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Non-invasive pulmonary function test on Morquio patients☆,☆☆

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ABSTRACT

In clinical practice, respiratory function tests are difficult to perform in Morquio syndrome patients due to their characteristic skeletal dysplasia, small body size and lack of cooperation of young patients, where in some cases, conventional spirometry for pulmonary function is too challenging. To establish feasible clinical pulmonary endpoints and determine whether age impacts lung function in Morquio patients non-invasive pulmonary tests and conventional spirometry were evaluated.

The non-invasive pulmonary tests: impulse oscillometry system, pneumotachography, and respiratory inductance plethysmography in conjunction with conventional spirometry were evaluated in twenty-two Morquio patients (18 Morquio A and 4 Morquio B) (7 males), ranging from 3 to 40 years of age.

Twenty-two patients were compliant with non-invasive tests (100%) with the exception of IOS (81.8%–18 patients). Seventeen patients (77.3%) were compliant with spirometry testing. All subjects had normal vital signs at rest including >95% oxygen saturation, end tidal CO_2 (38–44 mm Hg), and age-appropriate heart rate (mean = 98.3, standard deviation = 19) (two patients were deviated). All patients preserved normal values in the impulse oscillometry system, pneumotachography, and respiratory inductance plethysmography, although predicted forced expiratory total (72.8 ± 6.9 SE%) decreased with age and was below normal; phase angle (35.5 ± 16.5°), %rib cage (41.6 ± 12.7%), resonant frequency, and forced expiratory volume in 1 s/forced expiratory volume total (110.0 ± 3.2 SE%) were normal and not significantly impacted by age.

The proposed non-invasive pulmonary function tests are able to cover a greater number of patients (young patients and/or wheel-chair bound), thus providing a new diagnostic approach for the assessment of lung function in Morquio syndrome which in many cases may be difficult to evaluate. Morquio patients studied herein demonstrated no clinical or functional signs of restrictive and/or obstructive lung disease.

Abbreviations: ANOVA, analysis of variance; BMI, body mass index; CO_2, carbon dioxide; CS, chondroitin sulfate; C6S, chondroitin-6-sulfate; CV, coefficient of variation; ERT, enzyme replacement therapy; FDA, Food and Drug Administration; FEV_1, forced expiratory volume in 1 s; FEV_{TOT}, forced expiratory volume total; FVC, forced vital capacity; GAGs, glycosaminoglycans; HSCT, hematopoietic stem cell transplantation; IOS, impulse oscillometry; KS, keratan sulfate; MPS, mucopolysaccharidosis; MPS IVA, mucopolysaccharidosis IVA; MPS IVB, mucopolysaccharidosis IVB; NHANES, National Health and Nutrition Examination Survey; GALNS, N-acetyl-galactosamine-6-sulfate-sulfatase; PhRTB, phase relation during total breath; $\%FEV_{TOT}$, predicted forced expiratory volume total; PFTs, pulmonary function tests; PNT, pneumotachography; Xrs, reactance; Rrs, resistance; Rrs_5, resistance at 5 Hz; Rrs_{20}, resistance at 20 Hz; f_{RES}, resonant frequency; RIP, respiratory inductance plethysmography; TAA, thoracoabdominal asynchrony; TAM, thoracoabdominal motion; FEV_1/FEV_{TOT}, timed forced expiratory volume/forced expiratory volume total; TLC, total lung capacity; SpO_2, transcutaneous saturation of oxygen; VC, vital capacity.

☆ Conflict of interest:Francyne Kubaski, Shunji Tomatsu, Pravin Patel, Tsutomu Shimada, Li Xie, Eriko Yasuda, Robert W. Mason, William G. Mackenzie, Mary Theroux, Michael Bober, Helen M. Oldham, Tadao Orii, and Thomas H. Shaffer declare that they have no conflict of interests.

☆☆ Compliance with ethics guidelines:All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients and/or their guardians and the study was approved by the Institutional Review Board of the Institution (750932).

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1. Introduction

Morquio syndrome is an autosomal recessive disorder caused by a deficiency of N-acetylgalactosamine-6-sulfate sulfatase (GALNS) (mucopolysaccharidosis IVA, MPS IVA) and β-galactosidase (GLB1) (mucopolysaccharidosis IVB, MPS IVB). These enzymes are required for the catabolism of the glycosaminoglycans (GAGs): chondroitin-6-sulfate (C6S) and keratan sulfate (KS) [1–3]. Incidence varies among different populations from 1:76,000 to 1:640,000 live births [3–8].

Morquio syndrome includes skeletal dysplasia with short stature, kyphoscoliosis, platyspondyly, odontoid hypoplasia, genu valgum, pectus carinatum, and dental abnormalities. Other findings are ligamentous laxity, corneal clouding, and cardiac and pulmonary complications without neurological involvement [8–17]. Autopsied trachea showed tracheomalacia but little evidence of a narrow airway due to storage materials [9]. Difficulty of intubation and extubation was observed during the surgical procedure, which could be associated with tracheomalacia. Tracheomalacia can cause a twisting, tortuous trachea, leading to a high risk during anesthesia.

It has been reported that respiratory issues in patients with Morquio syndrome are associated with two conditions: 1) restrictive lung disease (inability to inspire) due to short stature and thoracic cage deformity [18,19,15,17,20,21], and 2) obstructive lung disease (inability to expire) due to tracheobronchial abnormalities, large tongue, and adenoidal, tonsillar, and vocal cord hypertrophy. These respiratory issues lead to a high mortality rate or high risk during anesthesia [18,17,21]. The functional signs of restrictive and obstructive lung disease are that the patients cannot breathe synchronously and cannot effectively maintain normal gas exchange even at rest.

