MUSCLE DYSFUNCTION AND EXERCISE LIMITATION IN ADOLESCENT IDIOPATHIC SCOLIOSIS.

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ABSTRACT (199 words)

Adolescent Idiopathic Scoliosis (AIS) can lead to ventilatory restriction, respiratory muscle weakness and exercise limitation. However, both the causes and the extent of muscle dysfunction remain unclear. **Aim:** To describe muscle weakness and how it relates to both lung function and tolerance to exercise in AIS patients. **Methods:** Lung and muscle function, together with exercise capacity, were assessed in 60 patients with pronounced spinal deformity (>40°) and in 25 healthy volunteers. **Results:** AIS patients presented only mild-to-moderate abnormal ventilatory patterns, the most frequent of which were restrictive abnormalities. Both the function of respiratory and limb muscles and exercise capacity were below normal limits in AIS patients, and indeed were significantly lower than in controls. Exercise capacity was found to correlate with the function of inspiratory, expiratory, upper limb and lower limb muscles, which, in addition, were reciprocally interrelated. The multivariate analysis showed that lower limb muscle function is the main contributor to exercise intolerance. There appeared to be no connection between spinal deformity and either lung function, muscle function or exercise capacity. We conclude that AIS patients show a generalized muscle dysfunction, which contributes to the reduction of their exercise capacity, even in the absence of severe ventilatory impairment.

**Key Words:** Spinal deformity, Lung function in disease, Skeletal Muscle dysfunction, Respiratory Muscle function

**Running Head:** Muscle dysfunction in Scoliosis
INTRODUCTION

Scoliosis, defined as a lateral curvature of the spine associated with vertebral rotation, results in chest deformity, back pain, ventilatory restriction, respiratory muscle weakness, exercise limitation and the subsequent impairment of health-related quality of life. The severity of the scoliosis is usually determined by the angle between the upper and lower limits of the deformity (Cobb’s method). Scoliosis is usually idiopathic but in some cases it can also be secondary to different neuromuscular, vertebral and connective tissue disorders. Depending on the age of the patient at the onset of the condition, idiopathic scoliosis can be classified as infantile (from birth to 3 years), juvenile (from 3 to 11 years) and adolescent (AIS) (11 years and older). The prevalence of scoliosis among adolescents is around 1-3%, and it frequently involves the thoracic spine. It is therefore no surprise to find that respiratory impairment is considered the most serious consequence of severe scoliosis, as patients frequently develop a progressive reduction in their lung volumes (restrictive ventilatory pattern), inspiratory muscle weakness, reduced exercise capacity, and can even suffer a sudden death episode. Classical therapy of AIS includes orthopaedic treatment, relative rest and/or rehabilitation and, in the most severe cases, surgery and/or ventilatory support. The causes of exercise limitation in this disorder have not been fully elucidated, but ventilatory restriction and subsequent cardiovascular deconditioning are the most commonly accepted. Another possible cause is limb muscle dysfunction, which has occasionally also been observed in some patients. However, there are relatively few studies which explore in depth the topography, severity and consequences of skeletal muscle dysfunction in AIS. The purpose of the present investigation is extensively to describe skeletal muscle function and its relationships with lung function, exercise capacity, body composition, and spinal deformity in young patients with pronounced thoracic AIS.
METHODS

PATIENTS AND STUDY DESIGN

This case-control study was conducted in accordance with the World Medical Association guidelines for research on humans\textsuperscript{17}. It was approved by our institutional Ethics Committee, and all patients and controls gave their written informed consent. The size of the sample was calculated on the basis of a previous pilot study\textsuperscript{18}, and the case group was made up of 60 consecutive patients with AIS recruited in the Departments of Orthopaedics at our two centres. All subjects showed pronounced spinal deformity, defined by a thoracic Cobbs’ angle of over $40^\circ$. Individuals with bronchial asthma, other pulmonary, cardiovascular or skeletal muscle problems, and anyone who had ever received spinal surgery, were excluded from the study. Twenty-five healthy volunteers of similar age and gender distribution to patients were used as controls. Both patients and volunteers were students with normal patterns of physical activity (as assessed by an standardized questionnaire), but who did not do any sport on a regular basis.

