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Effect of antituberculosis treatment on cardiopulmonary responses to exercise in miliary tuberculosis

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***Background & objectives*: Tuberculosis (TB) is a major health problem in the developing world. In this preliminary study, we report the effect of antituberculosis treatment (ATT) on cardiopulmonary responses to exercise in patients with miliary tuberculosis (MTB).**

***Methods*: The prospective study of cardiopulmonary responses to exercise in patients with MTB within one month of starting (n=14), on completion of ATT (n=7) and in 15 healthy subjects using the incremental exercise test was performed on a bicycle ergometer.**

***Results*: In MTB patients, mean body mass index (BMI), exercise duration (3.1 vs 4.6 min), work load (63 vs 91.4 watts), resting tachycardia, tachypnoea and the mean oxygen saturation improved significantly ($P<0.05$) with ATT. Mean oxygen consumption ($\dot{V}O_2$) at anaerobic threshold (546.7 vs 580.9 ml/min) and maximum exercise (1008.1 vs 1022 ml/min) were similar before and after ATT. In MTB patients, post-treatment mean body weight, BMI, resting heart rate, respiratory rate and oxygen saturation during maximum exercise were similar, but exercise duration (4.6 vs 6.2 min, $P<0.05$), work load (91.4 vs 145.5 watts, $P<0.05$), $\dot{V}O_2$ and oxygen pulse were significantly lower as compared to healthy subjects.**

***Interpretation & conclusion*: In MTB patients, though there was significant improvement in clinical parameters, functional abnormalities persisted on exercise testing after completion of ATT. As most patients with MTB are young and economically active, these observations obviously have long-term implications for these individuals.**

Key words Anaerobic threshold - exercise test - heart rate - miliary - oxygen consumption - oxygen saturation - respiratory rate - tuberculosis

Tuberculosis (TB) continues to be an important communicable disease in the world and has been declared a global emergency by World Health Organization[1-3]. It affects the young and economically productive segment of the population. The emergence of human immunodeficiency virus (HIV) infection has made the situation worse[4]. The abnormalities in pulmonary function tests and gas exchange in miliary tuberculosis (MTB) and the trend for improvement in these parameters with anti-tuberculosis treatment (ATT) has been reported earlier[2]. However, to date, no study has been done to understand the pathophysiology of exercise limitation in patients with MTB. In this preliminary study, we evaluated the relative importance of the cardiovascular and/or pulmonary responses to exercise in patients with MTB and the effect of ATT on these parameters.

Material & Methods

Study subjects: The study was done from January 1996 to December 1999 in the Department of Medicine, All India Institute of Medical Sciences, New Delhi, and patients were consecutively selected. The criteria for the diagnosis of MTB included (*i*) clinical presentation consistent with a diagnosis of TB; (*ii*) classical miliary pattern on the chest radiograph; (*iii*) histopathological or microbiological evidence of tuberculosis; (*iv*) bilateral diffuse miliary lesions demonstrated on high resolution computed tomographic scan (HRCT scan)[2]. All patients fulfilled the first three criteria with or without the last criterion.

Of the 30 MTB patients seen during the study period, 14 were enrolled who were able to understand and perform the exercise test. Feeling of well being to do the exercise as an important criterion, besides the informed consent of the patient. In fact, feeling of well being included the "adaptability level" of the patients to do bicycling with a bicycle ergometer. These were MTB patients who were chronically fifteen healthy subjects were enrolled for this study. Healthy subjects, selected from persons undergoing medical examination for employment underwent a baseline incremental exercise test. At this point, it needs to be appreciated that due to economic limitations of a resource-limited developing nation like India, MTB patients are usually very sick and toxic, when they report for initial evaluation in a hospital. Therefore, these patients were subjected to baseline exercise test within the first month of starting ATT, when they started experiencing a relative feeling of well-being to perform the test.

We repeated the exercise test in seven patients, who reported regularly for follow up, on completion of ATT. The remaining seven patients were from distant places and after showing clinical improvement on initial follow up of 2-3 months started reporting to their local health care providers for further treatment. All patients received standard ATT using rifampicin, isoniazid, pyrazinamide, ethambutol and/or streptomycin for a duration of nine (n=4) and 12 months (n=3)[5]. Written informed consent was taken from both MTB patients and healthy subjects. Both MTB patients and healthy subjects were adequately motivated and counseled to perform the test.

Protocol: The ventilatory parameters were obtained with the transfer test model C (Morgan, UK). The measurement of the pulmonary function tests has already been standardized in the respiratory laboratory of our hospital[2].

