Beta-blocking therapy in patients with the Marfan syndrome and entire aortic replacement

Lilian J. Meijboom*a, Berend E. Westerhofb, Gijs J. Nollena, Jos A.E. Spaan,c, Bas A.J.M. de Mol,d, Michael J.H.M. Jacobs,e, Barbara J.M. Muldera,*

aDepartment of Cardiology, Academic Medical Center, Amsterdam, The Netherlands
bTNO Biomedical Instrumentation, Academic Medical Center, Amsterdam, The Netherlands
cMedical Physics, Academic Medical Center, Amsterdam, The Netherlands
dDepartment of Surgery, Academic Medical Center, Amsterdam, The Netherlands
eDepartment of Surgery, University Hospital Maastricht, Maastricht, The Netherlands

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Abstract

Objective: β-blocking therapy is the standard therapy in non-operated Marfan patients, however its efficacy after entire aortic replacement is unknown. The aim of this study was to describe the influence of (nearly) entire aortic replacement and β-blocking therapy on blood pressure and wave reflections in Marfan patients.

Methods: Four Marfan patients (mean age 31 ± 3 years) and 8 age matched control subjects were studied. Blood pressure and wave reflections (reflection coefficient and augmentation index) were studied by means of magnetic resonance imaging, continuous non-invasive blood pressure measurements and applanation tonometry. Patients were studied with atenolol, labetalol and without β-blocking therapy.

Results: In Marfan patients, aortic systolic pressure (129 ± 13 vs 114 ± 10 mmHg), pulse pressure (58 ± 13 vs 40 ± 5 mmHg), wave speed (11 ± 3 vs 4 ± 0.4 m s⁻¹) and reflection coefficient (65 ± 22 vs 41 ± 5%) were significantly increased compared to controls. There was no difference in aortic pressure between various medications in Marfan patients (atenolol 129/76 mmHg, labetalol 121/75 mmHg and without β-blocking therapy 129/71 mmHg). Higher reflection coefficients were seen in patients with atenolol compared to discontinued medication (73 ± 18 vs 65 ± 22%), and also the augmentation index was higher with atenolol compared to labetalol and discontinued medication (24 ± 22 vs 17 ± 17 vs 22 ± 22%, respectively).

Conclusion: Our results describe increased pulse pressure, systolic pressure, wave speed and wave reflections in four Marfan patients after entire aortic replacement. The use of atenolol or labetalol did not decrease aortic pressure and with atenolol increased wave reflections were observed. Therefore, the beneficial effect of atenolol in these patients is doubtful.

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Keywords: Marfan syndrome; Graft; β-Blocking therapy; Wave reflections

1. Introduction

Availability of surgical techniques for prophylactic aortic root replacement have greatly improved life expectancy in the Marfan’s syndrome [1–3]. However, after aortic root replacement patients with Marfan’s syndrome deserve continued attention, because aneurysms and dissection of the aorta may develop beyond the site of the graft [4]. Due to improvements in surgical techniques it is currently possible to replace the entire aorta with a Dacron graft [5,6]. In these patients, vulnerable Marfan tissue is still left in the button of main side branches at reimplantation sites [7,8].

In non-operated patients with Marfan’s syndrome, use of β-adrenergic blocking therapy has been shown to reduce the rate of aortic dilation and the development of aortic dissection [9,10]. After aortic surgery β-blocking therapy is frequently continued, however its efficacy has never been demonstrated. Rigidity of the artificial grafts and increased vascular resistance during β-adrenergic blockade may increase wave reflections in the aorta, thereby increasing wall stress in the main side branches [11–13].
The aim of the present observational study was to investigate blood pressure and wave reflections in patients with Marfan’s syndrome after entire aortic replacement and to describe the influence of β-blocking agents on aortic pressure.

2. Material and methods

2.1. Study subjects and protocol

Four patients with Marfan’s syndrome after entire or nearly entire aortic replacement were studied. Table 1 describes the patient characteristics.