TECHNIQUES

Nutritional and Body composition

Body weight was assessed using a conventional weighing chair (SECA, Berlin, Germany). The body mass index (BMI, kg/m\textsuperscript{2}) was calculated as the body weight divided by the square of the height predicted by arm span, whereas body composition, including proportions of water, fat free mass, fat mass, and the fat free mass index (FFMI), was determined using bioelectrical impedance (Bodystat, Isle of Man, UK).

Spinal Deformity

Back deformity was assessed in anteroposterior and lateral spine radiographies by two independent observers. For the measurement of the Cobbs’ angle two lines were drawn parallel to the end plates of the vertebral bodies at the beginning and at the end of the curve
in the anteroposterior projection. Subsequently, a third and fourth line were drawn perpendicular to each of the first two lines, and defined the Cobb’s angle.

**Lung function**

All individuals performed forced spirometry (Datospir92, Sibel, Barcelona, Spain). In addition, static lung volumes, airway resistance, diffusing capacity for CO (Masterlab, Jaeger, Würzburg, Germany) and oxygen saturation (ARTEMAR MM205 Oximeter, Medical AB, Stockholm, Sweden) were determined in AIS patients using standard procedures. All lung function variables except oxygen saturation are expressed as a percentage of the predicted values for the local population. Arm span was again used for calculation of the predicted height. Ventilatory and gas exchange abnormalities were defined as follows: **obstructive ventilatory pattern**, ratio of forced expiratory volume in the first second to forced vital capacity (FEV1/FVC) < 70 %; **restrictive ventilatory pattern**, FVC and total lung capacity (TLC) < 80 % predicted and FEV1/FVC ≥ 70 %; **mixed ventilatory pattern**, similar abnormal percentages but without previous criteria for obstructive or restrictive abnormalities; and **gas exchange impairment**, oxygen saturation ≤ 98 % and/or single-breath CO transfer factor (DLco) < 80% predicted.

**Respiratory muscle function**

The **strength of respiratory muscles** was assessed in all individuals by measuring maximal inspiratory and expiratory pressures at the mouth (MIP and MEP, respectively). These pressures were generated during maximal efforts performed against an occluded airway. While MIP was obtained from residual volume (RV), MEP was determined from TLC. The mouthpiece used in the manoeuvres (SIBEL, Barcelona, Spain) had a small orifice to minimize the participation of face and mouth muscles, and was connected to a pressure transducer attached to a digital recorder (BIOPAC, BIOPAC Systems, Schooner, CA, USA). The highest value of three reproducible manoeuvres (<5% variability between
values) was used for the analysis, and reference values were those previously published for a Mediterranean population\textsuperscript{24}.

The \textit{endurance of inspiratory muscles} was assessed in all subjects using a threshold loading test as previously described\textsuperscript{25}. In short, individuals breathed against incremental threshold loads until exhaustion and the maximal pressure that they could maintain for at least 60 seconds was defined as the maximal sustainable pressure (P\textsubscript{Thmax}).

\textbf{Limb muscle function}

\textit{Handgrip strength} (HG) was measured in all subjects with a hydraulic dynamometer (JAMAR 5030J1, Chicago, IL, USA) attached to the digital recorder. All subjects were seated with their shoulder adducted and neutrally rotated, the elbow flexed at 90°, and the forearm and wrist in a neutral position. Each individual pressed the dynamometer, making at least three manoeuvres with each hand (dominant and non-dominant). The highest value of three valid and reproducible manoeuvres was used in the analysis. Reference values published by Mathiowetz et al. were used for subjects older than 18 years\textsuperscript{26}, whereas predictions for younger individuals were obtained from our own laboratory database (unpublished data).

