and maintained for 4½ min. After deflation of the cuff, the first 10 beats of the pulsed Doppler images were recorded and stored. B-mode images of the