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ORIGINAL ARTICLE

Endothelial function in children and adolescents with mucopolysaccharidosis

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Abstract
Background Although coronary artery pathology is a prominent feature of mucopolysaccharidosis (MPS), it may be underestimated by coronary angiography because of its diffuse nature. It is also generally assumed that cardiovascular risk is increased in MPS and reduced following hematopoietic stem cell transplantation (HSCT) or enzyme replacement therapy (ERT), but this has never been formally evaluated. Non-invasive methods of assessing vascular endothelial function may provide a measure of cardiovascular risk in MPS. We evaluated endothelial function, using digital reactive hyperemia, in youth with MPS and in healthy controls.
Methods Digital reactive hyperemic index (RHI) was measured in 12 children and adolescents (age 10.3±3.9 years old; 11 boys) with treated MPS and nine age- and gender-matched (11.4±4.0; 8 boys) healthy controls. An independent t-test was used to compare RHI between individuals with MPS and controls.
Results Children and adolescents with MPS (MPS type II: N=5; type I: N=4; type VI: N=3) whether treated by HSCT (N=4) or ERT (N=8) had significantly lower RHI compared to controls (MPS 1.22±0.19 vs. controls 1.46±0.32, $p<0.05$).
Conclusion These preliminary findings suggest that children and adolescents with treated MPS have significantly poorer endothelial function when compared to healthy controls. Further investigation into the utility of endothelial function for risk stratification and the long term implications of reduced endothelial function in MPS is warranted.

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Introduction

Deposition of glycosaminoglycans in mucopolysaccharidosis (MPS) occurs in the myocardium, the cardiac valves, and the coronary arteries of all types of MPS resulting in ventricular hypertrophy, cardiac failure, cardiac valve dysfunction, and diffuse narrowing of the epicardial coronary arteries (Braunlin et al. 2011). Hematopoietic stem cell transplantation (HSCT) and enzyme replacement therapy (ERT) have become therapeutic options for some MPS syndromes and appear to reverse ventricular hypertrophy and preserve ventricular function, although the effect on the cardiac valves appears to be minimal (Braunlin et al. 2003; Braunlin et al. 2006). HSCT dramatically lengthens lifespan in MPS I (Moore et al. 2008) and myointimal thickening was absent 14 years after HSCT (Braunlin et al. 2001) in an individual case of severe MPS I. The effect of ERT on coronary pathology is less straightforward. Sudden cardiac death with evidence of fresh myocardial infarction has been demonstrated in an individual with attenuated MPS I who had received two years of ERT (Lin et al. 2005).

Cardiac studies in MPS have utilized two-dimensional ultrasound and Doppler techniques focused primarily on myocardial function, ventricular hypertrophy, and the cardiac valves. Cardiac ultrasound and Doppler techniques have

also described increased aortic root diameter (Hinek and Wilson 2000) and increased ascending aortic stiffness (Nemes et al. 2008) in untreated MPS disorders. Because of the lack of a reliable non-invasive test, little is known about the status of the coronary arteries in MPS either before or after treatment. Defining the extent of coronary artery involvement during life in the MPS syndromes is important since sudden death is not uncommon in untreated individuals (Krovetz et al. 1965). MPS coronary artery disease is a diffuse process occurring within the epicardial coronary arteries and, just as with cardiac transplant vasculopathy, it is easily underestimated by standard coronary angiography (Braunlin et al. 1992; Cai et al. 2011). Coronary angiography is both invasive and can be unreliable in the assessment of coronary artery involvement in MPS diseases and other techniques, such as transthoracic or intravascular ultrasound, cardiac MRI or CT angiography, remain to be validated in MPS. Consequently, the ability of a non-invasive technique, already proven to be useful in assessing vascular structure and function in traditional atherosclerotic cardiovascular disease, might provide a means by which to assess the level of cardiovascular risk in MPS. Ideally, by providing information about the likelihood of a future adverse cardiovascular outcome, results from these assessments may aid in risk stratification and could be used as endpoints in interventions.

