Analysis of the upper airway by the acoustic reflection method in children with mucopolysaccharidosis

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Analysis of the upper airway by the acoustic reflection method in children with mucopolysaccharidosis

Running head: Acoustic reflection in mucopolysaccharidosis

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Summary

Background

Upper airway obstruction is common in children with mucopolysaccharidosis. The acoustic reflection method is a noninvasive technique that can analyse the calibre of the upper airways. The aim of the study was to evaluate the feasibility of the acoustic reflection method in children with mucopolysaccharidosis, and to compare the characteristics of the upper airways evaluated by the acoustic reflection method in patients with mucopolysaccharidosis to matched healthy counterparts.

Methods

Open, single centre, prospective, study

Results

Accurate acoustic reflection measurements could be obtained in 7 of 10 patients (mean age: 10.4 ± 3.9 years; mucopolysaccharidosis type II (n=3); type IV (n=2), type VI (n=1), and fucosidosis (n=1)). The mean minimum cross-sectional area was lower in mucopolysaccharidosis patients (1.6 ± 0.3 cm²) as compared to 14 healthy counterparts (1.8 ± 0.3 cm²; p=0.03). The mean resistance of the airways was significantly higher in the MPS group (7.9 ± 1.8 cmH₂O.l⁻¹.s) as compared to the controls (5.5 ± 1.2 cmH₂O.l⁻¹.s; p=0.006).

Conclusion

This study is the first to analyze the upper airways by the noninvasive acoustic reflection method in children with mucopolysaccharidosis. Due to a lack of cooperation, reliable measurements could only be obtained in 70% of a selected group of patients. Children with mucopolysaccharidosis have significant upper airway obstruction as assessed by the reduction of the minimal cross-sectional area of the upper airways and the increase in airway resistance.

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For Peer Review

Introduction

Mucopolysaccharidoses (MPS), OMIM 252700, are a group of rare metabolic inherited disorders caused by the lack or deficiency of specific lysosomal enzymes involved in the degradation of mucopolysaccharids (glycosaminoglycans).¹ The accumulation of partially degraded molecules interferes with cell, tissue, and organ function. Depending on the MPS subtype, the disease may display various degrees of severity. Mental retardation is common and often severe but may be absent in some MPS (MPS VI).

Upper airway obstruction and its management is a challenging concern in children and adults with MPS. Due to tissue infiltration, airway obstruction may affect the different levels of the respiratory tract. Patients may present narrowed nasal airways, adenotonsillar hypertrophy, macroglossy, thickened tongue, a short and infiltrated neck, and a narrowed pharynx and larynx with a thickened epiglottis. This airway obstruction is associated with an increase in morbidity even in early childhood.² Indeed, severe obstructive sleep apnoea syndrome has been reported in children with MPS.³⁻⁷ This upper airway obstruction may also complicate the perioperative anaesthetic management, for endotracheal intubation is known to be especially difficult in MPS patients because of soft tissues infiltration and frequent cervical spine malformations. Intubation may require an endoscopic procedure⁸⁻¹⁰ and is not always able to prevent a fatal outcome even for routine procedures.¹¹

The acoustic reflection method (ARM) is an interesting noninvasive technique based on the analysis of the reflection of a single transient planar wave, allowing the calculation of the longitudinal cross-sectional area profile of the examined cavity. An analysis of the mechanical properties of the airways by the forced-oscillations method is also possible by this technique.¹² The ARM has been first reported in humans in

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1980 by Fredberg et al.¹³ Since then, ARM has been used to explore the pharyngeal cavity in snoring patients (acoustic pharyngometry)^{14,15}, the nasal compliance (acoustic rhinometry)¹⁶, the obstruction of endotracheal tubes by mucus plugging¹⁷, the misplacement of endotracheal tubes¹⁸, the vocal tract dimensions in adolescents¹⁹ and in children with Down syndrome.²⁰ The ARM has also been used to measure tracheal size and distensibility in healthy adults and patients with cystic fibrosis or achondroplasia.^{21,22}

We have recently evaluated the feasibility and established normal values of the upper airways by the ARM in a large group of healthy children. Accurate measurements could be obtained in all the children older than 2 years of age.²³ Normal values of the minimal cross sectional area (MCAv), which corresponds to the narrowest part of the upper airways (i.e the subglottic region), were established and correlated mainly with height, and to a lesser extend with age and weight. As children with MPS may present upper airway obstruction, we hypothesised that the ARM may be particularly adapted to this population because this technique is noninvasive, simple, and rapid, with a procedure taking less than one minute.

The aim of the present study was to evaluate by the feasibility of the ARM in children with MPS, and to compare the characteristics of the upper airways evaluated by the ARM in patients with MPS to a matched group of healthy children.

Material and methods

Patients

The study was proposed to the parents of 10 patients with MPS, followed in our institution and expected to be able to perform the ARM manoeuvre. To be included, the patient had to be free of any acute upper or lower airway disease since at least one month. The ARM measurements were realised during a scheduled hospital visit or hospitalisation.

The following information was assessed from the patient's chart: history of endotracheal intubation and/or any respiratory or upper airway disease, and sleep studies when available.

Control group

A control group was recruited among siblings of the patients and a large group ($n > 60$) of outpatients from the otolaryngology department (mostly for middle ear surgery). All controls were free of any upper or lower airway disease or symptom since at least 3 months. The control group was secondarily established in order to match with the MPS patients' height, weight, and body mass index (BMI).

The study was approved by our institutional board and written consent was obtained from all the patients and the controls when possible, and all the parents.

