ORIGINAL ARTICLE

Follow up of aerobic capacity in children affected by severe acute respiratory syndrome

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ABSTRACT

Background and objective: **The aim of this study was to investigate the aerobic capacity of children 3 years after they were diagnosed with severe acute respiratory syndrome (SARS).**
Methods: **Twenty-seven patients who completed both pulmonary function and maximal aerobic capacity tests at 6 and 15 months after the acute illness were invited to return for reassessment.**
Results: **Twenty-one patients (median age 18.2 years, interquartile range (IQR) 16.5–19.7) completed all investigations at 36 months. Pulmonary function was normal in all patients. Maximal aerobic capacity, peak oxygen pulse (peak VO_2) and ventilatory anaerobic threshold showed significant improvements compared with values measured at 6 months in both boys and girls. In girls, ventilatory efficiency (ventilatory equivalents for oxygen and carbon dioxide) and perfusion of the lungs (end-tidal partial carbon dioxide pressure) had not increased further compared with the values measured at 15 months. Although peak VO_2 improved further at 36 months in patients with or without persistent radiological abnormalities, the values were 68% (IQR 50–84) and 74% (IQR 60–99), respectively, of those for normal control subjects.**
Conclusions: **There were improvements in aerobic capacity at 36 months in children affected by SARS; however, the measured values remained suboptimal.**

Key words: aerobic capacity, children, pulmonary function, severe acute respiratory syndrome.

SUMMARY AT A GLANCE

This long-term follow-up study demonstrated that the aerobic capacity of children improved three years after the diagnosis of severe acute respiratory syndrome, but the values remained suboptimal.

INTRODUCTION

Severe acute respiratory syndrome (SARS) is a contagious respiratory infection caused by the SARS coronavirus.[1–3] The spectrum of disease and its progression are very different in children compared with adults. No fatalities have been reported among children, and the clinical course and radiological changes were much milder.[4–6] All subjects from a cohort of 47 paediatric SARS patients showed complete clinical recovery 6 months after diagnosis, and lung function was normal in >90% of these patients.[7]

A reduction in aerobic exercise capacity 3 months after hospital discharge has been reported in some adult SARS survivors.[8] There was persistent impairment in adults at 6 and 12 months after onset of the illness.[9,10] We previously reported that aerobic capacity was impaired at 6 and 15 months after the diagnosis of SARS in a cohort of 47 children.[11] The mechanism of reduced aerobic capacity in children affected by SARS is not fully understood, but it is probably a consequence of impaired perfusion of the lungs during peak exercise as well as deconditioning. In the present study, aerobic capacity and pulmonary function were examined in the same group of children at 36 months, and comparisons were made with the values measured 6 and 15 months after the acute illness.

METHODS

Subjects

This was a prospective, follow-up study of children who had recovered from SARS and who participated in our previous assessments.[11] There was serological confirmation of SARS coronavirus infection for all these children, they were <18 years of age at the time of diagnosis, and had no symptoms of upper respiratory tract infection in the 2 weeks preceding the assessment of aerobic capacity. The study was approved by the ethics review board of the Chinese University of Hong Kong. Written consent was obtained from the patients and their parents.

Assessment of patients

All patients were interviewed and examined by a paediatrician. Their body mass was measured using electronic scales (Seca Delta Model 707, SECA, Hamburg, Germany), and height was measured using a Harpenden stadiometer (Holtain Ltd, Crosswell, UK). Six months after the diagnosis of SARS, all patients underwent pulmonary function tests and high-resolution computed tomography (HRCT), and performed a maximal treadmill exercise test. All patients who had successfully completed the maximal exercise test at 6 months were invited to repeat the maximal treadmill exercise and pulmonary function tests at 15 and 36 months.

The methodological details for pulmonary function tests and HRCT have been described in our previous publication.[7] The pulmonary function tests results were expressed as percentages of predicted normal values using local reference values.[12] All HRCT images were reviewed by a paediatric radiologist who assessed the images for the presence and distribution of residual radiological abnormalities. The radiologist was blinded to the clinical information and pulmonary function status of the patients.