Endothelial dysfunction, considered to be a sign of early atherosclerosis, can be assessed with non-invasive techniques such as digital reactive hyperemia. Endothelial function assessed by this method correlates well with coronary artery blood flow (Bonetti et al. 2004) and cardiovascular risk factors (Hamburg et al. 2008), independently predicts adverse cardiovascular events (Rubinshtein et al. 2010), is relatively easy to perform and demonstrates good reproducibility (Selamet Tierney et al. 2009). Although the etiology of atherosclerosis in MPS likely differs from that of traditional coronary artery disease, endothelial function testing may be useful for indentifying individuals with MPS who are at the highest risk of experiencing a cardiovascular event. Therefore, the primary objective of this study was to evaluate the feasibility of performing endothelial function assessments in MPS and to compare endothelial function in individuals with treated MPS to healthy controls.

Methods

Study design and participants

This was a cross-sectional study of 12 children and adolescents (age 5–17 years old) with treated MPS and nine age- and gender-matched healthy controls. Individuals with MPS were recruited from two sources: 1) the 2009 National MPS Society annual family meeting and 2) a group of MPS patients who visited the University of Minnesota for clinical care. Endothelial function data from healthy controls were obtained from a study of insulin resistance and cardiovascular risk at the University of Minnesota that utilized an identical vascular testing protocol. The controls were selected (without knowledge of RHI values) based on age and gender in an attempt to match the groups as closely as possible for these factors. Cardiac echocardiogram data in the MPS patients were obtained from chart review. The protocol was approved by the University of Minnesota Institutional Review Board and consent/assent was obtained from parents/participants.

Measurement of endothelial function

Seated blood pressure was obtained on the right arm using manual auscultation with a sphygmomanometer after at least five minutes of quiet rest. Study participants had fasted for at least four hours prior to endothelial function assessment. Endothelial function was measured by digital reactive hyperemia using the EndoPAT device (Itamar Medical, Caesarea, Israel). Following 10 minutes of quiet rest in the supine position, finger probes were placed on the index fingers to measure baseline and reactive hyperemic pulse amplitude. After collection of baseline data, a blood pressure cuff on the upper forearm was inflated to a suprasystolic level for five minutes. Following cuff release, the change in pulse amplitude during reactive hyperemia was measured for five minutes. The ratio of the hyperemic and the baseline pulse amplitude (corrected for the same ratio on the control finger) was calculated and expressed as the reactive hyperemic index (RHI). Reproducibility of this technique in children and adolescents has shown a mean difference in RHI, measured one week apart, of 0.12 and within subject variation of 0.16 (Selamet Tierney et al. 2009).

Statistical analysis

Independent t-tests were used to compare variables between the MPS and control group. Chi-square analysis was used to evaluate gender and race by group. A p-value less than 0.05 was considered statistically significant. Data are presented as mean±standard deviation.

Results

EndoPAT studies were attempted in 16 individuals with MPS but were unsuccessful in four due to the well-known ‘trigger finger’ deformity associated with MPS. Clinical variables including age, gender, blood pressure, and RHI values in MPS and controls are shown in Table 1. There

Table 1 Clinical characteristics of MPS patients and healthy controls

Variables	MPS (N=12)	Controls (N=9)	P-value
Age (years)	10.3±3.9	11.4±4.0	0.53
Gender (males/females)	11/1	8/1	0.83
Systolic blood pressure (mmHg)	111±9	112±14	0.76
Diastolic blood pressure (mmHg)	67±4	58±7	0.002
Reactive hyperemic index	1.22±0.19	1.46±0.32	0.048

were no statistically significant differences between groups for age, gender, or systolic blood pressure. The study subjects were predominantly male, a fact that was partly due to five (42%) of them having Hunter syndrome, which occurs only in males (Table 2). MPS patients had significantly higher diastolic blood pressure compared to controls (MPS 67±4 mmHg vs. controls 58±7 mmHg, $p<0.002$). MPS patients had significantly lower RHI compared to controls (MPS 1.22±0.19 vs. controls 1.46±0.32, $p<0.05$) (Fig. 1).