The acoustic reflection measurement

The device used in this study, as well as its calibration method, has been previously described.^{12,24} Briefly, the acoustic reflection device consists in a Plexiglas tube of 22 cm in length and 16 mm in diameter. Two microphones (piezoresistive pressure transducers, 8510-B; Endevco France, Le Pré Saint-Gervais, France) are

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inserted on the tube which is connected to a horn driver. The ‘microphone’ side of the tube is oriented toward the patient, and the other one toward open air. An acoustic wave (0.2 – 6 kHz) is generated by the horn driver, which is driven by a personal computer via a digital-to-analog converter; microphone outputs are fed into an analog-to-digital converter (14 bits, 24-μs sampling period).

For a reliable ARM measurement, the subject has to breathe by mouth during ≈ 4 s. As such, only the airways beyond the mouth were analyzed. During these 4 seconds, the ARM device generates 10 consecutive acoustic waves at a frequency of 2.5 Hz and the corresponding areas distance curves are inferred. As previously shown, ARM measurements are influenced by the position of the head and the connecting equipment.²⁵⁻²⁸ For the recording, the subjects were thus asked to have their head in a neutral position and to breathe through an elastomer mouthpiece (Air Safety Ltd, ref A539, Morecambe, United Kingdom) and a single use filter (Intersurgical Clear-Guard™, ref 1664, Wokingham, United Kingdom).

Data are given on a 2 dimensional graph with the distance from the end of the wave tube on the x-axis and the cross-sectional area on the y-axis (Figure 1). A program calculates the cross-sectional area of the airway as a function of the distance along the longitudinal axis with a spatial step increment $\Delta L \cong 0.4$ cm. For every point on the x-axis value, i.e. distance on the airway, the mean value of the 10 curves is calculated but if the coefficient of variation of the 10 curves area exceeds 10% the test is discarded and a new test is performed. A visual control by the operator of the 10 curves (allowing to hand-mark the appropriate areas), as well as the checking of an eventual rejection of a measurement, are systematically associated to this computer analysis. The analysis software also gives the results of each measurement in a numerical format, allowing an accurate estimation of

surfaces and resistances, as well as the analysis of defined portions of the studied airways chosen by the clinician. For the purpose of the present study, the mean pharyngeal and tracheal cross-sectional airway surface, as well as the minimal airway area value, (MCAv) were calculated. The choice of the landmarks is made according to the curve's profile and the knowledge of the anatomy of the upper airways. Clearly, and by comparison to the classic procedure as recently described by Xue et al.^{19,20}, our procedure implies a subjective part in the determination of landmarks. This choice was dictated by the expected lack of cooperation of children with mental retardation. In order to deemphasise the effect of any error on the landmarks definition, we only focussed on parameters that are not, or very partially, affected by the landmarks choice. We used thus the MCAv and mean area over a region of interest and we disregarded the cavity length and the cavity volume.

The software allows also the calculation of the mechanical properties of the respiratory system by the forced oscillations technique, as previously demonstrated.¹² The system's impedance, defined as the ration between pressure and flow at the mouth, appears as a function of the frequency. Here, the patient's airways' total resistance (R) was defined as the average of the real part of the impedance between 15 and 45 Hz.

Statistical analysis

Data were expressed as mean $\pm$ standard deviation. Comparison between the patients and the controls was performed using Student's T Test. A *p* value less than 0.05 was considered statistically significant.

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Results

Patients and feasibility

Thirty-eight children with a MPS are followed in our institution: MPS III, n=22 (58%), mean age 11.8 ± 2.3 year-old; MPS II, n=9 (24%), mean age 10.3 ± 1.1 year-old; MPS IV and VI, n=3 each (8%), mean age 8.5 ± 1.7 and 21 year-old respectively; and 1 (2%) other MPS type, aged 10.5 years. Patients “non suitable for ARM” were pre-selected by our paediatrician neurologist (BH), as they were expected to be unable to perform the ARM manoeuvres because of severe mental retardation and/or major behaviour problems. Ten patients were selected and participated to the study (Figure 2).

Accurate ARM measurements could only be obtained in 7 patients. Indeed, despite pre-selection, 3 patients were unable to breathe normally by mouth for 3 to 4 seconds despite the pre-selection on their capacity, patience, adequate explanations, and parental reassurance (Table 1). No patient with a MPS III could be included because of severe mental retardation and behavioural disorders. One patient had a fucosidosis, considered as a Hurler-like syndrome.²⁹

Among the 7 patients, 4 patients had no respiratory symptoms, 3 patients complained of dyspnea at exertion (n=3) and 2 (#6 and #7) had documented nocturnal alveolar hypoventilation and were treated by long-term noninvasive positive pressure ventilation (NPPV). The sleep studies of these 2 patients during spontaneous breathing and before initiation of NPPV showed a desaturation index of 34 and 36 per hour, hypoxemia (minimum pulse oximetry (SpO_2) $66 \pm 5.6\%$) and hypercapnia (maximum transcutaneous carbon dioxide ($PtcCO_2$) 49 ± 5.6 mmHg) (Table 2). One of these two patients previously underwent an endoscopic examination showing an infiltration of the posterior pharyngeal wall, the base of the

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3 tongue, and the epiglottis, with a tongue base obstruction and a granular aspect of
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5 the mucosa.
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8 All patients had previously undergone an endotracheal intubation for a surgical
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10 procedure (adenoidectomy, dental care, spine surgery). Four patients (#1, #5, #6 and
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12 #7) had a history of difficult intubation, which required the use of a fiberoptic
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14 bronchoscope for 2 of them (#5 and #6). None had a history of tracheotomy.
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17 The characteristics of the patients are given in Tables 2 and 3.
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20 21 22 *Control group* 23