With the subject comfortably seated on bicycle ergometer, an incremental exercise test to the limit of tolerance was performed. The initial exercise load was selected depending on the expected performance of the patient. The subject had to breathe through a low resistance unidirectional valve attached to the mouth piece. The inspiratory port of the valve was connected to a turbine which

was calibrated to give an electrical signal in terms of the inspired volume which was constantly displayed on the instrument panel. The expiratory port of the unidirectional valve was connected by flexible large tubing to a mixing chamber to allow the expired air to enter from the top and flow out from an opening at the bottom of the chamber. The mixed expired air concentration of O_2 and CO_2 was calculated from the port near the exit pole of the mixing chamber. All calibrations for O_2 and CO_2 gas meter, heart rate meter and work load meter were performed with the help of a computer (Magna 88, UK) and appropriate software (Wyvern, UK). A time lag was built in the software to give online display of the O_2 consumption, ventilation and heart rate on the visual display unit of the computer. The blood pressure recording was obtained manually with a mercury sphygmomanometer every two to three minutes till the maximal tolerable work load and at the end of four minutes recovery. The subjects were continuously monitored for leaks at the mouth piece and encouraged to maintain correct cycle pedaling frequency.

Heart rate (HR) was monitored beat-by-beat from the R-R interval of the ECG signal. The electric signals from the above devices underwent analog-to-digital conversion and were processed by digital computation for the online breath-by-breath determination of oxygen uptake ($\dot{V}O_2$), CO_2 output ($\dot{V}CO_2$), and ventilation ($\dot{V}E$). The data of minute ventilation ($\dot{V}E$), heart rate, mixed expired O_2 and CO_2 concentration, O_2 pulse and actual work load in watts were stored in the computer. The data for the systemic blood pressure and end tidal CO_2 concentration were manually recorded. The results of ventilatory equivalents of O_2 ($\dot{V}E/\dot{V}O_2$) and CO_2 ($\dot{V}E/\dot{V}CO_2$) and O_2 pulse were calculated by the computer using Wyvern software. The oxygen saturation was measured with a finger probe connected to an oximeter (Ohmeda BIOX 3700, USA).

The anerobic threshold (AT) was measured as the $\dot{V}O_2$ at which: (*i*) the respiratory exchange ratio increased abruptly without hyperventilation, and (*ii*) the ventilatory equivalent for O_2 ($\dot{V}E/\dot{V}O_2$) started to increase progressively without an increase in the ventilatory equivalent for CO_2 ($\dot{V}E/\dot{V}CO_2$). AT was expressed as absolute value of O_2.

The pulmonary parameters before and after exercise were analyzed as follows: (*i*) The breathing reserve (BR), *i.e.*, the unused fraction of the potential ventilation at maximal work level (1-$\dot{V}E$ max/MVV) where $\dot{V}E$ max is the ventilation at maximal exercise and MVV is the maximal voluntary ventilation at rest; and (*ii*) the breathing pattern at rest and during exercise as measured by changes in respiratory rate. The cardiovascular oxygen transport capacity during exercise was estimated in the three groups by: (*i*) the analysis of the heart rate reserve (HRR) calculated as 1-[(HRmax-HRrest) (HRpred max-HRrest], where HRmax is the heart rate at maximum exercise, HRrest is the resting heart rate and HRpred max is the maximum heart rate predicted for age; (*ii*) the determination of the AT; and (*iii*) the maximum aerobic capacity ($\dot{V}O_2$max).

On termination of exercise, the subject was asked to discontinue pedaling, but continue to breathe through the mouth piece during the two minute recovery time. Online data acquisition was continued for 4 min in order to record the recovery data. On review of the data, if it appeared that the test was terminated prematurely because of inadequate effort and/or evident technical malfunction, a repeat test after a period of 30 to 45 min was performed.

Statistical analysis: The comparison of healthy subjects with pre- and post-treatment groups respectively was done using unpaired t-test. The effect of ATT was evaluated using Wilcoxon's ranked-sum test. A value of $P<0.05$ was considered significant.

Table I. Demographic characteristics in miliary tuberculosis (MTB) patients (pre & post-treatment) and healthy subjects

Group (n) (M:F)	Age (yr)	Haemoglobin (g/dl)
MTB patients (14) (6:8)	27.1 ± 3.5	12.7 ± 2.2
Healthy subjects (15) (7:8)	25.7 ± 3.9	13.4 ± 0.8
Pre-treatment* (7) (5:2)	28.7 ± 11.3	12.5 ± 1.9
Post-treatment* (7) (5:2)		13.9 ± 1.5

Values are mean ± SD
Exercise test was repeated in 7 patients, who reported regularly for follow up, on completion of anti-tuberculosis therapy

Results

Demographic characteristics: The characteristics of the study population are given in Table I. The exercise test was repeated in 7 patients on completion of ATT (4 patients at nine months and 3 patients at 11 months). All healthy subjects had normal complete blood count and chest radiograph.

