Rib Cage Deformities Alter Respiratory Muscle Action and Chest Wall Function in Patients with Severe Osteogenesis Imperfecta

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Abstract

Background: Osteogenesis imperfecta (OI) is an inherited connective tissue disorder characterized by bone fragility, multiple fractures and significant chest wall deformities. Cardiopulmonary insufficiency is the leading cause of death in these patients.

Methods: Seven patients with severe OI type III, 15 with moderate OI type IV and 26 healthy subjects were studied. In addition to standard spirometry, rib cage geometry, breathing pattern and regional chest wall volume changes at rest in seated and supine position were assessed by opto-electronic plethysmography to investigate if structural modifications of the rib cage in OI have consequences on ventilatory pattern. One-way or two-way analysis of variance was performed to compare the results between the three groups and the two postures.

Results: Both OI type III and IV patients showed reduced FVC and FEV₁ compared to predicted values, on condition that updated reference equations are considered. In both positions, ventilation was lower in OI patients than control because of lower tidal volume (p<0.01). In contrast to OI type IV patients, whose chest wall geometry and function was normal, OI type III patients were characterized by reduced (p<0.01) angle at the sternum (pectus carinatum), paradoxical inspiratory inward motion of the pulmonary rib cage, significant thoraco-abdominal asynchronies and rib cage distortions in supine position (p<0.001).

Conclusions: In conclusion, the restrictive respiratory pattern of Osteogenesis Imperfecta is closely related to the severity of the disease and to the sternal deformities. Pectus carinatum characterizes OI type III patients and alters respiratory muscles coordination, leading to chest wall and rib cage distortions and an inefficient ventilator pattern. OI type IV is characterized by lower alterations in the ventilatory function. These findings suggest that functional assessment and treatment of OI should be differentiated in these two forms of the disease.

Citation: LoMauro A, Pochintesta S, Romei M, D’Angelo MG, Pedotti A, et al. (2012) Rib Cage Deformities Alter Respiratory Muscle Action and Chest Wall Function in Patients with Severe Osteogenesis Imperfecta. PLoS ONE 7(4): e35965. doi:10.1371/journal.pone.0035965

Editor: James West, Vanderbilt University Medical Center, United States of America

Received November 15, 2011; Accepted March 27, 2012; Published April 27, 2012

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Funding: This work was supported by a grant of Fondazione Cariplo: Health Innovation Network Technology @ Lecco (HINT@Lecco). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

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Introduction

Osteogenesis imperfecta (OI) is a genetically heterogeneous group of congenital disorders of collagen synthesis characterized by brittle bones leading to different levels of skeletal deformities and frequent multiple fractures.

OI exhibits a broad range of clinical severity, ranging from multiple fracturing in utero to normal adult stature and a low fracture incidence [1,2]. Although new types of OI syndrome have been recently introduced [3], the traditional classification proposed by Sillence et al. [4,5] considers four main groups according to the phenotypic variability, i.e. type I, II, III, and IV. OI type I is the mildest form characterized by blue sclerae; perinatal lethal OI type II, also known as congenital OI; OI type III, the most severe non-lethal form characterized by multiple fractures with normal sclera, progressive long bones, spine deformities and short stature; and OI type IV, a moderate form with normal sclerae [5–7].

Life expectancy in OI type IV is similar to general population, while in type III is reduced [8] with cardiopulmonary insufficiency and respiratory infections being the leading causes of death in these patients, and their prevention and treatment are important factors for prognosis [9,10].

Although it is reasonable to postulate that structural alterations of the chest wall, namely spinal and rib cage deformities, may contribute to cardiopulmonary problems in severe OI, few authors reported data on deformities and pulmonary function [11,12].

The hypothesis of the present paper is that structural modifications of the rib cage due to OI have important consequences on ventilation at rest in terms of chest wall function. To test this hypothesis we noninvasively measure kinematics and...
volume changes of chest wall in OI patients in two different positions in order to show possible differences between the moderate (type IV) and the most severe (type III) forms and to find possible correlations between chest wall deformities, pulmonary function and ventilatory pattern.