In two thirds of the patients and all controls subjects the \textit{strength of the quadriceps muscle} was also assessed, using the technique described in a previous paper\textsuperscript{27}. In short, quadriceps isometric maximum voluntary contraction (QMVC) was obtained through a brief (3 sec.) effort, performed with one leg and then with the other, the patients being seated with both trunk and thigh fixed on a rigid support of an exercise platform (Domyos HGH 050; Decathlon, Lille, France). The dynamometer was connected to the recording system and the highest value from three reproducible manoeuvres was used for the analysis. Reference values were those published by Bohannon\textsuperscript{28}.

\textbf{Exercise capacity}
This was determined through a standardized incremental exercise test. In short, subjects pedalled in an electrically braked cycloergometer (Ergoselect 1000 L, Ergoline GmbH, Bitz, Germany), and were encouraged to continue until they could no longer sustain the target frequency (45 to 50 r.p.m.). Loads were increased by 25 watts every 2 minutes. Different ventilatory, cardiovascular metabolic and oxygenation variables were monitored throughout the test using a calibrated exercise system (Oxycom Alpha, Jaeger Würzburg, Germany), a standard electrocardiograph (Hewlett Packard 78352A, Bad Homburg, Germany), an automatic sphygmomanometer, and a finger probe connected to the aforementioned digital recorder. Normal values published by Jones et al. were used as the reference for physiological parameters \(^{29}\), except for the maximum heart rate, which was calculated from a standard equation published by Wasserman et al. \(^{30}\). Finally, dyspnea and leg discomfort were measured using Borg scales, from zero (none) to 10 (maximal) both at rest and at the end of the exercise test.

**Statistical Analysis**

Values are expressed as mean±SD. Since the distribution of different quantitative variables was normal (tested using the Kolmogoroff-Smirnoff test), comparisons between groups were made using the parametric t-tests, whereas the relationships between different variables in AIS patients were evaluated using the Pearson’s coefficient. Only hypothesis-driven correlations were tested. Subsequently, different variables were also analysed using a multiple-regression model. A p-value of \(\leq 0.05\) was considered as significant.
RESULTS

General and Nutritional Characteristics

The main general data for both groups are presented in Table 1. Patients showed lower body weight, BMI and FFMI than controls, and all of them showed pronounced spinal deformity.

Lung Function

Although mean values for most of lung function variables were within the normal range (see Table 2), they showed significant impairment when compared with those obtained in controls. In addition, as many as a half of the patients presented an abnormal ventilatory pattern (Table 3). Pure restrictive ventilatory abnormalities were very frequent, and only small percentages of patients showed either mixed or pure obstructive patterns. In all but one case, ventilatory abnormalities were only mild to moderate. Gas exchange at rest was abnormal only in a relatively low proportion of the AIS patients, who showed mild reductions in DLco and/or oxygen saturation. No significant correlations were found between the severity of the spinal deformity (as assessed by the thoracic Cobb’s angle) and different lung function variables.

Respiratory Muscle Function.

Most of the patients with AIS showed respiratory muscle dysfunction (83%), characterized by reduced MIP, MEP and/or Pth\textsubscript{max} (Table 2 and Figure 1A). In addition, all these variables were significantly lower in patients than in controls. Interestingly, a direct relationship was found between respiratory muscle strength (expressed by either MIP or MEP) and lung function impairment (as represented by FVC) (Figures 1B and 1C). However, we did not detect any significant correlations between respiratory muscle function and the severity of the spinal deformity.

Limb Muscle Function
The strength of limb muscles was reduced in more than a half of the patients (53% for the non-dominant handgrip and 61% for the non-dominant quadriceps muscle, respectively), the values being lower than those obtained in control subjects (Table 2). No differences were observed between data obtained in dominant and non-dominant sides for either the hands or the legs. Interestingly, the strength of both non-dominant and dominant handgrip and quadriceps muscles directly correlated with that of respiratory muscles (with MIP, r=0.338, p<0.05, and r=0.568, p<0.001; with MEP, r=0.278, p=0.05, and r=0.455, p<0.01, respectively). Moreover, the strength of both non-dominant handgrip and the quadriceps muscle were directly related to FFMI (r=0.667 and 0.598, respectively, p<0.01 both).