Maximal treadmill exercise test

Aerobic capacity was assessed by a maximal treadmill exercise test using the Bruce protocol.[13] Details of the testing procedure have been reported previously.[11] Peak oxygen consumption (peak VO_2) was also calculated as a percentage of predicted values for age and gender for comparisons.[14] Ventilatory anaerobic threshold was used as an indicator of the submaximal response.[15] Functional lung capacity was also determined as breathing reserve during peak exercise.[16]

Statistical analysis

Continuous and categorical data are presented as medians (interquartile range (IQR)) and number (percentage). Spearman's ρ correlation coefficients were calculated to test for associations between resting lung function and aerobic capacity parameters, and to assess the associations among age, body weight, height and changes in exercise response at 6 months compared with 36 months after the diagnosis of SARS. Friedman tests were used to compare the differences in physical characteristics, resting lung function and exercise responses at 6, 15 and 36 months after the diagnosis of SARS. Wilcoxon signed rank tests were used to test the significance of differences in values measured at any two of the three visits, with an adjusted significance level of $P < 0.016$. Mann–Whitney U-tests were used to test the significance of differences at each visit between subjects with or without radiological abnormalities of the thorax, as detected at 6 months, and to compare the clinical characteristics at 6 months between subjects who returned for all visits and those who did not return at 15 months and/or at 36 months. The chi-square test was used to compare categorical or dichotomous data. All statistical analyses were performed using SPSS for Windows release 13.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Forty-seven subjects (45% females) were recruited and participated in the initial assessment at 6 months. Eight of these subjects were too young to perform a peak VO_2 running test at the initial assessment, and five did not satisfy the criteria for a maximal effort. As a result, complete data were available for 34 patients, of whom 27 returned for repeat examinations at 15 months after the onset of the illness. At 36 months, six subjects declined reassessment; the main reasons being work commitments or time clashes with school activities. Subjects who declined reassessments at 15 and/or 36 months ($n = 13$) were similar in age, body weight, height, body mass index and resting pulmonary function but had significantly lower absolute peak VO_2 (1205 (IQR 938–1474) vs 1563 (IQR 1182–2241) mL/min, $P = 0.024$) and mass-related peak VO_2 (22.9 (IQR 19.0–26.2) vs 29.8 (IQR 22.4–37.3) mL/kg/min, $P = 0.032$) at 6 months, as compared with subjects who returned for all reassessments ($n = 21$) ($P < 0.05$). For the remaining 21 subjects (43% females), complete exercise data were available at the 36-month assessment. The median age of these 21 subjects was 18.2 years (IQR 16.5–19.7) (range 10.8–21.2), with a corresponding median height of 167 cm (IQR 154–171) and median weight of 60 kg (IQR 47.5–71.6).

All 21 subjects satisfied the criteria for maximal effort.[17,18] Muscle soreness, exhaustion and shortness of breath were the common reasons for termination of the exercise test. Spearman's correlation analysis showed that there was no significant association between resting lung function and the endurance parameters in these subjects. There was no association among the changes in age, body weight and height, and the change in exercise responses from 6 months to 36 months. The maximal and submaximal exercise responses of the participants are shown in Table 1. The absolute values for peak VO_2,

Table 1 Maximal and submaximal exercise responses at 6, 15 and 36 months in children affected by severe acute respiratory syndrome ($n = 21$, nine females)