Methods

Ethics Statement
The research protocol was approved by the local ethics committee of the Scientific Institute E.Medea, Bosisio Parini, Lecco, Italy (approval n. 19/07-CE) and written informed consent was obtained from all patients (or parent). We obtained informed consent from the next of kin on the behalf of the minors/children participants involved in the study.

Patients
Twenty-two patients affected with osteogenesis imperfecta were recruited for this study. The diagnosis of OI was made on the basis of the following clinical and radiological findings: susceptibility to frequent fractures from the mildest trauma, varying degrees of short stature, progressive skeletal deformities, blue sclerae, dentinogenesis imperfect, joint laxity, early loss of hearing, genetic and/or biochemical analysis with heterozygosity of dominant mutations in one of the two genes (COL1A1 and COL1A2) encoding the chains of type I collagen, with quantitative (mild or moderate forms) or qualitative (severe or lethal forms) defect of the synthesis of type I collagen [2].

Seven patients were classified as type III, the most severe form of OI and 15 patients as type IV.

Twenty six healthy subjects were recruited as control group.

Two type III patients were under nocturnal non-invasive ventilation; 7 patients (5 type III, 2 type IV) were not ambulant; one type IV patient showed basilar impression; one type IV patient had costal fractures secondary of a car crash occurred three months before the study.

Pulmonary function tests
Measurements of forced vital capacity (FVC), forced expiratory volume in one second (FEV)\textsubscript{1}, subdivision of lung volumes (Functional Residual Capacity, FRC; Residual Volume, RV and Total Lung Capacity, TLC) by the nitrogen washout technique were performed (Vmax series 22, SensorMedics, Yorba Linda, CA). Spirometric and lung volumes predicted values were calculated using gender, age and height, according to the most commonly used equations of Quanjer et al [13] but also to more recent equations of Kuster et al [14], valid on a wider range of ages.

Nocturnal oxygen saturation (SpO\textsubscript{2}) was measured using a digital pulse oximeter (Nonin, 8500 digital pulse oximeter Quitman, TX). Pulse oximeter was positioned by specialized personnel and only recordings longer than 8 h were considered as acceptable, otherwise measurements were repeated during the following night.

Kinematic Analysis
Total and compartmental chest wall volumes were measured by Opto-Electronic Plethysmography (OEP System; BTS, Milan, Italy) [15,16]. The system, based on eight special infrared video cameras working at a sampling rate of 60 Hz, computes the 3D coordinates of retro-reflective markers placed on the trunk of the subject according to specific anatomical points from clavicles to pubis. When patients were lying supine on the bed, 52 markers were placed over the anterior chest wall surface [17,18], while an 89 markers configuration was used for measurements in the seated position [16]. Patients and controls were analyzed during three minutes of spontaneous quite breathing in awake diurnal state firstly in seated and successively in supine position.

Chest wall volumes and ventilatory pattern
Chest wall was divided into three compartments: pulmonary rib cage (RCp), under the action of rib cage muscles, abdominal rib cage (RCa), under the insertion action of diaphragm and abdomen (AB), under the action of the diaphragm and the expiratory abdominal muscles.

The volume of the entire chest wall (V\textsubscript{CW}) and its compartments (V\textsubscript{RCp}, V\textsubscript{RCa}, V\textsubscript{AB}) were noninvasively measured by Opto-Electronic Plethysmography. Figure 1 shows an example of thoraco-abdominal volume traces during ten seconds of spontaneous supine quite breathing of a type III patient and an healthy subject. In this representative example, for clarity, the volumes of the two rib cage compartments are summed to provide total rib cage volume.

From variations of V\textsubscript{CW} during breathing the ventilatory pattern, in terms of minute ventilation, breathing frequency, tidal volume and percentage contribution of each compartment to tidal volume was determined for each position.