**Exercise Capacity.**

Data obtained in the exercise test are shown in Table 2. A vast majority of the patients (91%) presented a mild-to-severe reduction in exercise capacity, the limiting symptom being leg discomfort in all cases. Moreover, exercise capacity (represented by the maximum work rate, WRmax) correlated positively with the strength of both respiratory and peripheral muscles (Figure 2), but once again, no significant relationship was observed with either the severity of the spinal deformity or with lung function. The multivariate analysis using the percentage of predicted values did not add any further information, since only MEP reached a significant value for the prediction of exercise capacity. However, since prediction equations for peripheral muscle strength had not been validated to the same degree as those corresponding to either lung function, respiratory muscle force or exercise, we also performed this multivariate analysis using actual values. This approach clearly identified the function of peripheral muscles as the main factor contributing to exercise capacity (R²=0.623, p<0.001 for the overall analysis; p=0.02 for the lower limb strength and p=0.05 for handgrip; in this case, the strength of expiratory muscles did not
reach statistical significance, p=0.08). Moreover, the prediction of the WRmax turns out to be a function of the following equation:

\[
WRmax = 0.335 \times (MEP) + 1.435 \times (HG) + 1.244 \times (QMVC) - 0.175 \times (MIP) - 3.629
\]

where both HG and QMVC were those obtained in the non-dominant limbs.

**DISCUSSION.**

The present study demonstrates that young AIS patients with pronounced spinal deformity present generalized skeletal muscle weakness and exercise limitation, even in the absence of major ventilatory defects. Moreover, muscle function was the main predictor of exercise limitation and appeared not to be markedly influenced by the degree of the spinal deformity. These novel results reveal the central role played by muscle dysfunction in clinical manifestations of AIS and strongly suggest that this abnormality is probably the consequence of systemic rather than local factors.

**Lung Function.**

In keeping with most of the previous reports, ventilatory abnormalities were very common (52%) and respiratory restriction was the most frequent feature found in our patients. However, functional impairment was only mild-to-moderate in most cases, and did not correlate with the level of thoracic deformity. Most surprisingly, obstructive abnormalities were also present in a non-negligible number of individuals (14% if both pure obstructive and mixed ventilatory patterns are taken into account). This has also been occasionally reported in AIS, but is thought to be less prevalent and might be related to the possible influence of chest deformity and/or respiratory muscle dysfunction on the cross-sectional area of the airways.

Many studies had already looked into lung function in patients with scoliosis, exploring in particular the relationships between the chest deformity and ventilatory impairment. Some of these reports have concluded that the former is the main
cause of the latter\textsuperscript{8,9}. Other authors, by contrast, obtained similar results to those found in the present study and have been unable to establish a direct link between the severity of spinal deformity and lung function\textsuperscript{35-37}. These discrepancies can be explained by the heterogeneity of the populations included in the different studies, where idiopathic scoliosis was frequently mixed with secondary scoliosis, and clinical subtypes, severity of chest deformities and smoking histories were very diverse. To avoid any confusion that might arise from such factors, the present study included only patients with clinical AIS and severe thoracic deformity, with no relevant smoking history or associated respiratory diseases. Another potential technical limitation of many of the previous studies is the extensive use of the actual height of the patients, which can be significantly decreased in scoliosis, for calculations of predicted values. This could have contributed to the overestimation of patients’ functional data and the subsequent underestimation of their respiratory impairment. To avoid this limitation, arm-span was used in the present study to calculate the theoretical height of the patients\textsuperscript{38}. One plausible explanation for the fact that neither our own nor some of the previous studies have detected any relationship between thoracic deformity and lung function may be the contribution of respiratory muscle impairment to the values obtained in the lung function assessment. It is a well-attested fact that an impairment in respiratory muscle function can result in or contribute to different ventilatory abnormalities in respiratory and neuromuscular disorders. This is also suggested by the relationship observed in the present study between maximal respiratory pressures and FVC.