24 The control group consisted of 14 healthy children (mean age 7.3 ± 2 years)
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26 who were matched to the patients with regard to height and weight (Table 3). The
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28 ARM recording was successful in all the subjects. Due to the impaired growth and
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30 development of MPS patients, the healthy subjects matched for height and weight
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32 were significantly younger than the patients ($p=0.04$).
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38 39 *Cross-sectional area values* 40

41 The MPS patients had a significantly lower mean MCAv than their healthy
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43 counterparts ($1.6 \pm 0.3 \text{ cm}^2$ and $1.8 \pm 0.3 \text{ cm}^2$ for MPS patients and controls,
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45 respectively; $p=0.03$) (Figure 3 and 4 and Table 3). The mean pharyngeal and
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47 tracheal area values were also lower in the MPS group than in the controls, but this
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49 difference was not statistically significant. Concerning the individual data, MCAv
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51 results were clearly different from the controls for 4 MPS patients (patients #3, #5, #6,
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53 and #7). Of note, 2 of these patients (patients #6 and #7) were those with severe
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55 upper airway obstruction treated with NPPV. Because of the abnormal MCAv results
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60 in the two other patients (patients #3 and #5), sleep studies were performed.

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Although the results were within the normal range, the apnoea index was 1 and the hypopnoea index was 2 in patient #3, and the patient #5 had a hypopnoea index of 5 and spent 12% of sleep time with a low SpO₂ between 90 and 95%.

Upper airways resistance

The mean resistance (R) of the upper airways was higher in the MPS group (7.9 ± 1.8 cmH₂O.l⁻¹.s) than in the control group (5.5 ± 1.2 cmH₂O.l⁻¹.s) (p=0.0064) (Figure 4 and Table 3).

Again, when looking at the individual data, the R results were clearly different from the controls for 4 MPS patients (patients #3, #4, #6, and #7). These 4 patients comprised 3 of the previous patients (patients #3, #6, and #7). The last patient (#4) is scheduled for a sleep study in the coming weeks.

These complementary data are given in table 2.

Discussion

This study shows that the ARM is able to identify a significant reduction of the upper airway calibre in children with MPS. Indeed, the mean MCAv was significantly lower and the mean airway resistance was significantly higher in 7 patients with MPS as compared to a matched control group. However, individual results were without the normal range in 5 of the 7 patients, of whom 2 were treated with NPPV for severe upper airway obstruction.

Technical issues

We chose the ARM as a tool to study the upper airways in patients with MPS, in whom cooperation may be difficult, because this technique is simple, noninvasive and takes only several seconds. We have recently reported the excellent feasibility of this technique which can be realized in healthy children after the age of 2 years. However, because of a lack of cooperation, mental retardation, and behavioural problems, reliable, accurate ARM measurements could only be obtained in 7 out of 10 selected patients. The experience of our team in performing ARM recordings in children was undoubtedly helpful but was not sufficient. Moreover, if the pre-selection of our patients allowed us to achieve enough successful recordings to obtain workable data, the extension of our results to all the paediatric MPS population must be made with caution. We could only perform ARM measurement in 7/38 (18%) of all our MPS patients and even if this percentage may be improved (inclusion of adults, multiple examinations in an optimal environment), examination of the total population seems unrealizable. Of note, no patient with a MPS III could be studied.

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Exploring the airways of MPS patients is challenging. Evaluations have been done with CT-scanning but in addition to the irradiation it delivers, this imaging technique also requires cooperation and hold breathing for a few seconds to give reliable data. This seems difficult to achieve in MPS patients, especially in the stressogenic supine position in the scanner machine.³⁰ Fiberoptic examination gives accurate morphological data but may also be difficult to perform in children with behavioural problems, and does not provide reliable airway measurements because of the distortion of the images in the optic fibre and the bias of images' interpretation by one practitioner only. However, at least one fiberoptic examination seems recommendable prior to a general anaesthesia in MPS patients.³¹

Clinical relevance of the results

The MCAv is the most important parameter for the evaluation of the upper airway because the minimal airway diameter influences both the clinical presentation and the therapeutic management.³² In healthy subjects, the MCAv corresponds to the subglottic area, which is physiologically the narrowest region of the upper airways. As none of our patients had a history of airway surgery or prolonged intubation, it is likely that their MCAv also corresponds to the subglottic area. The mean MCAv value was significantly reduced in the group of patients with MPS compared to the control group. This can be explained by the infiltration of the airways' wall by the partially degraded molecules inherent to MPS. The mean values of the pharynx and the trachea cross-sectional areas also showed a trend to be reduced compared to healthy children, but this did not reach statistic significance. A significant threshold might have been reached with the inclusion a larger group of patients. Even if the

ARM has been successfully used in several studies to assess nasal cavities, we intentionally chose not to perform such measurements in our patients because of the difficulty of achieving an accurate nasal recording in patients with behavioural problems.

The overall resistance of the airways was significantly higher in the MPS group as compared to the control group. This can be explained by the modification of the wall compliance, and the reduction of the cross-sectional area of the pharynx, larynx, and trachea, and the lower airways.

Interestingly, the patients with obstructive sleep apnoea and a need for a nocturnal NPPV (#6 and #7) had clearly MCAv and airway resistance values outside the normal range. This led us to screen the 3 patients having also abnormal values for upper airway obstruction by a sleep study. The sleep results of these clinically asymptomatic patients were not totally normal (Table 2), underlining the potential value of the ARM as a screening tool for the detection of mild and/or subclinical OSAS in patients with MPS.

Interestingly, MPS patients with abnormal MCAv and airway resistance seemed to be older than those with normal values (12.6 vs. 7.9 years of age). This may be explained by the progressive infiltration of the airways' wall with time. Further studies are warranted to evaluate the usefulness of systematic sleep studies in older patients with MPS in order to detect clinically asymptomatic upper airway obstruction.