Chest wall dimensions and deformity
To characterize chest wall geometry several geometrical parameters were calculated from 3D marker coordinates measured by Opto-Electronic Plethysmography in seated position at end-expiration [18]. These included trunk height, chest wall surface and total and compartmental trunk volumes. The latter were obtained as the volume enclosed by the surface obtained by triangulating all the markers. Several additional parameters including medio-lateral and antero-posterior diameter, perimeter and cross sectional area were calculated at five vertical levels (Louis’ angle, xiphoid process, lower costal margin, umbilical and iliac crest) (figure 2). In addition, to quantitatively describe the geometrical deformity of the rib cage (pectus carinatum) the angles subtended at the sternal level on the transversal plane (figures 2a and 2c) and on the sagittal plane (figures 2b and 2d) were calculated.

Thoraco-abdominal asynchronies
Dynamic thoraco-abdominal asynchronies were quantified by determining the phase shift angle ($\Phi_{TA}$) between volume variations of V\textsubscript{RCp} and V\textsubscript{AB} waveforms. $\Phi_{TA}$ was derived from the ratio of the distance m delimited by the intercepts of V\textsubscript{RCp} (y-axis)-V\textsubscript{AB} (x-axis) loop on a line parallel to the x-axis at 50% of $\Delta V_{RCp}$ divided by $\Delta V_{AB}$ (s) and computed as $\Phi_{TA} = \sin^{-1}(m/s)$ [19,20]. In a similar way, dynamic asynchrony between the two rib cage compartments was calculated as the phase shift angle between V\textsubscript{RCp} and V\textsubscript{RCa} waveforms ($\Phi_{RCa}$). By convention a positive angle means that RCp expansion is leading on RCa (or AB) expansion; on the contrary negative angles describe the reverse situation.

Labored Breathing Index (LBI) [21] was calculated as the ratio between the sum of maximal V\textsubscript{RCp}, V\textsubscript{RCa}, V\textsubscript{AB} variations and tidal volume (maximal V\textsubscript{CW} variation).

Spinal deformity assessment
Radiographic measurements included standard standing antero-posterior and lateral views of the entire spine. Thoracic scoliosis was measured using the Cobb method. If two curves were present, the largest thoracic curve was used.
Statistical analysis

Anthropometric, spirometric and lung function data of the three groups were compared using a one-way Analysis of Variance with disease as independent factor. To compare ventilatory pattern data between the groups in the two postures, a two-way Analysis of Variance was performed with posture and disease as independent factors. Post-hoc tests were based on Holm-Sidak method. Data in tables are expressed as mean±standard deviation, in figures as mean±standard error. Significance was determined by p<0.05.

Figure 1. Thoraco-abdominal volume variations during spontaneous breathing. Time courses of the volumes of the rib cage (sum of the pulmonary and abdominal rib cage), abdomen and total chest wall during ten seconds of consecutive breaths at rest in supine position in a representative OI type III patient (left panels) and a representative healthy control subject (right panels). The thick lines highlight a single breath. doi:10.1371/journal.pone.0035965.g001

Figure 2. Assessment of chest wall geometry and rib cage deformity by markers’ projections. Experimental set-up for the analysis of chest wall volumes via optoelectronic plethysmography in supine (a) and seated (b) position on a representative OI type III patient. c: schematic view of the markers on the transversal plane at the xiphosternal level, in which medio-lateral diameter (distance between markers A and B), antero-posterior diameter (distance between markers C and D), area (grey area) and transversal angle (angle formed between lines CE and CF) are shown; d: schematic view of the markers on the sagittal plane in which trunk height (distance between markers G and H), and sagittal sternal angle (enclosed within lines CL and CM) are shown. doi:10.1371/journal.pone.0035965.g002
Table 1. Osteogenesis imperfecta (OI) patients’ and healthy controls characteristics.