Data for each individual subject, including the type of MPS, treatment status, cardiac ultrasound findings, and RHI are listed in Table 2. Three types of MPS were present: type I (Hurler, Hurler-Scheie syndromes), N=4; type II (Hunter syndrome), N=5; type VI (Maroteaux-Lamy syndrome), N=3. Eight MPS patients were being treated with ERT and four had undergone HSCT. When categorized by type of MPS, all subjects with MPS VI (subjects 5, 11, 12) tended to have higher RHI values. When categorized by underlying cardiac pathology, RHI values tended to be lower if more serious valve pathology was noted by echocardiogram. Cardiac function was normal in all subjects (shortening fraction ≥28%).

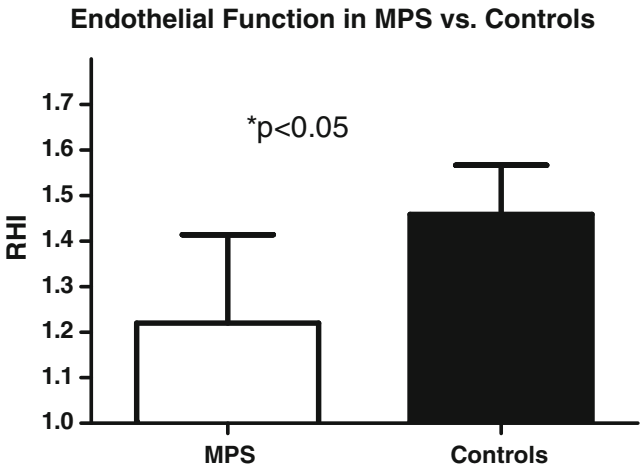

Fig. 1 RHI in MPS (open bar) and healthy controls (solid bar)

Discussion

The primary finding of this study is that children and adolescents with treated MPS have significantly lower endothelial function when compared to healthy controls. These preliminary data provide support for the use of endothelial function as a biomarker of cardiovascular risk in MPS and are in agreement with a similar study performed in individuals with Fabry disease, another lysosomal storage disease leading to intravascular accumulation of glycosphingolipid (Kalliokoski et al. 2006). In that study, brachial flow-mediated dilation was abnormal when compared to controls and endothelial function was similarly depressed in treated (ERT) and untreated patients. Since all of the MPS patients in our study were treated by either ERT or HSCT, our findings also imply that impaired vascular function may persist even after therapy. Therefore, individuals with MPS

Table 2 Subtype of MPS, RHI and echocardiographic findings in MPS patients

Subject	MPS type-Rx	RHI	Shortening fraction	Mitral regurgitation	Peak mitral gradient mmHg	Aortic regurgitation	Peak aortic gradient mmHg
1	I-HSCT	1.00	45	1-2+	*	None	13
2	I-HSCT	1.42	40	Trace	Normal	None	Normal
3	II-ERT	1.03	37	Prolapse 1+	Normal	Trace mechanical valve	19
4	I-HSCT	1.49	38	*	E=9	Trace-1+	10
5	VI-ERT	1.41	34	Prolapse 1+	Normal	Trace	Normal
6	II-ERT	1.12	44	1+	3	None	3
7	II-ERT	1.14	43	None	Normal	*	19
8	II-ERT	1.09	39	1+	Normal	2-3+	Normal
9	II-ERT	1.01	48	1+	Normal	None	Normal
10	I-ERT	1.11	49	None	None	None	None
11	VI-HSCT	1.31	*	*	*	*	*
12	VI-ERT	1.51	*	*	*	*	*

Rx=treatment type; *=data unavailable

may remain at increased risk for negative cardiovascular outcomes even though they are receiving therapies that reduce other symptoms and progression of the disease. Although we did not compare treated versus non-treated MPS, it is possible that non-treated have even poorer endothelial function.