	Gender	6 months	15 months	36 months	P value
Height, cm	Boys	169 (161–174)	170 (163–175)*	170 (165–174)*	**0.005**
	Girls	153 (149–163)	154 (149–164)	155 (150–165)	0.085
Weight, kg	Boys	63.1 (49.0–70.4)	66.2 (52.0–71.9)	65.6 (57.9–74.2)	0.059
	Girls	47.0 (43.8–59.6)	48.0 (42.9–59.0)	47.6 (45.8–61.6)	0.264
BMI, kg/m^2	Boys	22.3 (19.6–24.3)	22.3 (19.9–25.2)	21.8 (19.3–26.1)	0.472
	Girls	21.5 (18.6–23.8)	21.8 (18.8–23.8)	21.2 (18.9–24.3)	0.459
Peak VO_2, mL/min	Boys	2102 (1620–2674)	1895 (1500–2392)	2404 (2002–2945)*†	**0.002**
	Girls	1099 (915–1426)	1403 (1179–1622)	1535 (1301–1685)*	**0.004**
Peak VO_2, mL/kg/min	Boys	36.5 (30.1–38.3)	32.9 (27.4–38.3)	38.4 (35.0–41.8)†	**0.009**
	Girls	22.2 (20.5–23.7)	28.3 (24.6–31.2)	28.6 (27.1–32.5)*	**0.032**
Peak RER	Boys	1.2 (1.2–1.3)	1.3 (1.1–1.3)	1.3 (1.2–1.3)	0.581
	Girls	1.2 (1.1–1.3)	1.2 (1.1–1.3)	1.3 (1.1–1.3)	0.217
Peak heart rate, beats/min	Boys	194 (179–197)	191 (185–202)	191 (180–200)	0.856
	Girls	191 (185–194)	191 (179–193)	180 (167–181)	0.054
Peak O_2 pulse, mL/beat	Boys	11.0 (8.2–13.3)	9.8 (8.3–11.9)	12.8 (10.3–15.1)*†	**0.002**
	Girls	5.4 (4.8–6.8)	7.0 (5.8–7.9)	7.6 (7.1–8.8)*†	**0.002**
Peak V_E/VO_2	Boys	34.5 (32.5–40.9)	33.1 (29.2–36.3)	33.1 (30.0–37.1)	0.097
	Girls	54.4 (49.0–62.8)	37.1 (35.4–38.4)*	36.1 (33.7–40.9)*	**0.001**
Peak V_E/VCO_2	Boys	29.3 (25.9–35.8)	26.9 (24.8–29.9)	27.9 (24.0–29.3)*	0.076
	Girls	47.6 (40.5–50.5)	32.9 (29.6–34.2)*	31.1 (27.7–31.8)*	**0.001**
$P_{ET}O_2$, mm Hg	Boys	109 (107–112)	112 (106–114)	112 (109–115)	0.486
	Girls	82 (81–101)	115 (112–117)	114 (112–118)	0.121
$P_{ET}CO_2$, mm Hg	Boys	42.0 (33.0–45.0)	45.0 (38.0–46.0)	40.0 (38.0–46.0)	0.636
	Girls	26.0 (24.0–33.0)	37.0 (35.0–43.0)*	39.0 (36.0–40.5)*	**0.001**
VAT, mL/min	Boys	1388 (983–1546)	1123 (969–1389)	1406 (1264–1920)*†	0.060
	Girls	724 (585–830)	755 (680–1098)	1043 (828–1311)*†	**0.008**
VAT, mL/kg/min	Boys	21.2 (16.7–24.1)	19.5 (15.3–22.6)	23.4 (19.5–28.2)	0.234
	Girls	14.4 (12.4–15.8)	16.2 (15.5–18.7)	21.1 (18.6–21.6)*	**0.008**
‡Breathing reserve, mL/min	Boys	47.1 (19.9–64.6)	63.2 (36.7–93.7)*	58.9 (38.7–83.8)	0.174
	Girls	35.0 (20.7–40.9)	53.9 (41.3–64.3)*	49.3 (40.4–63.8)*	**0.032**

* Significantly different from the value at 6 months ($P < 0.016$, Wilcoxon signed rank test).

† Significantly different from the value at 15 months ($P < 0.016$, Wilcoxon signed rank test).

‡ Breathing reserve is expressed as the difference between the predicted maximal voluntary ventilation (MVV) and the ventilation (V_E) at peak exercise, whereas predicted MVV is calculated as $FEV_1 \times 40$.[15,16]

Values are median (interquartile range). P values were determined using Friedman tests. P values in bold indicate that they are <0.05.

