

## Assessment of functional capacity and pulmonary in pediatric patients renal transplantation

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### ABSTRACT

**Introduction:** Pediatric patients undergoing kidney transplantation can present changes in pulmonary function and functional capacity for exercise. **Objective:** To evaluate the functional capacity and pulmonary function in children and adolescents undergoing kidney transplantation. **Method:** Children and adolescents aged six to 18 years of age were evaluated in Outpatient Clinic of Nephrology, Hospital da Criança Santo Antônio, Santa Casa de Porto Alegre, RS, Brazil in period the june of 2010 the march of 2011. Pulmonary capacity was assessed by spirometry and maximal respiratory pressures and functional capacity through 6-minute walk test (6MWT). **Results:** The sample comprised 25 patients, 14 (56%) males with a mean age of  $13.5 \pm 3.3$  years. From, 19 (76%) underwent dialysis before transplantation. Mean forced vital capacity (FVC) was  $97.91 \pm 24.32\%$  and forced expiratory volume in one second (FEV1)  $100.53 \pm 17.66\%$  from predicted value. In the 6MWT, the patients walked 229.14 meters less than predicted ( $p < 0.001$ ). The maximum inspiratory pressure (MIP) was significantly lower than predicted, and the difference in  $\text{cmH}_2\text{O}$   $-24.63$  ( $p = 0.03$ ), as the maximum expiratory pressure (MEP), with a difference of  $49.27 \text{ cmH}_2\text{O}$  ( $p < 0.001$ ). By correlating, functional capacity, spirometry and maximal respiratory pressures, find an association between FVC and 6MWT ( $r = 0.52$ ,  $p = 0.01$ ) and FVC and MIP ( $r = 0.54$ ,  $p = 0.01$ ). **Conclusion:** Reduced functional capacity and maximum respiratory pressures were diagnosed in a small cohort of pediatric patients after kidney transplantation. Better the functional capacity and Pimax better the FVC.

**Keywords:** adult children, exercise, kidney transplantation, spirometry.

### INTRODUCTION

At present, an estimated 1.4 million individuals worldwide are undergoing renal replacement therapy, which annually grows by approximately 8%. Successful therapy is associated with a significant improvement in the survival rate and quality of life, in addition to cost reduction compared with dialysis.<sup>1</sup> The annual estimated cost associated with hemodialysis in Brazil is approximately R\$ 14.000.000,00.<sup>2</sup>

Renal transplantation is considered to be the most effective therapy for the treatment of chronic renal insufficiency (CRI), and can potentially improve or normalize renal function. Moreover, it is the treatment of choice for nearly all etiologies, particularly in patients with terminal or preterminal uremia.<sup>3,4</sup>

Because renal transplant is indicated in cases of CRI, the complications with which these patients present prior to replacement therapy, such as fluid overload, respiratory infections, acidosis, pulmonary fibrosis and calcifications, and alterations in the ventilation/perfusion rate, should be considered. Subsequently, such changes may lead to the development of other pulmonary disorders, such as edema or pleural effusion. Among the more common pulmonary alterations are limitations to airflow in the distal airways, obstructive disorders, and reduced pulmonary diffusion capacity.<sup>5-8</sup>

According to Paul *et al.*, in a study of pediatric CRI patients, mean values of vital capacity (VC) and forced expiratory volume in the first second ( $FEV_1$ ) were found to be lower than those in the healthy population.<sup>9</sup>

In a study by Kalender *et al.*,<sup>10</sup> it was observed that adult patients also show a decrease in maximal inspiratory pressure values (MIP) and maximal expiratory pressure (MEP); uremic myopathy was suggested as the possible cause of this decrease in diaphragmatic and skeletal muscular strength.<sup>10</sup> In addition to these changes, CRI patients show a reduction in physical ability, which declines with the start of renal replacement therapy, thus affecting performance in daily life activities and occupational tasks and leading to a worsening of health-related quality of life.<sup>11,12</sup>

However, despite the pulmonary consequences associated with CRI and dialytic treatment, information on the physiological effects and possible chronic pulmonary alterations in patients under renal replacement therapy remains scarce.<sup>13</sup> In addition, the consequences to respiratory function after renal transplant are also unclear, particularly in the pediatric population. Therefore, in this study, we aimed to assess functional capacity and pulmonary function in children and adolescents who received renal transplants and to investigate possible associations between pulmonary function and functional capacity.