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Conclusions

This study is the first that analyses the upper airways (nose excluded) by the ARM in children with a MPS. Patients with MPS have a significant reduction of the minimal cross-sectional area of the upper airways and an increase of the airways' resistance, as compared to a matched control group.

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List of abbreviations

MPS: mucopolysaccharidosis

ARM: acoustic reflection method

MCAv: minimum cross-sectional area value

BMI: body mass index

NRS: noninvasive respiratory support

OSAS: obstructive sleep apnea syndrome

Competing interests

The authors declare that they have no competing interests.

Authors' contribution

The study was designed by NL, RV, and BF. Patients' selection was made by BH. Measurements and data management were made by NL. Technical supervision was made by BL. The manuscript was written and approved by all the co-authors.

Authors' information

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3 **Legends of the Figures**
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8 **Figure 1**
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10 Typical acoustic recording curves in a healthy subject
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12 Two-dimensional recording; X: distance from microphones (cm) Y: area of airways'
13 cross-section
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15 1: mouthpiece and filter; 2: mouth and oropharynx 3: pharynx; 4: larynx and trachea;
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17 5: bronchi (artefacts)
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25 **Figure 2**
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27 Selection of subjects eligible for the acoustic reflection measurement among the
28 patients with a mucopolysaccharidosis followed in our institution
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34 **Figure 3**
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36 An acoustic reflection tracings in a patient with mucopolysaccharidosis (patient).
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38 Note the reduced value of the mean cross sectional area and of the cross-sectional
39 area all along the airway (arrows)
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46 **Figure 4**
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48 Mean cross sectional area values and resistance values of the patients with
49 mucopolysaccharidosis and the control subjects; black-filled circles correspond to the
50 2 patients with mucopolysaccharidosis treated by long term noninvasive positive
51 pressure ventilation.
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Table 1: comparison of the patients with mucopolysaccharidosis able or not to perform an adequate acoustic reflection measurement (ARM)

	Patients able to perform an ARM recording n=7	Patients unable to perform an ARM recording n=3
Age (y)	10.4	15.2
Gender	M: n=6; F: n=1	M: n=3
<i>Type of MPS</i>		
Type II	3	2
Type III	0	1
Type IV	2	0
Type VI	1	0
Fucosidosis	1	0

y: years; M: male; F: female

Table 2: characteristics of the patients

Patient	Gender	Condition	Age (y)	Height (cm)	Weight (kg)	Mental retardation	History of difficult intubation	Sleep study < 6 months	Minimal sleep SpO ₂	RDI	DI (/h)	Snoring index	Maximal sleep CO ₂ (mmHg)	NPPV
#1	M	MPS II: Hunter syndrome	5.8	120	30	Severe	Yes	No						No
#2	M	MPS IV-A: Morquio syndrome	7	110	19	None	No	No						No
#3	M	MPS IV-A: Morquio syndrome	7.5	95	17	None	No	Yes	93%	6	0	61		No
#4	F	Fucosidosis	10.5	125	25	Severe	No	No						No
#5	M	MPS II: Hunter syndrome	11.5	135	36	Severe	Yes	Yes	91%	5	0	55	45	No
#6	M	MPS II: Hunter syndrome	15	134	32	Severe	Yes	n/a	65%	7	34	8	64	Yes
#7	M	MPS VI: Maroteaux-Lamy syndrome	15.6	131	35	Mild	Yes	n/a	70%	17	36	82	53	Yes

M: male; F: female; MPS: mucopolysaccharidosis; y: years; SpO₂: pulse oximetry; RDI: respiratory disturbance index; DI: desaturation index; /h: by hour; CO₂: carbon dioxide; NPPV: noninvasive positive pressure ventilation; n/a: non applicable.

Table 3: acoustic measurements in MPS patients and healthy subjects

	MPS patients		Healthy subjects		
	Mean $\pm$ SD	Range	Mean $\pm$ SD	Range	p
Anthropometry					
Age	10.4 $\pm$ 3.9	5.8-15.6	7.3 $\pm$ 2	4.1-10.4	p=0.04
Height (cm)	121.4 $\pm$ 14.6	95-135	120.9 $\pm$ 12	95-133	p=0.4651
Weight (kg)	27.7 $\pm$ 7.5	17-36	26.2 $\pm$ 7.3	19-39	p=0.3366
BMI (kg.cm ⁻²)	18.5 $\pm$ 2	16-20.8	17.9 $\pm$ 3.5	14.6-22	p=0.3098
Acoustic measurements					
MCAv (cm ²)	1.6 $\pm$ 0.3	1.3-2	1.8 $\pm$ 0.3	1.5-2.4	p=0.0329
Mean pharyngeal airway surface (cm ²)	2.2 $\pm$ 0.6	1.3-2.8	2.5 $\pm$ 0.3	1.9-3.1	p=0.15
Mean tracheal airway surface (cm ²)	1.8 $\pm$ 0.3	1.3-2.4	2 $\pm$ 0.3	1.7-2.4	p=0.06
R (cmH ₂ O.l ⁻¹ .s)	7.9 $\pm$ 1.8	5.6-10.1	5.5 $\pm$ 1.2	3.3-6.9	p=0.0064

MPS: mucopolysaccharidosis; SD: standard deviation; BMI: body mass index; R: airway resistance; MCAv: minimal cross-sectional area value

Analysis of the upper airway by the acoustic reflection method in children with mucopolysaccharidosis

Running head: Acoustic reflection in mucopolysaccharidosis

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Summary

Background

Upper airway obstruction is common in children with mucopolysaccharidosis. The acoustic reflection method is a noninvasive technique that can analyse the calibre of the upper airways. The aim of the study was to evaluate the feasibility of the acoustic reflection method in children with mucopolysaccharidosis, and to compare the characteristics of the upper airways evaluated by the acoustic reflection method in patients with mucopolysaccharidosis to matched healthy counterparts.