Among the potential factors that may have influenced the RHI values is the presence of cardiac valve disease. Decreased brachial artery flow-mediated dilation has been reported in normal adults with either mitral or aortic valve stenosis (Poggianti et al. 2003; Tekin et al. 2008). The effect of mitral and/or aortic regurgitation, as was seen in our subjects, on flow-mediated dilation has not been reported. The specific type of MPS may also affect the results of our study. Severe coronary artery disease is a well-known finding in both MPS I and MPS II, which both accumulate dermatan- and heparan-sulfated glycosaminoglycans. It is not surprising then that the RHI values for subjects with MPS I or MPS II were generally among the lowest. By contrast, it is not clear that coronary artery disease occurs as frequently or severely in MPS VI where only dermatan-sulfated glycosaminoglycans accumulate. Accordingly, in our study the RHI values for all three subjects with MPS VI were among the highest of those studied.

Although the EndoPAT device is portable, relatively easy to use, and demonstrates good reproducibility, its use in individuals with MPS is somewhat limited due to the 'trigger finger' deformity often seen in this condition. This method was unsuccessful in 25% of the individuals with MPS in this study. A second limitation to use of the digital hyperemic response is the potential for carpal tunnel syndrome which is present in all individuals with MPS I, II and VI (White and Harmatz 2010). Even though arterial supply to the hand lies exterior to the flexor retinaculis, nervous control of the arterial supply to the hand lies within this ligament and potentially could attenuate the flow-mediated responses. Thirdly, the effect of thickened skin, a common feature of the MPS syndromes, on RHI response is unknown. It is possible that the thickened skin in MPS patients is less compliant, which could potentially inhibit the volume changes elicited by hyperemia in the fingers. Lastly, although the EndoPAT device has been used in other pediatric studies, no normative values exist and it remains to be formally validated in children and adolescents. In sum, considering the above issues, results of this study should be interpreted with caution.

Despite being more technically challenging to perform, the brachial artery flow-mediated dilation technique may be a preferred approach for assessing endothelial function in MPS. This method has been widely-used in the pediatric population (Urbina et al. 2009), is generally considered to be a valid measure of endothelial function, and avoids any effects that might be related to accumulation of glycosaminoglycan in the tenosynovium of the wrist and potential issues associated with skin thickness. Another method of vascular assessment that may prove useful in MPS is the measurement of carotid artery intima-media thickness. Unlike coronary angiography, this method is non-invasive and can detect concentric narrowing and thickening of the artery wall. The method has been standardized in pediatric populations and normal values for children and adolescents have been established (Urbina et al. 2009). Wang and colleagues (Wang et al. 2011) recently demonstrated that MPS patients have increased carotid intima-media thickness compared to age- and gender-matched controls. These data provide early evidence of the potential usefulness of this technique in cardiovascular risk stratification.

Strengths of this study include the use of a novel and reproducible non-invasive measure of endothelial function, and the relatively close age- and gender-matching of the healthy controls to the study population. One limitation of the study is the small sample size which precluded us from performing sub-analyses on the effect of age, MPS type, and echocardiogram abnormalities on endothelial function. While the effect of cardiac valve disease on endothelial function is not entirely clear, both aortic and mitral valve disease have been shown to affect carotid intima-medial thickness (Demircan et al. 2007; Kablak-Ziembicka et al. 2005).

In conclusion, these preliminary findings suggest that children and adolescents with MPS, despite treatment, have significantly lower endothelial function when compared to healthy controls. Pending further evaluation in larger studies, endothelial function testing may have clinical utility as a means for identifying individuals with MPS who are at the highest cardiovascular risk. However, due to the limitations of using the EndoPAT in this population, other endothelial function techniques, such as brachial artery flow-mediated dilation and measures of arterial structure, such as carotid intima-media thickening, should be explored. Future research should seek to confirm these findings in a larger sample of MPS patients and investigate the significance and potential long-term implications of endothelial dysfunction in youth with MPS.

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