## METHODS

The present cross-sectional study evaluated the functional capacity and pulmonary capacity of children and adolescents who received renal transplants; it was performed at the outpatient nephrology unit of the Santo Antônio Children's Hospital - Irmandade Santa Casa de Misericórdia de Porto Alegre (ISCMPA), RS, between June 2010 and March 2011.

This study was approved by the Ethics and Research Committee of the ISCMPA, as well as of the Methodist University Center of the IPA. Parents or guardians of the participants agreed to their participation and signed the Free and Informed Consent Form.

In this study, we evaluated patients aged between 6 and 18 years who had undergone renal transplantation. We excluded individuals who presented with

hemoptysis, retinal detachment, hypertensive crisis, tracheotomy, hydrocephalus, myelomeningocele, abdominal hernia, pneumothorax, pulmonary or pleurocutaneous fistula, or recent surgery or trauma of the upper respiratory tract, abdomen, or chest.

The clinical, demographic, and anthropometric data were collected using a research form, standardized by the authors, which contained clinical variables such as time since transplant and cause of CRI; anthropometric variables such as weight, height, and body mass index (BMI); and results of laboratory tests, including creatinine and urea tests. In addition, pulmonary function, maximal respiratory pressure value, and functional capacity were assessed, as described below.

### PULMONARY FUNCTION

For assessment of pulmonary function, a Spirodoc® spirometer (Medical International Research) was used to measure the following variables: forced expiratory volume in the first second ( $FEV_1$ ), forced vital capacity (FVC), forced expiratory flow ( $FEF_{25-75\%}$ ), and peak expiratory flow (PEF). The number of attempts took into consideration 3 acceptable and 2 reproducible curves. However, if the reproducibility criteria were not met, new procedures had to be conducted and were repeated as often as necessary. The values were recorded as absolute and percent predicted, according to the reference values previously established in the literature for age and gender.<sup>14</sup>

### MAXIMAL RESPIRATORY PRESSURE

Vacuum manometry was used for assessment of the maximal respiratory pressure, using a digital vacuum manometer, the MVD 300 model (Microhard System, Globalmed - Brazil), and the absolute values were measured in  $cmH_2O$ . In agreement with the guidelines, up to 5 procedures were repeated for performance of the test, with at least 3 acceptable measurements. Wilson's equation was used for analysis of normality of maximal respiratory pressure values.<sup>15</sup>

### FUNCTIONAL CAPACITY

Functional capacity was assessed through the 6-minute walk test (6MWT). It was performed according to the rules of the American Thoracic Society, as adapted by Geiger *et al.*<sup>16</sup> The expected distance for

each patient was calculated by the specific formulas for sex, age, and height.<sup>16</sup>

### STATISTICAL ANALYSIS

The data were stored in a database using the Excel 2007 program. Continuous variables are described as mean and standard deviation (symmetrical distribution) or median and interquartile range (asymmetrical distribution). Qualitative variables are described as absolute and relative frequencies. Associations were determined using Pearson's correlation test (symmetrical distribution) or Spearman's correlation coefficient (asymmetrical distribution).

For comparison of the spirometric variables, maximal respiratory pressure values, and 6MWT results, the *t*-test was used.

The statistical analysis was performed using the SPSS (Statistical Package for Social Sciences) statistical program, version 18.0. The adopted significance level was 5% ( $p < 0.05$ ).

### RESULTS

The study sample consisted of 25 patients, with a mean age of  $13.5 \pm 3.3$  years; 14 (56%) patients were male. The patient characteristics are described in Table 1.