Methods

Open, single centre, prospective, study

Results

Accurate acoustic reflection measurements could be obtained in 7 of 10 patients (mean age: 10.4 ± 3.9 years; mucopolysaccharidosis type II (n=3); type IV (n=2), type VI (n=1), and fucosidosis (n=1)). The mean minimum cross-sectional area was lower in mucopolysaccharidosis patients ($1.6 \pm 0.3 \text{ cm}^2$) as compared to 14 healthy counterparts ($1.8 \pm 0.3 \text{ cm}^2$; $p=0.03$). The mean resistance of the airways was significantly higher in the MPS group ($7.9 \pm 1.8 \text{ cmH}_2\text{O.l}^{-1}.\text{s}$) as compared to the controls ($5.5 \pm 1.2 \text{ cmH}_2\text{O.l}^{-1}.\text{s}$; $p=0.006$).

Conclusion

This study is the first to analyze the upper airways by the noninvasive acoustic reflection method in children with mucopolysaccharidosis. Due to a lack of cooperation, reliable measurements could only be obtained in 70% of a selected group of patients. Children with mucopolysaccharidosis have significant upper airway obstruction as assessed by the reduction of the minimal cross-sectional area of the upper airways and the increase in airway resistance.

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Summary word count: 228

Keywords: mucopolysaccharidosis; acoustic reflection method; acoustic pharyngometry; children; upper airways

For Peer Review

Introduction

Mucopolysaccharidoses (MPS), OMIM 252700, are a group of rare metabolic inherited disorders caused by the lack or deficiency of specific lysosomal enzymes involved in the degradation of mucopolysaccharids (glycosaminoglycans).¹ The accumulation of partially degraded molecules interferes with cell, tissue, and organ function. Depending on the MPS subtype, the disease may display various degrees of severity. Mental retardation is common and often severe but may be absent in some MPS (MPS VI).

Upper airway obstruction and its management is a challenging concern in children and adults with MPS. Due to tissue infiltration, airway obstruction may affect the different levels of the respiratory tract. Patients may present narrowed nasal airways, adenotonsillar hypertrophy, macroglossy, thickened tongue, a short and infiltrated neck, and a narrowed pharynx and larynx with a thickened epiglottis. This airway obstruction is associated with an increase in morbidity even in early childhood.² Indeed, severe obstructive sleep apnoea syndrome has been reported in children with MPS.³⁻⁷ This upper airway obstruction may also complicate the perioperative anaesthetic management, for endotracheal intubation is known to be especially difficult in MPS patients because of soft tissues infiltration and frequent cervical spine malformations. Intubation may require an endoscopic procedure⁸⁻¹⁰ and is not always able to prevent a fatal outcome even for routine procedures.¹¹

The acoustic reflection method (ARM) is an interesting noninvasive technique based on the analysis of the reflection of a single transient planar wave, allowing the calculation of the longitudinal cross-sectional area profile of the examined cavity. An analysis of the mechanical properties of the airways by the forced-oscillations method is also possible by this technique.¹² The ARM has been first reported in humans in

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1980 by Fredberg et al.¹³ Since then, ARM has been used to explore the pharyngeal cavity in snoring patients (acoustic pharyngometry)^{14,15}, the nasal compliance (acoustic rhinometry)¹⁶, the obstruction of endotracheal tubes by mucus plugging¹⁷, the misplacement of endotracheal tubes¹⁸, the vocal tract dimensions in adolescents¹⁹ and in children with Down syndrome.²⁰ The ARM has also been used to measure tracheal size and distensibility in healthy adults and patients with cystic fibrosis or achondroplasia.^{21,22}

We have recently evaluated the feasibility and established normal values of the upper airways by the ARM in a large group of healthy children. Accurate measurements could be obtained in all the children older than 2 years of age.²³ Normal values of the minimal cross sectional area (MCAv), which corresponds to the narrowest part of the upper airways (i.e the subglottic region), were established and correlated mainly with height, and to a lesser extend with age and weight. As children with MPS may present upper airway obstruction, we hypothesised that the ARM may be particularly adapted to this population because this technique is noninvasive, simple, and rapid, with a procedure taking less than one minute.

The aim of the present study was to evaluate by the feasibility of the ARM in children with MPS, and to compare the characteristics of the upper airways evaluated by the ARM in patients with MPS to a matched group of healthy children.

Material and methods

Patients

The study was proposed to the parents of 10 patients with MPS, followed in our institution and expected to be able to perform the ARM manoeuvre. To be included, the patient had to be free of any acute upper or lower airway disease since at least one month. The ARM measurements were realised during a scheduled hospital visit or hospitalisation.

The following information was assessed from the patient's chart: history of endotracheal intubation and/or any respiratory or upper airway disease, and sleep studies when available.

Control group

A control group was recruited among siblings of the patients and a large group ($n > 60$) of outpatients from the otolaryngology department (mostly for middle ear surgery). All controls were free of any upper or lower airway disease or symptom since at least 3 months. The control group was secondarily established in order to match with the MPS patients' height, weight, and body mass index (BMI).

The study was approved by our institutional board and written consent was obtained from all the patients and the controls when possible, and all the parents.