**Muscle Dysfunction**

The loss of muscle function was very frequent among our patients and affected all the different muscle groups explored in the present study: inspiratory, expiratory, upper limbs and lower limbs, as well as dominant and non-dominant extremities. Some previous studies have assessed muscle function in AIS patients. However, most of these reports confined
themselves to the determination of respiratory muscle strength, which was found to be impaired to variable degrees\textsuperscript{9,34}. To the best of our knowledge, only Kearon et al. explored different muscle territories, reporting that the strength of both respiratory and limb muscles was reduced in AIS patients\textsuperscript{16}. This was associated with a reduction in the calculated lean mass, suggesting a role for nutritional abnormalities and/or muscle deconditioning. Our work serves to confirm and extend these previous findings. This is the first study to explore body composition along with muscle function, as well as assessing respiratory muscle endurance in AIS patients. For one thing, it shows that, as suggested by indirect calculations performed by Keaton et al.\textsuperscript{16}, fat free mass is decreased in such individuals. Moreover, this reduction was proportional to that of limb muscle strength. This suggests that the former should have contributed to the latter in our patients. In addition, the current investigation demonstrates that respiratory muscle endurance is also impaired in AIS patients. Endurance is a very important functional property, which is probably even more relevant than maximal strength for daily life activities. It is less dependent than strength on muscle mass, and is more related to the aerobic capacity of the muscle. Unfortunately, the assessment of muscle endurance is relatively difficult\textsuperscript{27,39} and there is also a lack of reference values, both of which facts which might well explain the absence of previous reports.

The causes of muscle dysfunction in AIS remain unclear but our results suggest a relevant role for systemic mechanisms. Several different factors can influence muscle function. Some of them, such as the nutritional status, the level of physical activity or systemic inflammation, can be shared by different muscles, while others are specific for each muscle group. Inspiratory muscles, for instance, are probably subject to increased mechanical loads secondary to the spinal deformity and the ventilatory defects present in AIS patients. In addition, their length-force relationships can be altered as a consequence of chest deformity. Expiratory muscles for their part, might also be subject to increased
mechanical loads in AIS. However, the impact of geometrical distortion should be less important in this muscle group, the main representatives of which are in the abdominal wall. In this context of mechanical difficulties, it is not surprising that MIP and MEP were reduced in our AIS patients. However, the latter also presented peripheral muscle dysfunction, and it is unlikely that this could also be a direct result of changes occurring in the thorax. Impairment of the limb muscles function must be explained by other factors. Moreover, the fact that muscle function impairment was generalized and proportional across different muscle groups in our patients, along with a corresponding reduction in FFMI, reinforces the hypothesis that systemic factors also play a relevant role in muscle dysfunction associated with AIS. The loss of muscle mass is one well-known cause of muscle dysfunction, and it can partially explain the loss of limb strength in our patients. A second possibility, which can also contribute to the loss of muscle mass, is muscle deconditioning. This factor can act on muscle status both directly and indirectly, through a decrease in the anabolic stimuli that the action of a given muscle causes in the others. However, there are several arguments against a relevant role for muscle deconditioning in our patients. First of all, muscle impairment involved both dominant and non-dominant hands to a similar extent. The muscles of the dominant hand might be less affected by deconditioning than the contralateral ones, since self-care activities probably persist even in advanced sedentarism and the rate of strength decline with age is slower in the dominant than in the non-dominant upper limb. In addition, involuntary deconditioning proved to be very unlikely in our young patients, since their ventilatory defect was too mild to induce significant changes in their lifestyle. However, we cannot rule out a voluntary reduction in the level of their physical activity. In fact, this recommendation has been common for a long time in the management of AIS, and in any case, patients with marked scoliosis will almost certainly avoid those situations such as sport or outdoor activities where their deformities would be more evident. However, our patients reported a normal level of
ordinary activities and, in accordance with more recent evidence\textsuperscript{43,44}, the most extensive clinical practice in our area is to recommend exercise. Therefore, muscle deconditioning might have been present but our results suggest the presence of additional factors. These might include hormonal-related and inflammatory phenomena. On the one hand, female patients with AIS frequently show hypoestrogenic manifestations, which can include reduced bone density and decreased muscle mass\textsuperscript{45}. On the other hand, low nocturnal melatonin levels have occasionally been reported in some subgroups of patients with scoliosis, such as those with rapid progression\textsuperscript{46}. Melatonin might play a relevant role in the preservation of muscle mass under a variety of conditions by inhibiting cytokine release\textsuperscript{47}. Unfortunately, determination of estrogen and melatonin levels were not included in the present study. Finally, a very recent report suggests that oxidative stress and local inflammation are present in the peripheral muscles of adult patients with chest restriction\textsuperscript{48}, and this fact has been shown to contribute to muscle dysfunction in other entities such as COPD or sepsis\textsuperscript{49}.