TABLE 1 SAMPLE CHARACTERIZATION	
Sample variables (n = 25)	
Age (years)*	13.5 ± 3.3
Male n (%)	14 (56.0)
Weight (kg)*	43.15 ± 11.90
Height (cm)*	148.90 ± 13.60
BMI (kg/cm <sup>2</sup> )*	19.30 ± 3.80
Creatinine (mg/dL)**	1.2 (0.90-1.45)
Urea (mg/dL)*	49.28 ± 30.42
CRITime	
Up to 1 year, n (%)	4 (20)
1 to 5 years, n (%)	11 (44)
5 to 10 years, n (%)	7 (28)
More than 10 years, n (%)	2 (8)
Time since transplant	
Up to 1 year, n (%)	7 (28)
1 to 5 years, n (%)	12 (48)
5 to 10 years, n (%)	4 (16)
More than 10 years, n (%)	2 (8)

\* Mean and standard deviation; \*\* Median (minimum and maximum); BMI: Body mass index.

With regard to the underlying illness, 12 patients (48%) had CRI due to renal diseases (glomerulopathy, dysplasia, nephrotic syndrome, and reflux nephropathy), 5 (20%) had CRI due to systemic diseases (lupus, nephropathic cystinosis, and uremic hemolytic syndrome), 4 (16%) had CRI due to urinary or renal infections, and 4 (16%) had CRI due to unidentified renal disease. Nineteen (76%) had received dialysis prior to the transplantation.

Spirometry was performed on 21 patients. Four patients did not undergo the examination because of technical problems with the equipment. The mean predicted values were  $97.91\% \pm 24.32\%$  for FVC,  $100.53\% \pm 17.66\%$  for FEV<sub>1</sub>,  $73.95\% \pm 21.56\%$  for PEF, and  $101.57\% \pm 21.56\%$  for FEF<sub>25-75%</sub>.

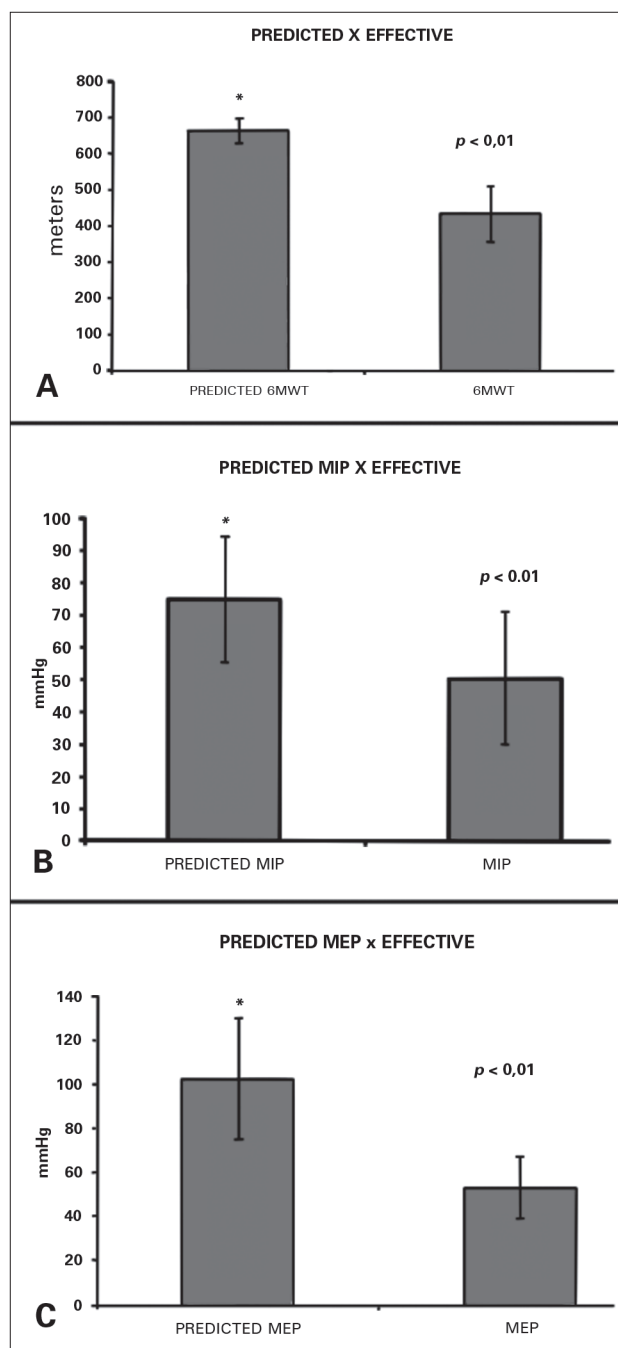
When we compare the distance walked in the 6MWT with the predicted values for age and height, the subjects walked an average of 229.14 meters less than the predicted value ( $p < 0.001$ ), reaching only 65% of the predicted values. The MIP was significantly lower than the expected value, with a difference of  $-24.63$  cmH<sub>2</sub>O ( $p = 0.03$ ); the MEP was also significantly lower than the expected value, with a difference of  $49.27$  cmH<sub>2</sub>O ( $p < 0.001$ ). The data are shown in Figure 1. The correlations between functional capacity and pulmonary function are shown in Table 2.