The acoustic reflection measurement

The device used in this study, as well as its calibration method, has been previously described.^{12,24} Briefly, the acoustic reflection device consists in a Plexiglas tube of 22 cm in length and 16 mm in diameter. Two microphones (piezoresistive pressure transducers, 8510-B; Endevco France, Le Pré Saint-Gervais, France) are

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inserted on the tube which is connected to a horn driver. The ‘microphone’ side of the tube is oriented toward the patient, and the other one toward open air. An acoustic wave (0.2 – 6 kHz) is generated by the horn driver, which is driven by a personal computer via a digital-to-analog converter; microphone outputs are fed into an analog-to-digital converter (14 bits, 24-μs sampling period).

For a reliable ARM measurement, the subject has to breathe by mouth during ≈ 4 s. As such, only the airways beyond the mouth were analyzed. During these 4 seconds, the ARM device generates 10 consecutive acoustic waves at a frequency of 2.5 Hz and the corresponding areas distance curves are inferred. As previously shown, ARM measurements are influenced by the position of the head and the connecting equipment.²⁵⁻²⁸ For the recording, the subjects were thus asked to have their head in a neutral position and to breathe through an elastomer mouthpiece (Air Safety Ltd, ref A539, Morecambe, United Kingdom) and a single use filter (Intersurgical Clear-Guard™, ref 1664, Wokingham, United Kingdom).

Data are given on a 2 dimensional graph with the distance from the end of the wave tube on the x-axis and the cross-sectional area on the y-axis (Figure 1). A program calculates the cross-sectional area of the airway as a function of the distance along the longitudinal axis with a spatial step increment $\Delta L \cong 0.4$ cm. For every point on the x-axis value, i.e. distance on the airway, the mean value of the 10 curves is calculated but if the coefficient of variation of the 10 curves area exceeds 10% the test is discarded and a new test is performed. A visual control by the operator of the 10 curves (allowing to hand-mark the appropriate areas), as well as the checking of an eventual rejection of a measurement, are systematically associated to this computer analysis. The analysis software also gives the results of each measurement in a numerical format, allowing an accurate estimation of

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3 surfaces and resistances, as well as the analysis of defined portions of the studied
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5 airways chosen by the clinician. For the purpose of the present study, the mean
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7 pharyngeal and tracheal cross-sectional airway surface, as well as the minimal
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9 airway area value, (MCAv) were calculated. The choice of the landmarks is made
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11 according to the curve's profile and the knowledge of the anatomy of the upper
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13 airways. Clearly, and by comparison to the classic procedure as recently described
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15 by Xue et al.^{19,20}, our procedure implies a subjective part in the determination of
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17 landmarks. This choice was dictated by the expected lack of cooperation of children
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19 with mental retardation. In order to deemphasise the effect of any error on the
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21 landmarks definition, we only focussed on parameters that are not, or very partially,
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23 affected by the landmarks choice. We used thus the MCAv and mean area over a
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25 region of interest and we disregarded the cavity length and the cavity volume.
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32 The software allows also the calculation of the mechanical properties of the
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34 respiratory system by the forced oscillations technique, as previously
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36 demonstrated.¹² The system's impedance, defined as the ration between pressure
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38 and flow at the mouth, appears as a function of the frequency. Here, the patient's
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40 airways' total resistance (R) was defined as the average of the real part of the
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42 impedance between 15 and 45 Hz.
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48 *Statistical analysis*

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50 Data were expressed as mean $\pm$ standard deviation. Comparison between the
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52 patients and the controls was performed using Student's T Test. A *p* value less than
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54 0.05 was considered statistically significant.
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Results

Patients and feasibility

Thirty-eight children with a MPS are followed in our institution: MPS III, n=22 (58%), mean age 11.8 ± 2.3 year-old; MPS II, n=9 (24%), mean age 10.3 ± 1.1 year-old; MPS IV and VI, n=3 each (8%), mean age 8.5 ± 1.7 and 21 year-old respectively; and 1 (2%) other MPS type, aged 10.5 years. Patients “non suitable for ARM” were pre-selected by our paediatrician neurologist (BH), as they were expected to be unable to perform the ARM manoeuvres because of severe mental retardation and/or major behaviour problems. Ten patients were selected and participated to the study (Figure 2).

Accurate ARM measurements could only be obtained in 7 patients. Indeed, despite pre-selection, 3 patients were unable to breathe normally by mouth for 3 to 4 seconds despite the pre-selection on their capacity, patience, adequate explanations, and parental reassurance (Table 1). No patient with a MPS III could be included because of severe mental retardation and behavioural disorders. One patient had a fucosidosis, considered as a Hurler-like syndrome.²⁹

Among the 7 patients, 4 patients had no respiratory symptoms, 3 patients complained of dyspnea at exertion (n=3) and 2 (#6 and #7) had documented nocturnal alveolar hypoventilation and were treated by long-term noninvasive positive pressure ventilation (NPPV). The sleep studies of these 2 patients during spontaneous breathing and before initiation of NPPV showed a desaturation index of 34 and 36 per hour, hypoxemia (minimum pulse oximetry (SpO₂) $66 \pm 5.6\%$) and hypercapnia (maximum transcutaneous carbon dioxide (PtcCO₂) 49 ± 5.6 mmHg) (Table 2). One of these two patients previously underwent an endoscopic examination showing an infiltration of the posterior pharyngeal wall, the base of the

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3 tongue, and the epiglottis, with a tongue base obstruction and a granular aspect of
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5 the mucosa.
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8 All patients had previously undergone an endotracheal intubation for a surgical
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10 procedure (adenoidectomy, dental care, spine surgery). Four patients (#1, #5, #6 and
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12 #7) had a history of difficult intubation, which required the use of a fiberoptic
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14 bronchoscope for 2 of them (#5 and #6). None had a history of tracheotomy.
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17 The characteristics of the patients are given in Tables 2 and 3.
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20 21 22 *Control group* 23