**Exercise Capacity.**

Most of the patients included in the present study showed significant exercise limitation. Moreover, variables related to muscle function were the main predictors of exercise capacity in our patients. Although reductions in exercise capacity have been previously observed in AIS\textsuperscript{10,16}, our results are impressive. Most authors of previous studies believe that ventilatory and cardiac limitations are the main causes of impairment in exercise capacity among AIS patients\textsuperscript{10,16}. However, this hypothesis is not supported by our present data, where ventilatory reserve at peak exercise was relatively high (46%), no changes were observed in blood oxygenation, and all patients stopped exercising due to leg symptoms. Moreover, we found a significant relationship between exercise capacity and function in different muscle groups. In the same regard, Kearon et al. reported that exercise potential was not related either to the severity of the spinal deformity or to the ventilatory
defect, but rather to inspiratory muscle function. Although a cause-effect relationship cannot be established within the parameters of the present study, our results strongly suggest a relevant role for muscle dysfunction in exercise limitation shown by AIS patients. However, we cannot entirely rule out a role for cardiovascular or ventilatory factors in specific AIS subpopulations. Moreover, discrepancies with some of the previous studies are probably related with the different stages of the disease. At the relatively early phase of the AIS presented by our patients, muscle dysfunction appears to be predominant. However, as the disease progresses, lung function and cardiac impairment due to chest deformity will be more decisive in limiting the exercise capacity. A progressive restrictive ventilatory pattern will appear, ventilation-perfusion mismatching and subsequent hypoxemia/hypercapnia will develop, and even cor pulmonale will occur, all these factors contributing to exercise limitation.

**Muscle dysfunction and AIS aetiology.**

By definition, AIS is an entity of unknown aetiology. However, different authors have suggested that a dysfunction of muscle tone might occur in individuals with a genetic predisposition, who would develop an abnormally flexible spine during the relatively long growth phase. In other words, according to this theory, muscle dysfunction might be the cause and not the consequence of AIS. In addition, there is some evidence of the presence of abnormalities in the neural mechanisms involved in the control of posture in AIS patients. Moreover, structural studies of paraspinal muscles have shown changes in the proportion of different fiber types, myofilament disarrays (a sign of muscle damage) and shortened sarcomeres. In some cases, not only paraspinal but also respiratory and leg muscles were found to be structurally and/or functionally abnormal. In keeping with all these findings, our results can also be interpreted as the expression of a primary and systemic muscle disorder, which might have led to both spinal deformity and...
a generalized muscle dysfunction. However, more studies are needed to prove such a challenging hypothesis.

**Potential limitations of the study.**

One of the potential limitations of the present study is that only two thirds of the patients were assessed for leg muscle strength. Actually, the measurement of quadriceps force was incorporated when the pilot phase was concluded and upper limb muscle dysfunction was systematically detected. However, there are still a significant number of subjects with this functional evaluation, and data are very consistent with those obtained in the other muscle territories.

Another potential problem, as previously mentioned, is the possible unreliability of the predicted values for young individuals in many of the tests included in the study. To prevent this, we chose equations which were obtained in populations within the same or similar age groups as that of the patients. Moreover, we also included a control healthy population of similar age and gender distribution to the patients. This, in addition, provides us with a benchmark for tests in which no reference values are available.