The four patients with Marfan’s syndrome were studied without β-blocking therapy, with 100 mg atenolol daily and 200 mg labetalol daily, subsequently. Patients underwent magnetic resonance imaging (MRI) immediately followed by non-invasive blood pressure measurements (Finometer™) and applanation tonometry of the carotid arteries, initially without β-blocking therapy and 3 weeks later with atenolol. Patients were switched to labetalol and after three weeks only Finometer™ and applanation tonometry were performed. Due to logistical reasons we were not able to perform MRI scans during labetalol medication. Details of the study protocol are summarized in Fig. 1. A group of 8 age and sex matched healthy subjects without vascular disease (mean age 30 ± 5 years; 5 men, 3 women) served as a reference population. They underwent MRI and Finometer™ without β-blocking therapy. The local ethical committee approved the study and individual oral and written information was obtained in each patient.

2.2. Magnetic resonance imaging

Imaging was performed on Siemens Vision 1.5 Tesla MR system (Siemens Medical Systems, Erlangen, Germany). Image acquisition was triggered on the electrocardiogram. Conventional breath-hold contrast-enhanced-3D gradient-echo MR angiography (CE-MRA) was used to visualize the entire aorta.

For assessment of aortic flow curves and for the elastic properties of the Dacron aorta the following sequences were applied. A high resolution gradient echo pulse sequence with a velocity encoding gradient was applied perpendicular to the aorta at three levels: perpendicular to (1) the ascending and (2) descending aorta at the level of the bifurcation of the pulmonary artery, and (3) just above the aortic bifurcation [10]. During the flow measurements, blood pressure and heart rate were measured by means of a Dinamap oscillometric blood pressure monitor.

Flow wave velocity (FWV, ms⁻¹) of the entire aorta (between level 1 and 3) was defined as: the ratio of distance between the levels and the time difference between arrival of the pulse wave at these levels. The flow wave was considered to arrive at a certain level when the mean flow reached half of its maximum value. We call this velocity the wave speed.

2.3. Pressure transformation from finger to aorta by waveform reconstruction

Finger arterial pressure was measured using Finometer™, the latest development of TNO Biomedical Instrumentation and successor of Finapres™ and Portapres (FMS, Amsterdam, The Netherlands). Measurements were performed directly after the MRI scan was made. The patients were supine and at rest to mimic the situation in the scanner. Finger pressure was reconstructed to brachial pressure by Finometer [14,16], and filtered to aortic pressure afterwards with a filter similar to those published in literature [17,18]. Reconstructed aortic pressure was averaged over the last 2 min of the recording of supine rest.

| Table 1 | Patient characteristics
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<tbody>
<tr>
<td>Age/gender</td>
<td>Family history</td>
<td>Medication</td>
<td>Previous aortic surgery</td>
</tr>
<tr>
<td>Marfan 1</td>
<td>31/F</td>
<td>For Marfan syndrome</td>
<td>Lisonipril 5 mg daily</td>
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<td></td>
<td></td>
<td>For dissection</td>
<td>Atenolol 100 mg daily</td>
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<td></td>
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<td></td>
<td>Acenocoumarol</td>
</tr>
<tr>
<td>Marfan 2</td>
<td>33/M</td>
<td>For Marfan syndrome</td>
<td>Captopril 50 mg daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>For dissection</td>
<td>Atenolol 100 mg daily</td>
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<tr>
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<td></td>
<td></td>
<td>Acenocoumarol</td>
</tr>
<tr>
<td>Marfan 3</td>
<td>27/M</td>
<td>For Marfan syndrome</td>
<td>Atenolol 100 mg daily</td>
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<td></td>
<td></td>
<td>For dissection</td>
<td>Acenocoumarol</td>
</tr>
<tr>
<td>Marfan 4</td>
<td>29/F</td>
<td>For Marfan syndrome</td>
<td>Labetalol 200 mg daily</td>
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F, Female; M, Male.
2.4. Reflection coefficient

When pressure and flow are known at a certain site of the arterial system, the pressure wave can be split in an incident (forward moving) and a reflected (backward moving) component [19]. The formulas are:

\[ P_i = \frac{P_m + Z_c F_m}{2} \]  
\[ P_r = \frac{P_m - Z_c F_m}{2} \]

(1a)
(1b)

\( P_i \) and \( P_r \) are incident and reflected pressure waves, \( P_m \) and \( F_m \) are measured pressure and flow, respectively. \( Z_c \) is the characteristic impedance at the site of the measurement.