BMI, body mass index; O_2 pulse, oxygen consumption per heart beat; $P_{ET}O_2$ and $P_{ET}CO_2$, end-tidal oxygen tension and end-tidal carbon dioxide tension, respectively; RER, respiratory exchange ratio; VAT, ventilatory anaerobic threshold; V_E/VO_2 and V_E/VCO_2, ventilatory equivalent for oxygen and carbon dioxide output, respectively; VO_2, oxygen consumption.

ventilatory anaerobic threshold and peak oxygen pulse were significantly higher at 36 months than at 6 months, both in boys and girls. Mass-related peak VO_2 was significantly higher at 36 months than at 6 months in girls. Ventilatory equivalents for oxygen and carbon dioxide were significantly lower at 15 months and 36 months than at 6 months, whereas end-tidal partial carbon dioxide pressure was significantly higher at 15 and 36 months than at 6 months in girls. Breathing reserve during peak exercise was significantly higher at 15 months than at 6 months in both boys and girls.

Fourteen subjects showed abnormal HRCT findings 6 months after the diagnosis of SARS,[12] but only 10 subjects (7 females) participated in the 36-month follow up. There were no significant differ-ences in physical characteristics, use of medications including systemic corticosteroids during hospital-ization, length of hospital stay or lung function parameters between those with normal or abnormal HRCT findings. The results of pulmonary function tests for the subjects with normal or abnormal HRCT findings at the three assessment time points are pre-sented in Table 2. Friedman tests showed that there were no significant differences between the three visits for any of the pulmonary function parameters within each group, except for percentage predicted forced vital capacity ($P = 0.006$), which was signifi-cantly lower at 6 months than at 15 months or 36 months. For all patients, all pulmonary function parameters at each visit were within the normal range.

Table 2 Results of pulmonary function tests at 6, 15 and 36 months in children affected by severe acute respiratory syndrome, with normal or abnormal high-resolution computed tomography (HRCT) findings at 6 months

% Predicted values	Normal HRCT ($n = 11$, two females)			Abnormal HRCT ($n = 10$, seven females)		
	6 months	15 months	36 months	6 months	15 months	36 months
FVC	92 (82–98)	96 (85–101)	98 (82–104)	93 (80–97)	99 (89–107)*	102 (92–111)*
FEV_1	92 (83–98)	96 (90–103)	94 (88–103)	94 (81–100)	101 (89–105)*	98 (91–111)
FEV_1/FVC	102 (91–107)	105 (100–109)	102 (95–108)	103 (94–107)	104 (88–109)	100 (89–106)
$FEF_{25-75\%}$	93 (77–118)	110 (88–123)	104 (88–124)	95 (78–115)	100 (80–124)	90 (63–109)
TLC	101 (95–112)	103 (95–125)	97 (93–105)	97 (93–118)	116 (94–139)	100 (89–124)
DL_{CO}	131 (103–143)	121 (113–140)	109 (102–126)	103 (96–120)	113 (95–143)	111 (100–122)

* Significantly different from the value at 6 months ($P < 0.016$, Wilcoxon signed rank test).

Values are medians (interquartile range).

DL_{CO}, diffusing capacity of carbon monoxide; $FEF_{25-75\%}$, forced mid-expiratory flow; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; TLC, total lung capacity.