**Conclusions.** Young AIS patients show a generalized muscle dysfunction, which might play an important role in their exercise limitation, and which occurs even in the absence of advanced ventilatory impairment. The causes of such a muscle function impairment still remain obscure but present data strongly suggest that they are related to systemic factors. Our results add novel information to the traditional conception of AIS as a spinal disorder which only affects the physical performance of patients when a severe ventilatory defect is present. Further understanding of the causes and systemic consequences of AIS will enable clinicians to recommend more effective therapies.
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TABLE 1: General and Nutritional characteristics

<table>
<thead>
<tr>
<th>GENERAL CHARACTERISTICS</th>
<th>AIS PATIENTS</th>
<th>CONTROLS</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N, (female/male)</td>
<td>60 (50/10)</td>
<td>25 (20/5)</td>
<td>ns</td>
</tr>
<tr>
<td>Age, years</td>
<td>20 ± 3</td>
<td>21 ± 2</td>
<td>ns</td>
</tr>
<tr>
<td>Smoking, % (pack/year)</td>
<td>12% (0.5±0.3)</td>
<td>13% (0.5±0.2)</td>
<td>ns</td>
</tr>
<tr>
<td>Thoracic Cobb’s angle, °</td>
<td>56±17</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Lumbar Cobb’s angle, °</td>
<td>35±16</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Vertebrae involved, n</td>
<td>7 ± 1</td>
<td>--</td>
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</tbody>
</table>

| ANTHROPOMETRIC CHARACTERISTICS | | | |
|--------------------------------|-----------------|---------|
| BMI, kg/m²                      | 19.9 ± 3.2      | 22.4 ± 2.9 | *** |
| Weight, kg                      | 56 ± 10         | 62 ± 8   | **  |
| Calculated Height, cm (from the arm span) | 167 ± 9 | 167 ± 8 | ns |
| FFMI, kg/m²                     | 14.1±1.1        | 15.4±1.6 | **  |

**Abbreviations:** BMI, body mass index; FFMI, fat free mass index; ns, not significant; *, p< 0.05; **, p< 0.01; ***, p< 0.001
### TABLE 2: Lung function, Muscle function and Exercise

<table>
<thead>
<tr>
<th></th>
<th>AIS PATIENTS</th>
<th>CONTROLS</th>
<th>p</th>
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<tbody>
<tr>
<td><strong>LUNG FUNCTION</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% FEV₁/FVC</td>
<td>80 ± 6</td>
<td>84 ± 5</td>
<td>*</td>
</tr>
<tr>
<td>FEV₁, % pred.</td>
<td>83 ± 16</td>
<td>105 ± 11</td>
<td>***</td>
</tr>
<tr>
<td>FVC, % pred.</td>
<td>86 ± 14</td>
<td>105 ± 12</td>
<td>***</td>
</tr>
<tr>
<td>FRC, % pred.</td>
<td>86 ± 11</td>
<td>---</td>
<td>-</td>
</tr>
<tr>
<td>TLC, % pred.</td>
<td>89 ± 17</td>
<td>---</td>
<td>-</td>
</tr>
<tr>
<td>% RV/TLC</td>
<td>30 ± 9</td>
<td>---</td>
<td>-</td>
</tr>
<tr>
<td>DLco, % pred.</td>
<td>91 ± 11</td>
<td>---</td>
<td>-</td>
</tr>
<tr>
<td>SpO₂, % [FiO₂, 0.21]</td>
<td>99 ± 0.4</td>
<td>99.6 ± 0.3</td>
<td>ns</td>
</tr>
<tr>
<td><strong>MUSCLE FUNCTION</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MIP, cm H₂O (% pred)</td>
<td>85±26 (71±19)</td>
<td>112±16 (95±15)</td>
<td>*** (***)</td>
</tr>
<tr>
<td>MEP, cm H₂O (% pred)</td>
<td>105±36 (69±19)</td>
<td>143±39 (91±18)</td>
<td>*** (***)</td>
</tr>
<tr>
<td>Pthmax, cmH₂O</td>
<td>59 ± 20</td>
<td>97 ± 22</td>
<td>***</td>
</tr>
<tr>
<td>HG, dominant, kg (% pred)</td>
<td>27 ± 7 (78±14)</td>
<td>32 ± 7 (91±13)</td>
<td>*** (***)</td>
</tr>
<tr>
<td>HG, non-dominant, kg (% pred)</td>
<td>25 ± 7 (79±17)</td>
<td>30 ± 8 (95±14)</td>
<td>*** (***)</td>
</tr>
<tr>
<td>QMVC, dominant, kg (% pred)</td>
<td>38±11 (71±22)</td>
<td>46 ± 24 (95±28)</td>
<td>** (***)</td>
</tr>
<tr>
<td>QMVC, non-dominant, kg (% pred)</td>
<td>36±12 (73±20)</td>
<td>44 ± 21 (94±24)</td>
<td>** (***)</td>
</tr>
<tr>
<td><strong>EXERCISE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WRₘₐₓ, % pred</td>
<td>58 ± 15</td>
<td>97 ± 9</td>
<td>***</td>
</tr>
<tr>
<td>VO₂ₘₐₓ, % pred</td>
<td>60 ± 16</td>
<td>94 ± 11</td>
<td>***</td>
</tr>
<tr>
<td>VEmax, % pred</td>
<td>54 ± 19</td>
<td>67 ± 8</td>
<td>ns</td>
</tr>
<tr>
<td>RR, min⁻¹ (Δ % from baseline)</td>
<td>43 ± 8 (+126)</td>
<td>34 ± 7 (+88)</td>
<td>**</td>
</tr>
<tr>
<td>HRmax, % pred</td>
<td>79 ± 9</td>
<td>97 ± 8</td>
<td>***</td>
</tr>
<tr>
<td>SpO₂ at peak exercise, % (Δ % from baseline)</td>
<td>98.3±0.9 (-0.5)</td>
<td>99.2±0.7</td>
<td>ns</td>
</tr>
</tbody>
</table>