The Reflection coefficient (%) was defined as \( \frac{\text{magnitude of the reflected wave}}{\text{magnitude of the incident wave}} \times 100 \).

As pressure and flow in this study were not measured simultaneously, careful matching of the aortic pressure and flow waves was performed. Characteristic impedance was calculated as proposed in literature [19]. Measured pressure was then split in forward and backward components, using the above formulae.

2.5. Augmentation index

The carotid pressure wave contour was measured non-invasively by applanation tonometry from the right common carotid artery [15].

The augmentation index (%) was calculated from the carotid pressure wave contour and was defined as \( \text{amplitude of the secondary rise in systolic pressure/pulse pressure} \times 100 \).

The augmentation index was calculated on the same beat as was used to calculate the reflection coefficient.

2.6. Data analysis

The Mann–Whitney test was used to compare the results of control subjects to patients with Marfan’s syndrome after entire aortic replacement. A \( P \)-value of <0.05 was considered significant. Because of the low number of patients no statistical tests were performed within this group. The data are presented for descriptive purposes only.

3. Results

3.1. Blood pressure response

The mean systolic pressure and pulse pressure were significantly increased in patients with Marfan’s syndrome compared to healthy controls (129±13 vs 114±10 mmHg, \( P<0.05 \) and 58±13 vs 40±5 mmHg, \( P<0.05 \), respectively). No differences in systolic blood pressure, diastolic blood pressure and pulse pressure were observed when the patients were treated with atenolol, labetalol or without medical treatment (129/76 mmHg, 121/75 mmHg, 129/71 mmHg, respectively). Heart rate was decreased in the patients using atenolol compared to labetalol or discontinued medication (67±7 vs 74±9 vs 75±11 beats/min, respectively).

3.2. Reflection coefficient and augmentation index

Fig. 2 shows aortic pressure, corresponding incident and reflected wave, and flow curves from a control subject and a Marfan patient with and without atenolol.

The reflection coefficient was significantly increased in patients compared to controls (65±22 vs 41±5%, \( P<0.05 \)). (See Fig. 3) There was a trend towards higher reflection coefficients in patients using atenolol compared to patients without \( \beta \)-blocking therapy (73±18 vs 65±22%).

Fig. 3. Reflection coefficient and augmentation index

(c) Marfan 2, Atenolol

Fig. 2 In the left panel the aortic pressure and corresponding incident, \( I \) and reflected, \( R \) wave are shown from (a) a healthy control subject (b) a patient with Marfan’s syndrome without \( \beta \)-blocking therapy and (c) the same patient with atenolol. The reflection coefficient (%) is the ratio of the reflected wave to the incident wave times 100. In the right panel the corresponding flow curves are shown.
The highest augmentation index of the carotid arteries was observed when patients used atenolol compared to labetalol or discontinued medication (see Fig. 4) (24 ± 22 vs 17 ± 17 vs 22 ± 22%, respectively).

3.3. Wave speed

The wave speed was significantly higher in Marfan patients compared to healthy controls (11 ± 3 vs 4 ± 0.4 m s\(^{-1}\), \(P<0.05\)). No difference in wave speed was measured in patients both with and without atenolol (11 ± 3 vs 12 ± 2 m s\(^{-1}\)).

4. Discussion

In this study, we describe a new method to assess wave reflections in the aorta non-invasively using MRI and Finometer\textsuperscript{e}. Combined with non-invasively determined flow from MRI, we calculated incident and reflected pressure waves. The reflection coefficient, the ratio of the amplitudes of the waves, is only dependent on vasomotor tone of resistive vessels and vascular geometry. The augmentation index, however, is not only dependent on the magnitude of the incident and reflected wave, but also on their shapes and timing. As the shapes and timing of the incident and reflected waves cannot be determined exactly from the pressure only (as recorded from the carotid artery), the augmentation index may not be as accurate as the reflection coefficient.