| Anthropometry                          | OI type III | OI type IV | Control group |
|----------------------------------------|-------------|------------|---------------|
| Patients n (M/F)                       | 7 (5/2)     | 15 (8/7)   | 26 (17/9)     |
| Age (yrs)                              | 26.1 ± 16.3 | 15.9 ± 11.4 | 22.4 ± 18.3   |
| Height (cm)                            | 106.6 ± 14.7 | 127.7 ± 18.3 | 157.0 ± 23.2  |
| Weight (Kg)                            | 30.6 ± 15.3 | 39.6 ± 17.5 | 54.2 ± 24.4   |
| Body Mass Index (Kg/m²)\(^1\)         | 27.8 ± 13.9 | 23.2 ± 6.3  | 23.2 ± 6.3    |
| Body Surface Area (m²)\(^1\)           | 0.89 ± 7.00 | 1.16 ± 15.00 | 1.52 ± 0.45   |
| Trunk volume (L)                       | 11.5 ± 5.9  | 13.7 ± 7.7  | 15.8 ± 8.9    |
| Rib cage volume (% trunk volume)       | 63.7 ± 15.1 | 68.9 ± 4.9  | 71.6 ± 3.6    |
| Abdominal volume (% trunk volume)      | 36.3 ± 15.1 | 31.1 ± 4.9  | 28.4 ± 3.6    |
| Trunk Surface (m²)                     | 0.28 ± 0.11 | 0.32 ± 0.12 | 0.39 ± 0.13   |
| Trunk Height (cm)                      | 18.4 ± 5.6  | 27.6 ± 3.8  | 40.4 ± 6.5    |
| Medio-Lateral Diameter\(^1\) (cm)     | 27.7 ± 7.9  | 30.1 ± 7.0  | 31.4 ± 5.7    |
| Antero-Posterior Diameter\(^1\) (cm)  | 19.3 ± 7.0  | 20.8 ± 4.3  | 19.6 ± 4.0    |
| Perimeter\(^1\) (cm)                   | 0.80 ± 0.22 | 0.85 ± 0.19 | 0.85 ± 0.16   |
| Cross sectional area\(^1\) (cm²)      | 422.5 ± 252.4 | 523.3 ± 219.0 | 515.4 ± 199.8 |
| Transversal angle\(^1\) (degree)      | 161.6 ± 17.5 | 178.3 ± 10.5 | 181.7 ± 12.9  |
| Sagittal angle\(^1\) (degree)         | 155.8 ± 26.6 | 170.2 ± 13.9 | 170.1 ± 12.7  |
| Cobb Angle (deg)\(^2\)                | 54.7 ± 14.9 | 41.1 ± 14.2 | n.a.          |

Data are expressed as mean±standard deviation.

\(^1\)Body Mass Index = weight (Kg)/height (m)\(^2\).

\(^2\)Body Surface Area (m²) = 0.024265 \times height (cm)\(^0.5378\) \times weight (Kg)\(^0.3964\).

\(^3\)at sternal level.

\(^4\)maximal.

\(^5\)n.a. = not available.

doi:10.1371/journal.pone.0035965.t001

Results

Anthropometry, chest wall dimensions and deformity

Anthropometric characteristics of OI type III, OI type IV and controls are reported in table 1. Height was different among the three groups, being the lowest in OI type III patients. Weight and body surface area were lower in OI patients than controls. Among all the geometrical parameters, only two resulted different: trunk height (being lower in OI type III patients) and the angle at sternum level, both in sagittal and transversal planes. Patients with OI type III were characterized by lower angles (i.e., pectus carinatum) in contrast with the flatter sternum of both OI type IV and controls (figure 3).

All patients were characterized by severe or moderate scoliosis (Cobb Angle>20°). Average Cobb angle values were >40° in both OI types and no differences were observed.

Pulmonary function

Spirometric parameters, lung volumes and nocturnal saturation data are shown in table 2.

Spirometry and lung volume data were not available on patients younger than 9 years (2 type III and 6 type IV) due to their limited collaboration.

According to the most commonly used equations of Quanjer et al [13], patients showed FVC and FEV\(_1\) values (expressed as percentage of predicted values, %pred) within the normal range, with data of OI type III unexpectedly higher than predicted. Using more recent equations of Kuster et al [14], FVC (%pred) and FEV\(_1\) (%pred) became significantly lower in OI patients, particularly in OI type III. No differences were found using the two different predicted equations for TLC, RV and FRC. Finally, although OI type III patients showed a more pronounced tendency to decrease oxygen saturation (SpO\(_2\)) during the night compared to OI type IV, this was not significant.