**Abbreviations:** FRC, functional residual capacity; SpO₂, oxygen saturation; FiO₂, inspiratory fraction of oxygen; MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure; Pthmax, maximal sustainable inspiratory pressure; HG, handgrip; QMVC, quadriceps maximum isometric voluntary contraction; WRₘₐₓ, maximum work rate; VO₂ₘₐₓ, maximum oxygen uptake; VEmax, maximum minute ventilation; RR, respiratory rate; HRmax, maximum heart rate.  
* p< 0.05; ** p< 0.01; *** p< 0.001
TABLE 3. Ventilatory and gas exchange impairment observed in the group of AIS patients

<table>
<thead>
<tr>
<th>Condition</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal ventilatory pattern, n (%)</td>
<td>29</td>
<td>(48)</td>
</tr>
<tr>
<td>Restrictive pattern, n (%)</td>
<td>23</td>
<td>(38)</td>
</tr>
<tr>
<td>Obstructive pattern, n (%)</td>
<td>4</td>
<td>(7 )</td>
</tr>
<tr>
<td>Mixed pattern, n (%)</td>
<td>4</td>
<td>(7 )</td>
</tr>
<tr>
<td>Abnormal gas exchange, n (%)</td>
<td>9</td>
<td>(15)</td>
</tr>
</tbody>
</table>
FIGURE LEGENDS

FIGURE 1: (A) relationships between inspiratory and expiratory muscle pressures. Shaded areas indicate the impairment in just one of them, whereas the darkest area refers to the patients with both inspiratory and expiratory muscle dysfunction. (B) and (C) Relationships between lung function (represented by FVC) and the strength of either inspiratory or expiratory muscles (MIP and MEP, respectively).
Figure 1A, Martinez-Llorens et al.

Figure 1B, Martinez-Llorens et al.
FIGURE 2: Relationships between exercise capacity (represented by WRmax) and the strength of either (A) inspiratory (exemplified by maximal inspiratory pressure, MIP), (B) expiratory (as expressed by maximal expiratory pressure, MEP) and (C) limb muscles (represented here by quadriceps isometric force, QMVC).
Figure 2A. Martínez Llorens et al.

Figure 2B. Martínez Llorens et al.
Figura 2C. Martinez Llorente et al.