4.2. Wave reflections

In our study, wave reflections in the aorta were increased in patients with Marfan’s syndrome after entire aortic replacement compared to healthy controls. When the pressure pulse travels over a compliant vascular bed, wave speed is low and the reflected wave arrives back at the heart late in the cardiac cycle, i.e. in diastole. When the aortic valves are closed as the reflected wave arrives, the extra pressure aids the coronary perfusion\cite{20}. Due to the stiff Dacron graft, aortic wave speed is increased in our patients. The reflected wave arrives in systole causing an increase in pulse pressure and increase in augmentation index, implying an extra load to the left ventricle\cite{11,12}. In our patients with Marfan’s syndrome these larger reflected waves may form a threat for the button of main side branches at reimplantation sites\cite{7,8}. In the long term, dilation of the graft may be another risk factor for these patients, as Nunn et al. found that the degree of dilation tended to be more marked in hypertensive than in normotensive patients\cite{21}. Therefore, patients with a prosthetic aorta will benefit from medication which reduces wave reflections.

4.3. Effect of \(\beta\)-blocking therapy on aortic pressure and wave reflections

Use of \(\beta\)-blocking therapy has been shown to delay aortic dilation in non-operated patients with Marfan’s syndrome, but its efficacy has never been demonstrated after partial or entire aortic replacement. In our patient group, atenolol did not decrease mean aortic pressure probably as a result of increased wave reflections.

At least in two previous studies an increase in wave reflections was observed in hypertensive patients with \(\beta\)-adrenergic blocking therapy (atenolol or propranolol). In a study of 471 hypertensive patients, the augmentation index increased with atenolol (1.8%) and decreased with a perindopril/indapamide combination (3.1%)\cite{22}.

Fig. 3. Reflection coefficient in the descending aorta of control subjects and Marfan patients after entire aortic replacement with and without \(\beta\)-blocking therapy (atenolol). BB –, without \(\beta\)-blocking therapy.

Fig. 4. Augmentation index in the carotid arteries of Marfan patients after entire aortic replacement without \(\beta\)-blocking therapy, with atenolol and with labetalol. BB –, without \(\beta\)-blocking therapy.
In 12 hypertensive patients, Ting et al. [13] observed increased wave reflections after propranolol compared to discontinued medication during cardiac catheterisation. When propranolol was combined with an alpha blocker (prazosin), wave reflections decreased [13]. However, in other studies with hypertensive patients, atenolol caused a small decrease of wave reflections [23,24]. In contrast to the hypertensive patients, atenolol will not affect the wave speed in our patient group, because blood pressure lowering has no effect on the compliance of the Dacron aorta. The main reason for increased wave reflections with atenolol in our patients, may be the increased peripheral resistance due to adrenergically mediated vasoconstriction [13,22].

As has been described in previous studies, it seems preferable to prescribe anti-hypertensive medication with vasodilating properties to reduce the magnitude of wave reflections. In our study, no difference in mean aortic pressure was seen with labetalol, although the augmentation index was decreased with labetalol compared to atenolol in three patients and in one patient it remained constant. This is in agreement with the findings of Kelly et al, where the augmentation index was significantly lower with dilevalol (an isomer of labetalol) than with atenolol, in spite of an equal reduction of blood pressure [25].

4.4. Study limitations

The small number of patients precludes definite conclusions about the effect of beta-blocking therapy on aortic pressure and wave reflections. Larger numbers of patients with different comparison groups, including non-operated patients with Marfan syndrome, need to be studied to confirm our observational findings.

Blood pressure and flow were not measured simultaneously, because it is not yet possible to use the Finometer™ in the strong magnetic field of the MRI scanner. We took great care to select a pressure beat from the recording that was matched to the MRI flow pulse with respect to the heart frequency.

5. Conclusion

Our results describe that pulse pressure, systolic pressure, wave speed and wave reflections are significantly increased in patients with Marfan’s syndrome after entire aortic replacement compared to controls. Use of atenolol or labetalol did not decrease aortic pressure in these patients. A trend towards increased wave reflections was observed with atenolol in the Dacron aorta. Therefore, the beneficial effect of atenolol in patients with Marfan’s syndrome after entire aortic replacement is doubtful. However, beta-blocking therapy might still be useful in these patients because of heart rate reduction. Further studies with larger number of patients are needed to confirm our observations.