Ventilatory pattern

Minute ventilation and its two components, breathing frequency and tidal volume (VT), are summarized in table 3. In supine position there were no differences in minute ventilation, while VT and breathing frequency components were different, being lower the former and higher the latter in OI patients. No differences were found between type III and type IV. In the seated position minute ventilation was lower in OI patients than controls due to lower VT. Only in OI type III patients, breathing frequency was higher than controls.

Chest wall compartment volumes

Patients with OI type III were characterized by reduced contributions of rib cage compartments to VT as shown in figure 4. The percentage contribution of V\(_{RC,P}\) to VT in OI type III was reduced in seated position, being negative (i.e., paradoxical inward motion during inspiration) and lower compared to OI type IV and controls in supine. In OI type IV patients V\(_{RC,P}\) contribution was lower than controls only in seated position. Similarly, the V\(_{RCA}\) contribution to VT was reduced in OI type III patients compared
Discussion

Chest wall asynchrony

Patients with OI type III were characterized by high levels of dynamic thoraco-abdominal asynchronies as shown in figure 5. $\Phi_{TA}$ was lower in OI type III patients than OI type IV and controls, both in supine and seated position. $\Phi_{RC}$ was lower in OI type III patients than OI type IV and controls, but only in supine position. Accordingly, the LBI was higher in OI type III patients than OI type IV and controls, in both positions. In OI type III patients only, $\Phi_{TA}$, $\Phi_{RC}$ and LBI were significantly different between seated and supine position.

An implication of these findings is that rib cage deformities, rather than scoliosis which was present in both OI types, is the determinant of the altered breathing pattern in type III. The correlation between spirometric abnormalities and severe scoliosis in OI has been previously reported [11,12]. Widmann et al [12] did not find any correlation between kyphosis, chest wall deformities, assessed by radiographic measurements, and FVC. These findings are apparently in contrast with those of the present study, but it should be considered that we analyzed severe and
Table 2. Osteogenesis imperfecta (OI) patients’ pulmonary function test.

|                          | OI type III | OI type IV |
|--------------------------|------------|-----------|
| Spirometry (n)           | 5          | 9         |
| FVC (L)                  | 1.21 ± 0.7 | 2.31 ± 0.7|
| FVC (% pred)             | 115.7 ± 72.3 | 96.1 ± 26.7|
| FVC (% pred)             | 69.6 ± 31.5 | 86.3 ± 24.4|
| FEV1 (L)                 | 0.98 ± 0.5  | 2.04 ± 0.6 |
| FEV1 (% pred)            | 91.4 ± 50.8 | 98.1 ± 29.1|
| FEV1 (% pred)            | 59.4 ± 26.6 | 84.3 ± 24.2|
| FEV1/FVC                 | 81.4 ± 5.4  | 88.4 ± 3.8 |
| Lung Volume (n)          | 5          | 9         |
| TLC (L)                  | 2.2 ± 1.1  | 3.36 ± 1.2 |
| TLC (% pred)              | 109.3 ± 7.5 | 95.0 ± 26.2|
| TLC (% pred)             | 120.7 ± 27.3 | 87.3 ± 23.8|
| RV (L)                   | 0.72 ± 0.4  | 0.99 ± 0.6 |
| RV (% pred)              | 86.8 ± 14.2 | 82.0 ± 28.8|
| RV (% pred)              | 85.1 ± 10.8 | 79.4 ± 28.8|
| RV/TLC (%)               | 33.0 ± 9.7  | 28.4 ± 7.2 |
| FRC N2 (L)               | 0.85 ± 0.5  | 1.44 ± 0.6 |
| FRC N2 (% pred)          | 60.6 ± 37.9 | 74.8 ± 28.6|
| FRC N2 (% pred)          | 46.7 ± 21.9 | 59.3 ± 17.8|
| Nocturnal SpO2 (n)       | 7          | 15        |
| % time with SpO2<95%     | 17.7 ± 19.7 | 7.9 ± 13.5|
| Average SpO2 during all night | 91.9 ± 12.2 | 96.8 ± 2.4 |
| Nadir                    | 85.4 ± 8.1  | 87.7 ± 7.3 |