### DISCUSSION

It is known that chronic renal disease in stages 4 and 5 may present various musculoskeletal complications, and may also have an impact on pulmonary capacity; this fact may remain evident even after the patient has undergone renal replacement therapy.

Most patients in our study (48%) developed CRI due to renal diseases, followed by systemic diseases (20%). In a study by Malekahmadi *et al.*<sup>17</sup> that evaluated 55 teenagers between the ages of 11 and 18 years, the most common cause of CRI was glomerulonephritis (27.5%), followed by congenital disease (18.2%). In addition, 69.1% had a history of dialysis before the transplant; in our study, this prevalence was 76%. Data from the Latin American Pediatric Nephrology Society (ALANEPE) is the first kidney transplant record of countries in Latin America. Twenty countries were invited to take part in the study; the study sites were in Brazil (9), Argentina (4), Chile (4), Venezuela (3), Mexico (2), and 1

**Figure 1.** Comparison between predicted and measured values of the 6MWT and respiratory muscle strength. A: Predicted distance compared to effective distance. B: Inspiratory vs. performed muscle strength. C: Expiratory vs. performed muscle strength.



6MWT, 6-minute walk test; MEP: Maximal expiratory pressure; MIP: Maximal inspiratory pressure.

each in Cuba, Colombia, Costa Rica, Nicaragua, Guatemala, Ecuador, Honduras, Paraguay, and Peru, respectively. The record included 1458 patients, with a mean number of patients of 291 per year; 55% of recipients were male. The etiologies of disease included reflux uropathy/nephropathy

**TABLE 2** CORRELATIONS BETWEEN FUNCTIONAL CAPACITY AND PULMONARY FUNCTION

Variables	$p^*$	r
FVC x 6MWT	0.01	0.52
FVC x MIP	0.01	0.54
FVC x PEF	0.02	0.63
FVC x FEF <sub>25-75%</sub>	0.02	0.63

$p$ : Significance level; r: Correlation coefficient; FVC: Forced vital capacity; PEF: Peak respiratory flow; FEF<sub>25-75%</sub>: Forced expiratory flow between 25% and 75%.

(27%), glomerulopathies (24%), hypoplasia/dysplasia (11%), vascular (6%), congenital/hereditary (5%), and unknown (19%).<sup>18</sup>

As a result of CRI, which is characterized by the progressive and irreversible destruction of renal structures, the respiratory system undergoes alterations in respiratory drive, pulmonary mechanics, muscular function, and exchange of gases.<sup>19</sup>

In the present study, we observed a significant reduction of maximal respiratory pressure in patients after renal transplantation, to below what was expected in terms of age and height; in a study by Cury *et al.*, it was established that the use of immunosuppressant corticotherapy after renal transplantation may affect regeneration of muscular fibers, because oxidative metabolism and protein synthesis are compromised, thus contributing to the alteration in respiratory muscle strength found in these patients.<sup>20</sup>

A similar finding was observed in other studies, although with a sample consisting of adult patients with CRI.<sup>21,22</sup> In a study by Jatobá *et al.*, in which vacuum manometry was performed on patients aged 18 to 69 years with CRI, a decrease of 38.2% in MIP and 29% in MEP was observed.<sup>21</sup> We found no studies reporting the assessment of respiratory muscular strength in the pediatric population after renal transplantation, which demonstrates the importance of the need for studies in this population. This may help potentially contribute to the clarification of the mechanisms that result in pulmonary and muscular capacity alternations in these individuals even after renal replacement therapy.