24 The control group consisted of 14 healthy children (mean age 7.3 ± 2 years)
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26 who were matched to the patients with regard to height and weight (Table 3). The
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28 ARM recording was successful in all the subjects. Due to the impaired growth and
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30 development of MPS patients, the healthy subjects matched for height and weight
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32 were significantly younger than the patients ($p=0.04$).
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38 39 *Cross-sectional area values* 40

41 The MPS patients had a significantly lower mean MCAv than their healthy
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43 counterparts ($1.6 \pm 0.3 \text{ cm}^2$ and $1.8 \pm 0.3 \text{ cm}^2$ for MPS patients and controls,
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45 respectively; $p=0.03$) (Figure 3 and 4 and Table 3). The mean pharyngeal and
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47 tracheal area values were also lower in the MPS group than in the controls, but this
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49 difference was not statistically significant. Concerning the individual data, MCAv
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51 results were clearly different from the controls for 4 MPS patients (patients #3, #5, #6,
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53 and #7). Of note, 2 of these patients (patients #6 and #7) were those with severe
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55 upper airway obstruction treated with NPPV. Because of the abnormal MCAv results
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57 in the two other patients (patients #3 and #5), sleep studies were performed.
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Although the results were within the normal range, the apnoea index was 1 and the hypopnoea index was 2 in patient #3, and the patient #5 had a hypopnoea index of 5 and spent 12% of sleep time with a low SpO₂ between 90 and 95%.

Upper airways resistance

The mean resistance (R) of the upper airways was higher in the MPS group (7.9 ± 1.8 cmH₂O.l⁻¹.s) than in the control group (5.5 ± 1.2 cmH₂O.l⁻¹.s) (p=0.0064) (Figure 4 and Table 3).

Again, when looking at the individual data, the R results were clearly different from the controls for 4 MPS patients (patients #3, #4, #6, and #7). These 4 patients comprised 3 of the previous patients (patients #3, #6, and #7). The last patient (#4) is scheduled for a sleep study in the coming weeks.

These complementary data are given in table 2.

Discussion

This study shows that the ARM is able to identify a significant reduction of the upper airway calibre in children with MPS. Indeed, the mean MCAv was significantly lower and the mean airway resistance was significantly higher in 7 patients with MPS as compared to a matched control group. However, individual results were without the normal range in 5 of the 7 patients, of whom 2 were treated with NPPV for severe upper airway obstruction.

Technical issues

We chose the ARM as a tool to study the upper airways in patients with MPS, in whom cooperation may be difficult, because this technique is simple, noninvasive and takes only several seconds. We have recently reported the excellent feasibility of this technique which can be realized in healthy children after the age of 2 years. However, because of a lack of cooperation, mental retardation, and behavioural problems, reliable, accurate ARM measurements could only be obtained in 7 out of 10 selected patients. The experience of our team in performing ARM recordings in children was undoubtedly helpful but was not sufficient. Moreover, if the pre-selection of our patients allowed us to achieve enough successful recordings to obtain workable data, the extension of our results to all the paediatric MPS population must be made with caution. We could only perform ARM measurement in 7/38 (18%) of all our MPS patients and even if this percentage may be improved (inclusion of adults, multiple examinations in an optimal environment), examination of the total population seems unrealizable. Of note, no patient with a MPS III could be studied.

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Exploring the airways of MPS patients is challenging. Evaluations have been done with CT-scanning but in addition to the irradiation it delivers, this imaging technique also requires cooperation and hold breathing for a few seconds to give reliable data. This seems difficult to achieve in MPS patients, especially in the stressogenic supine position in the scanner machine.³⁰ Fiberoptic examination gives accurate morphological data but may also be difficult to perform in children with behavioural problems, and does not provide reliable airway measurements because of the distortion of the images in the optic fibre and the bias of images' interpretation by one practitioner only. However, at least one fiberoptic examination seems recommendable prior to a general anaesthesia in MPS patients.³¹

Clinical relevance of the results

The MCAv is the most important parameter for the evaluation of the upper airway because the minimal airway diameter influences both the clinical presentation and the therapeutic management.³² In healthy subjects, the MCAv corresponds to the subglottic area, which is physiologically the narrowest region of the upper airways. As none of our patients had a history of airway surgery or prolonged intubation, it is likely that their MCAv also corresponds to the subglottic area. The mean MCAv value was significantly reduced in the group of patients with MPS compared to the control group. This can be explained by the infiltration of the airways' wall by the partially degraded molecules inherent to MPS. The mean values of the pharynx and the trachea cross-sectional areas also showed a trend to be reduced compared to healthy children, but this did not reach statistic significance. A significant threshold might have been reached with the inclusion a larger group of patients. Even if the

ARM has been successfully used in several studies to assess nasal cavities, we intentionally chose not to perform such measurements in our patients because of the difficulty of achieving an accurate nasal recording in patients with behavioural problems.

The overall resistance of the airways was significantly higher in the MPS group as compared to the control group. This can be explained by the modification of the wall compliance, and the reduction of the cross-sectional area of the pharynx, larynx, and trachea, and the lower airways.

Interestingly, the patients with obstructive sleep apnoea and a need for a nocturnal NPPV (#6 and #7) had clearly MCAv and airway resistance values outside the normal range. This led us to screen the 3 patients having also abnormal values for upper airway obstruction by a sleep study. The sleep results of these clinically asymptomatic patients were not totally normal (Table 2), underlining the potential value of the ARM as a screening tool for the detection of mild and/or subclinical OSAS in patients with MPS.

Interestingly, MPS patients with abnormal MCAv and airway resistance seemed to be older than those with normal values (12.6 vs. 7.9 years of age). This may be explained by the progressive infiltration of the airways' wall with time. Further studies are warranted to evaluate the usefulness of systematic sleep studies in older patients with MPS in order to detect clinically asymptomatic upper airway obstruction.