Comparison of the exercise responses between subjects with normal ($n = 11$, two females) or abnormal HRCT findings ($n = 10$, seven females) showed that mass-related peak VO_2 was significantly lower in the subgroup with abnormal HRCT findings than in the subgroup with normal HRCT findings at 6 months ($P = 0.011$); however, the difference between the two subgroups was no longer significant at 36 months ($P > 0.05$). Considering that the gender ratio was different between the two subgroups, peak VO_2 was also compared with the predicted values for age and gender, as determined by Armstrong and Welsman.[14] Peak VO_2 at 6, 15 and 36 months in patients with normal HRCT findings was 72% (IQR 59–99), 68% (IQR 50–84) and 74% (IQR 60–99) of predicted values, respectively, whereas the corresponding values in patients with abnormal HRCT findings were 60% (IQR 48–73), 66% (IQR 59–75) and 68% (IQR 63–70), respectively (corresponding to the predicted peak VO_2 values of 2478 (IQR 1948–3139) mL/min, 2614 (IQR 2048–3313) mL/min and 2878 (IQR 2335–3810) mL/min, respectively).[14] Within-group comparison showed that there were significant improvements in mass-related peak VO_2 and ventilatory anaerobic threshold ($P < 0.016$ for both) from 6 months to 36 months in the subgroup of patients with abnormal HRCT findings. Peak oxygen pulse at 36 months improved significantly in both subgroups of patients ($P < 0.016$ for both) compared with the corresponding values at 15 months. Peak ventilatory equivalent for oxygen and ventilatory equivalent for carbon dioxide were significantly lower at 36 months than at 6 months in both subgroups ($P < 0.016$ for all).

From our observations, none of the patients reported participation in any rehabilitation or routine training program during the study period.

DISCUSSION

There have been a limited number of studies examining the impact of SARS on aerobic capacity, and most published studies were performed in adults.[8–10,19] To the best of our knowledge, this is the first study examining the later stage of recovery (36 months) in children and adolescents who contracted SARS coronavirus. The main finding from the present study was the persistence of suboptimal aerobic capacity 36 months after the initial acute illness.

Impairment of aerobic capacity has been reported in adult SARS patients.[8–10,19] Such impairment was consistently shown to be at variance with the lung function of these subjects, which was either normal or showed only mild abnormalities. We reported that aerobic capacity, as reflected by peak VO_2, was reduced in a cohort of asymptomatic children 6 and 15 months after the acute episode of SARS. We postulated that this impairment was the result of reduced perfusion of the lungs during peak exercise as well as deconditioning.[11]

The present results showed that peak VO_2, both in absolute terms and relative to body mass, increased significantly between 6 and 36 months in all subjects, most likely indicating recovery in these subjects.[20] With regard to the lowest value of peak VO_2 in a group of local 'healthy' adolescents (26 mL/kg/min),[21] 43% of the 21 patients in the present study had peak VO_2 values below 25 mL/kg/min at 6 months, as compared with 14% at 15 months and 6% at 36 months, reflecting reversal of the impairment in peak VO_2 in these patients. Ventilatory anaerobic threshold is the most frequently used measure of submaximal exercise response,[22,23] and the changes in ventilatory anaerobic threshold were in keeping with the changes in peak VO_2, reinforcing the notion that aerobic capacity did improve over time in all subjects. However, peak VO_2 values at 36 months in patients with normal and abnormal HRCT findings were only 74% and 68%, respectively, of the predicted values for age and gender determined by Armstrong and Welsman,[14] and these values would still be considered suboptimal.

The recovery of aerobic capacity at 36 months in girls can partly be explained by the normalization of ventilation parameters and blood oxygenation in the lungs. At 6 months, patients were noted to have inefficient ventilation, as reflected by significantly higher peak ventilatory equivalent for oxygen values compared with normal control subjects.[11] In the present

study, ventilatory equivalent for oxygen values in girls had returned to normal when they were examined at 15 months, and the values remained stable thereafter. End-tidal partial carbon dioxide pressure provides a reliable non-invasive estimate of $PaCO_2$,[24] and a low end-tidal partial carbon dioxide pressure value would indicate a high degree of alveolar V/Q mismatching.[15] A marked increase in end-tidal partial carbon dioxide pressure was noted in girls from 6 months to 15 months after the acute episode, but there was no further significant increase at 36 months. This finding supports the hypothesis that improved oxygenation of blood in the lungs plays a role in the documented improvement in aerobic capacity among girls. Furthermore, it would suggest that recovery of any pulmonary deficit due to SARS coronavirus infection had been established and was complete by 15 months. Whether exercise training and/or pulmonary rehabilitation would further enhance recovery is unknown.