Respiratory muscle weakness is a complication of CRI, as clearly reported in the literature. However, the cause of this weakness is uncertain. Some reports suggest that it is due to type II muscle fiber hypotrophy and to alterations in myofibrillary ATPase that may cause a deficit in energy utilization.<sup>19</sup>

Patients with CRI have muscle problems due to the development of several interrelated factors. These include a decrease in protein-calorie intake, muscular atrophy by lack of use, and muscular imbalance of proteins mainly affecting type II muscle fibers, reduction in vascular and capillary beds, presence of intravascular calcification, and decrease in local blood flow.<sup>23</sup> These factors may contribute to a reduction in functional capacity, which also has multiple causes including problems with the cardiorespiratory system and muscles, causing impairments in the capacity to capture, transport, and use oxygen. Studies have shown that the patient who undergoes renal transplantation usually has nutritional imbalances such as malnutrition or obesity. Moreover, metabolic and nutritional changes may arise due to surgical stress, immunosuppressant therapy, and adaptation of the body to the new organ; moreover, they can worsen existing problems or generate new abnormalities, such as protein-calorie malnutrition and obesity.<sup>24-27</sup>

In this study, it was observed that the functional capacity values assessed through the submaximal test (6MWT) were lower than the predicted values, and this reduction may have been influenced by the maximal respiratory pressure values that were also below normal levels.<sup>28</sup>

A study by Oh-Park *et al.* assessed functional capacity and reported that patients who underwent transplantation walked shorter distances than what was considered normal. This result is similar to the one found in our study, in which we were able to confirm that there was a reduction of > 200 m in the distance walked compared to the predicted value.<sup>24</sup>

In accordance with the findings in our study, Takken *et al.* observed that children with end-stage renal disease exhibited a significantly worse performance in the 6MWT compared to the reference values and that their performance was significantly associated with hematocrit and height. In our study, we did not make this association; however, we obtained a positive correlation with FVC.<sup>29</sup> The 6-minute walk test has also been performed by healthy children to generate reference values,<sup>30</sup> as well as by pediatric patients with end-stage renal disease.<sup>31</sup>

On the other hand, we did not find a significant reduction in measures of pulmonary function

in the patients under evaluation, although the mean values of FVC and PEF were lower than normal. This finding is similar to that of Kalender *et al.*,<sup>10</sup> in which the spirometric parameters and diffusion capacities were found to be normal in the transplanted group. Karacan *et al.*<sup>28</sup> also reported that transplantation improves the reduced functional residual capacity that is induced by complications of renal disease such as anemia, hyperparathyroidism, hypoalbuminemia, and electrolyte imbalances, although patients still exhibit decreased muscular strength.<sup>32</sup>

Some alterations found in CRI patients on dialysis are also observed in patients who have undergone transplantation, even after renal function has been restored. These changes may be partly attributed to immunosuppressant therapy, which generally involves corticosteroid use. This treatment is associated with reduction in protein synthesis and increased protein catabolism, which may cause difficulty for the complete restoration of kidney function in patients who have undergone transplantation. Data on the mean corticosteroid dose used by the patients in the study is not available, but it is known that these patients received this therapy and it could explain the decreased values of pulmonary function and functional capacity found in our study. However, the most influential factor affecting these patients is still unknown.<sup>32-34</sup>

A positive correlation was found between FVC and MIP and between FVC and functional capacity in the evaluated patients. This suggests that the higher the FVC value, the better the performance of an individual in the 6MWT, suggesting that FVC may have a direct influence on this test. In a study by Silva *et al.*, it was observed that individuals with CRI on hemodialysis and who took part in an inspiratory muscle training exercise walked longer distances in the 6MWT. This demonstrates that this population might benefit from muscle training programs, which could improve the quality of life of these individuals after renal replacement therapy.<sup>35</sup> The small sample size of this study is a limitation that may have influenced the results. Moreover, the scarcity of studies on posttransplant patients, especially in the pediatric population, for comparison of the clinical findings may be considered a limitation.



## CONCLUSION

In this study, we have concluded that respiratory muscle strength and functional capacity of children and adolescents who have undergone renal transplantation show significantly lower values than those of the pediatric population in general. Positive associations were also found between functional capacity and MIP and FVC.

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