Data are expressed as mean ± standard deviation. FVC: forced vital capacity; TLC: total lung capacity; RV: residual volume; FRC N2: functional residual capacity measured by N2 washout; SpO2: arterial oxygen saturation measured by pulse oximetry; %pred: percentage of predicted value. *: p<0.05, **: p<0.01 vs Quanjer et al. doi:10.1371/journal.pone.0035965.t002

Table 3. Ventilatory pattern of osteogenesis imperfecta (OI) patients’ and controls in seated and supine positions.

|                          | OI type III | OI type IV | Control group |
|--------------------------|------------|------------|---------------|
| Supine position          |            |            |               |
| Minute ventilation (L min⁻¹) | 4.65 ± 1.70 | 5.31 ± 1.81 | 6.41 ± 2.83 ||
| Breathing frequency (min⁻¹) | 25.6 ± 15.6 | ** 22.2 ± 5.7 | * 17.5 ± 4.1 |
| Tidal volume (L)         | 0.24 ± 0.14 | * 0.25 ± 0.11 | * 0.38 ± 0.18 ||
| Seated position          |            |            |               |
| Minute ventilation (L min⁻¹) | 4.51 ± 1.68 | *** 5.40 ± 2.05 | *** 8.42 ± 3.29 |
| Breathing frequency (min⁻¹) | 25.5 ± 15.1 | * 22.4 ± 6.5 | 18.6 ± 5.0 |
| Tidal volume (L)         | 0.23 ± 0.14 | *** 0.25 ± 0.09 | *** 0.48 ± 0.21 |

Data are expressed as mean ± standard deviation. *: p<0.05, **: p<0.01, ***: p<0.001 (vs control). **: p<0.001 (vs seated). doi:10.1371/journal.pone.0035965.t003
moderate forms of OI as two separate groups and a new method was introduced to dynamically assess chest wall geometry and thoraco-abdominal volume variations without using invasive radiations.

Another original aspect of the present study is the evaluation of the ventilatory pattern. In general, patients with severe osteogenesis imperfecta breathe with rapid and shallow breathing in both positions. The reduced ability of the rib cage compartment to expand is probably the cause of the reduced tidal volume and the concomitant increased breathing frequency could represent the compensatory mechanism to try to guarantee normal minute ventilation. However, this mechanism is not fully effective in the seated position, as shown by significantly lower minute ventilation in OI patients.

The relatively low number of patients could represent a limitation of this work, even if these patients behave very homogeneously. Despite these limitations, we believe that the findings of the present study might have important implications for the functional evaluation and the treatment of OI patients in clinics.

As recently pointed out by Stanojevic et al [28], special attention should be paid on choosing the algorithm for the predicted spirometric values. This is particularly true in Osteogenesis Imperfecta characterized by disproportionately distributed growth. We found that in our patients the standard reference equations proposed by Quanjer et al [13] and largely used in clinics, provide expected values of FVC and FEV\textsubscript{1} higher than normal. Similarly, Takken et al [22] showed that the reduced patients' height determines higher FVC and FEV\textsubscript{1} values even in children with OI type I, the mildest form of the disease. These high values of FVC and FEV\textsubscript{1} are probably artifactual, at least in OI type III, because it is known that cardio-pulmonary insufficiency and respiratory infections represent the leading cause of death in OI. In contrast, the equations proposed by Kuster et al [14] provides values of FVC and FEV\textsubscript{1}, expressed as percentage of predicted values, significantly lower than controls.

In conclusion, in patients with severe OI a direct relationship exists between the structural modifications of the rib cage and the pattern of volume variations during breathing. Patients with OI type III are characterized by pectus carinatum and inspiratory paradoxical motion of the pulmonary rib cage during quiet spontaneous breathing in supine position, associated to a high level of asynchrony between the three chest wall compartments. On the other hand, pectus carinatum, paradoxical motion and significant asynchronies between chest wall compartments are not features of type IV patients. These findings suggest that functional assessment and treatment of OI should be differentiated in these two forms of the disease.

Acknowledgments

Special thanks to dr. Gioconda Pietro Paolo for her helpful review.

Author Contributions

Conceived and designed the experiments: AA ALM MGD SP AP ACT. Performed the statistical analysis: AA ALM. Performed clinical evaluation of the patients: MGD SP.

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