Peak oxygen pulse is a surrogate marker for cardiac function, and provides an indication of stroke volume and arteriovenous difference.[15] Peak oxygen pulse was significantly reduced at 6 months in children recovering from SARS, as compared with healthy control subjects,[11] whereas peak oxygen pulse values increased markedly at 36 months. Lin *et al.* demonstrated that peak oxygen pulse increased with increasing age in both girls and boys.[25] It is possible that pronounced deconditioning as a result of SARS resulted in a decline in stroke volume, and the low peak oxygen pulse at 6 and 15 months also supported this. Increases in peak oxygen pulse at 36 months may be the result of cardiac remodelling in response to the resumption of normal activities of daily living; however, in a study of adult SARS survivors who had a more severe disease course, stroke volume remained unaffected.[26] Therefore, it is reasonable to assume that the improved peak oxygen pulse at 36 months in both boys and girls was more likely due to normal growth and development, rather than being associated with recovery from SARS. Arteriovenous difference is dependent on the availability of Hb, on oxygenation of blood in the lung and on the extraction of oxygen in the periphery.[15] Based on the fact that (i) patient Hb levels were within the normal range,[27] (ii) all patients achieved their target peak heart rate during the maximal exercise test, (iii) none of the patients had received a prolonged course of corticosteroid treatment, and (iv) normalization of breathing efficiency and oxygenation of blood in the lungs were established by 15 months, it is unlikely that increases in peak oxygen pulse could be explained by improvement in arteriovenous oxygen difference.

Aerobic capacity was suboptimal in these patients at 36 months after the initial illness. Individuals with low aerobic capacity may experience limitation in sustaining more demanding activities, as peak VO_2 is strongly correlated with time spent performing high-intensity leisure-time physical activities.[28] Aerobic capacity also contributes to cardiac workload and is associated with the growth of the heart during childhood and adolescence.[29] If aerobic capacity is persistently suboptimal in this group of patients, it is possible that the development of the heart would be hindered in these younger patients, as a result of insufficient cardiac workload stimulation of the left ventricle. Low aerobic capacity is also associated with an increased risk of cardiovascular disease.[30] It may, therefore, be beneficial for patients to participate in a well-structured moderate-to-high intensity exercise training program aimed at improving peak VO_2. In adult SARS patients, aerobic capacity was shown to improve significantly after a 6-week supervised exercise program.[31]

There were certain limitations to this study. First, data from only 21 out of a possible 47 patients were analyzed at 36 months. Aerobic capacity was poorer at 6 months in patients who did not return for reassessment than in those who did return. A lack of motivation, and difficulty in sustaining a relatively high-intensity workload during the previous exercise test, may have deterred some patients from returning for reassessment. Second, detailed assessments of physical activity were not performed for these patients. Changes in conditioning and in the habitual physical activity of these patients during the study period may also have contributed to changes in aerobic capacity at 36 months. However, to our knowledge, none of the patients participated in any routine exercise training during the study period. It is likely that the activity patterns of these patients were similar to those of other Hong Kong youngsters, which have been shown to be low.[32,33] Third, no comprehensive direct assessments of cardiac function were made. However, it is unlikely that there was any significant cardiac impairment as all subjects were normal at clinical examination and were able to achieve the maximum heart rates predicted for their age during peak exercise. Lastly, the reference values reported by Armstrong and Welsman[14] were used as local normal reference values for peak exercise tests were unavailable. McManus *et al.*[21] have shown that absolute peak VO_2 values were considerably lower in younger Chinese girls and boys than in similarly aged Caucasian children; however, by adolescence, the values were comparable to the predicted values for children of corresponding ages, as reported by Armstrong and Welsman. Therefore, the effects of using normal reference values determined for a different racial group should have been minimal.

In conclusion, this study is the most comprehensive analysis of post-SARS exercise responses in children and adolescents. Improvements in aerobic capacity were demonstrated over a period of 36 months after the initial illness; however, the values remained suboptimal when compared with normal reference values.

ACKNOWLEDGEMENTS

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