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Conclusions

This study is the first that analyses the upper airways (nose excluded) by the ARM in children with a MPS. Patients with MPS have a significant reduction of the minimal cross-sectional area of the upper airways and an increase of the airways' resistance, as compared to a matched control group.

For Peer Review

List of abbreviations

MPS: mucopolysaccharidosis

ARM: acoustic reflection method

MCAv: minimum cross-sectional area value

BMI: body mass index

NRS: noninvasive respiratory support

OSAS: obstructive sleep apnea syndrome

Competing interests

The authors declare that they have no competing interests.

Authors' contribution

The study was designed by NL, RV, and BF. Patients' selection was made by BH. Measurements and data management were made by NL. Technical supervision was made by BL. The manuscript was written and approved by all the co-authors.

Authors' information

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3 **Legends of the Figures**
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8 **Figure 1**
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10 Typical acoustic recording curves in a healthy subject
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12 Two-dimensional recording; X: distance from microphones (cm) Y: area of airways'
13 cross-section
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17 1: mouthpiece and filter; 2: mouth and oropharynx 3: pharynx; 4: larynx and trachea;
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19 5: bronchi (artefacts)
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25 **Figure 2**
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27 Selection of subjects eligible for the acoustic reflection measurement among the
28 patients with a mucopolysaccharidosis followed in our institution
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33 **Figure 3**
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35 An acoustic reflection tracings in a patient with mucopolysaccharidosis (patient).
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37 Note the reduced value of the mean cross sectional area and of the cross-sectional
38 area all along the airway (arrows)
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45 **Figure 4**
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47 Mean cross sectional area values and resistance values of the patients with
48 mucopolysaccharidosis and the control subjects; black-filled circles correspond to the
49 2 patients with mucopolysaccharidosis treated by long term noninvasive positive
50 pressure ventilation.
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Table 1: comparison of the patients with mucopolysaccharidosis able or not to perform an adequate acoustic reflection measurement (ARM)

	Patients able to perform an ARM recording n=7	Patients unable to perform an ARM recording n=3
Age (y)	10.4	15.2
Gender	M: n=6; F: n=1	M: n=3
<i>Type of MPS</i>		
Type II	3	2
Type III	0	1
Type IV	2	0
Type VI	1	0
Fucosidosis	1	0

y: years; M: male; F: female

Table 2: characteristics of the patients

Patient	Gender	Condition	Age (y)	Height (cm)	Weight (kg)	Mental retardation	History of difficult intubation	Sleep study < 6 months	Minimal sleep SpO ₂	RDI	DI (/h)	Snoring index	Maximal sleep CO ₂ (mmHg)	NPPV
#1	M	MPS II: Hunter syndrome	5.8	120	30	Severe	Yes	No						No
#2	M	MPS IV-A: Morquio syndrome	7	110	19	None	No	No						No
#3	M	MPS IV-A: Morquio syndrome	7.5	95	17	None	No	Yes	93%	6	0	61		No
#4	F	Fucosidosis	10.5	125	25	Severe	No	No						No
#5	M	MPS II: Hunter syndrome	11.5	135	36	Severe	Yes	Yes	91%	5	0	55	45	No
#6	M	MPS II: Hunter syndrome	15	134	32	Severe	Yes	n/a	65%	7	34	8	64	Yes
#7	M	MPS VI: Maroteaux-Lamy syndrome	15.6	131	35	Mild	Yes	n/a	70%	17	36	82	53	Yes

M: male; F: female; MPS: mucopolysaccharidosis; y: years; SpO₂: pulse oximetry; RDI: respiratory disturbance index; DI: desaturation index; /h: by hour; CO₂: carbon dioxide; NPPV: noninvasive positive pressure ventilation; n/a: non applicable.

Table 3: acoustic measurements in MPS patients and healthy subjects

	MPS patients		Healthy subjects		
	Mean $\pm$ SD	Range	Mean $\pm$ SD	Range	p
Anthropometry					
Age	10.4 $\pm$ 3.9	5.8-15.6	7.3 $\pm$ 2	4.1-10.4	p=0.04
Height (cm)	121.4 $\pm$ 14.6	95-135	120.9 $\pm$ 12	95-133	p=0.4651
Weight (kg)	27.7 $\pm$ 7.5	17-36	26.2 $\pm$ 7.3	19-39	p=0.3366
BMI (kg.cm ⁻²)	18.5 $\pm$ 2	16-20.8	17.9 $\pm$ 3.5	14.6-22	p=0.3098
Acoustic measurements					
MCAv (cm ²)	1.6 $\pm$ 0.3	1.3-2	1.8 $\pm$ 0.3	1.5-2.4	p=0.0329
Mean pharyngeal airway surface (cm ²)	2.2 $\pm$ 0.6	1.3-2.8	2.5 $\pm$ 0.3	1.9-3.1	p=0.15
Mean tracheal airway surface (cm ²)	1.8 $\pm$ 0.3	1.3-2.4	2 $\pm$ 0.3	1.7-2.4	p=0.06
R (cmH ₂ O.l ⁻¹ .s)	7.9 $\pm$ 1.8	5.6-10.1	5.5 $\pm$ 1.2	3.3-6.9	p=0.0064

MPS: mucopolysaccharidosis; SD: standard deviation; BMI: body mass index; R: airway resistance; MCAv: minimal cross-sectional area value

Figure 1

Figure 1
254x190mm (96 x 96 DPI)

Figure 2

Figure 2
254x190mm (96 x 96 DPI)

Figure 3

Figure 3
254x190mm (96 x 96 DPI)

Figure 4

Figure 4
254x190mm (96 x 96 DPI)