However, we do not know whether the flows are actually less or greater than normal individuals when normalized for smaller volumes and stature.

Spirometry clearly evaluates several assessments of static and dynamic volume measurements; however, this approach is considered an effort dependent test requiring cooperation between subject and examiner [22]. Young patients and wheel-chair bound, and/or post-operative patients with severe muscle weakness cannot be given such physical assessments.

In the last two decades, pulmonary function tests (PFTs) have been revised to analyze tidal breathing in patients who are minimally cooperative due to age or clinical condition. These include impulse oscillometry (IOS), pneumotachography (PNT), and respiratory inductance plethysmography (RIP), which have been used extensively in the minimally cooperative neonate and pediatric populations [22–28]. In addition, IOS provides more information about total respiratory system resistance [29].

A number of studies have shown the significance of using measurements of airway resistance and reactance at different oscillation frequencies such as IOS in various clinical settings, for detecting chest wall abnormalities, lung compliance disorders, airway obstruction, assessment of chronic obstructive pulmonary disease and asthma [29–32]. Furthermore, the use of a non-invasive PFT would accommodate a broader spectrum of patients (young and or/wheel-chair bound).

In contrast, to our knowledge, no systemic study has been performed to evaluate age-dependent oscillometry measurements for patients with Morquio syndrome or other skeletal dysplasias in comparison with conventional spirometry studies.

In the present study, we sought to elucidate age-dependent changes in pulmonary function utilizing non-invasive PFTs correlated with conventional spirometry (when possible) in patients with Morquio syndrome. In addition, we hypothesized that the age-dependent alterations in lung function can be correlated with the "small lungs" (compared to age-matched controls from a database group with normal stature) as measured with spirometry.

2. Materials and methods

2.1. Subjects

This was an open, non-controlled, single center, assessment study of patients diagnosed as Morquio A and B who were pulmonary asymptomatic at the time of the study. This study assessed key thoracopulmonary features. Patients with Morquio syndrome had one visit for clinical evaluation of lung function. All tests were clinically indicated and conducted on an out-patient basis at Nemours/Alfred I. duPont Hospital for Children. This study was conducted in accordance with the amended Declaration of Helsinki and it was approved by the institutional review board from the institution (750932). Informed consent was obtained from all patients and/or their guardians.

Twenty-two subjects with Morquio (18 Morquio A and 4 Morquio B), from 3 to 40 years of age were tested (mean = 16.5 years). Part of the physical examination included measuring height, weight, and systemic skeletal examinations. We used Morquio A growth charts [14] as reference for height, weight, and BMI. Measurement of standing height in patients was difficult due to skeletal deformities, which limited patients' ability to stand erect. To obtain consistent data, we performed several established measurements at least twice per patient. The patient lay on a flat surface with knees flattened to fully extend the legs. Standing height was also measured. For pulmonary function, arm length conversion to height was performed to determine predicted values for pulmonary standards, often used in our outpatient PFT laboratory for patients with skeletal deformities [33]. Finally, of the 22 patients, 17 (77.3%) were able to perform spirometry, leading to a limited profile of spirometry (3 young patients, 1 patient unable to perform and 1 non-cooperative patient). Data in the control subjects were derived from previous studies (National Health and Nutrition Examination Survey—NHANES III) [34].

2.2. Inclusion and exclusion criteria

The subjects were diagnosed as Morquio A and B by enzyme analysis. There were no exclusion criteria related to sex, age, ethnic background, scheduled operation, or physical ability.

2.3. Pulmonary function tests (PFTs)

2.3.1. Spirometry

All spirometry (Medgraphics Ultima PF; BreezeSuite Software; and PreVent Flow Sensor; St. Paul, MN) determinations were performed in our PF outpatient laboratory utilizing our standard operating procedures. As noted above, predicted values for an individual of normal stature were determined based on arm length [33] and evaluated in the BreezeSuite Software for the NHANES III data base [34]. Forced expiratory volume in 1 s (FEV_1), forced expiratory volume total (FEV_{TOT})/forced vital capacity (FVC)/vital capacity (VC), predicted forced expiratory volume total (%FEV_{TOT}), FEV_1/FEV_{TOT} (timed forced expiratory volume/forced expiratory volume total), and %Predicted (FEV_1/FEV_{TOT}) were determined from the best of 3 spirometric tracings.

2.3.2. Impulse oscillometry system (IOS)

IOS measures resistance (R) at different frequencies (R_5—peripheral airway resistance; R_{20}—central airway resistance) and reactance (movement of the air in the airways) [35]. The device used for the oscillatory measurements was the Master Screen-IOS device (E. Jaeger; Höchberg, Germany) [36–38]. For each impulse, 32 sample points were analyzed. Daily calibration using a calibration pump (3.0 ± 0.01 L SD, Jaeger; Höchberg, Germany) and a reference impedance of 0.2–2.5 kPa/L/s was performed. Briefly, small mechanical impulses were superimposed on the spontaneous breathing pattern. Through the phase relationship, the Zrs was partitioned into resistance (Rrs) and reactance (Xrs). Rrs included the airway, lung tissue, and chest wall