Pre-treatment MTB patients and healthy subjects: The mean duration of exercise (2.9 vs 6.2 min) and maximum work load (57 vs 145.5 watts) was significantly ($P<0.05$) lower and resting tachycardia (111 vs 86.5 bpm) significantly higher ($P<0.05$) in

Table II. Cardiovascular and respiratory variables in pre- and post-treatment in miliary patients and normal subjects at rest and maximal exercise

Variable	Healthy subjects (n=15)	Pre-treatment (n=14)	Post-treatment (n=7)
Weight (kg)	59 ± 9	47 ± 12*	56.7 ± 16.5
Body mass index (kg/m^2)	20.6 ± 2.8	18.4 ± 3.7	21.8 ± 5
Duration of exercise (min)	6.2 ± 1.4	2.9 ± 0.6*	4.6 ± 1.1*
Maximum work load (watts)	145.5 ± 29.9	57 ± 25.3*	91.4 ± 48.3*
Heart rate (beats/min):			
Rest	86.5 ± 15.3	111.1 ± 16.6*	98 ± 13.3
Maximum exercise	179.6 ± 11.7	149.9 ± 17.8*	161.6 ± 16.5*
$\dot{V}O_2$ *(ml / min)*:			
Rest	289.1 ± 35.4	235.7 ± 79.8*	175.3 ± 74.4
Maximum exercise	2218 ± 507.4	935 ± 407.3*	1022 ± 379.3*
AT (*ml/min*)	1254 ± 294	495.2 ± 259.5*	580.9 ± 153.8*
O_2 *pulse (ml/beat)*:			
Rest	3.1 ± 0.6	1.9 ± 0.8*	2.1 ± 0.7*
Maximum exercise	11.7 ± 2.1	6.4 ± 3.2*	6.5 ± 2.9*
Heart rate reserve (%)	7.5 ± 5.0	36.7 ± 15.5*	25.6 ± 13.8*
Respiratory rate (frequency/min):			
Rest	20.1 ± 5.4	26.1 ± 6.5*	19 ± 5.1
Maximum exercise	39.8 ± 10	45.5 ± 12	37.3 ± 9.5
$\dot{V}E$(*l*/min):			
Rest	11.5 ± 3	8.9 ± 3.7*	9.0 ± 3.5
Maximum exercise	72.2 ± 15.3	35.7 ± 15.1*	35.4 ± 18.8*
Breathing reserve (%)	38.4 ± 14.8	53.8 ± 25.2*	53.8 ± 25.2*
Oxygen saturation (%):			
Rest	98.8 ± 0.7	96.9 ± 1.1*	96.7 ± 1.1
Maximum exercise	98.3 ± 0.8	93.8 ± 2.8*	95.6 ± 1.8*

Values are mean ± SD
$\dot{V}O_2$, oxygen consumption; AT, anaerobic threshold; $\dot{V}E$, minute ventilation; *$P<0.05$ compared to normal subjects

pre-treatment MTB patients as compared to healthy subjects. Likewise, at maximum exercise, the heart rate achieved by patients with MTB was significantly lower than healthy subjects. At rest, AT and maximum exercise, MTB patients had a significantly (P<0.05) lower oxygen uptake ($\dot{V}O_2$) as compared to control subjects. The rest values for oxygen pulse were lower in the MTB group as compared to healthy subjects. At maximum exercise, MTB patients achieved significantly lower $\dot{V}E$ than healthy subjects (35.7 vs 72.2 l/min) and oxygen saturation was significantly lower in MTB patients as compared to healthy subjects (93.8 vs 98.3%) (Table II).

Table III. Cardiovascular and respiratory variables in miliary TB patients before and after anti-tuberculosis treatment at rest and maximal exercise

Variable	Pre-treatment (n=7)	Post-treatment (n=7)
Weight (kg)	49 ± 16	56.7 ± 16.5*
Body mass index (kg/m^2)	18.4 ± 4.5	21.8 ± 5*
Duration of exercise (min)	3.1 ± 0.7	4.6 ± 1.1*
Maximum work load (watts)	63 ± 31.2	91.4 ± 48.3*
Heart rate (beats/min):		
Rest	113.9 ± 19.4	98 ± 13.3*
Maximum exercise	157.3 ± 17.4	161.6 ± 16.5
$\dot{V}O_2$ (ml/min):		
Rest	273.1 ± 97.2	175.3 ± 74.4*
Maximum exercise	1008.1 ± 357.4	1022 ± 379.3
AT (ml/min)	546.7 ± 271.8	580.9 ± 153.8
O_2 pulse (ml/beat):		
Rest	2.2 ± 0.9	2.1 ± 0.7
Maximum exercise	6.6 ± 2.9	6.5 ± 2.9
Heart rate reserve (%)	29.1 ± 13.5	25.6 ± 13.8
Respiratory rate(frequency/min):		
Rest	26.6 ± 8.4	19 ± 5.1*
Maximum exercise	48.3 ± 10.6	37.3 ± 9.5*
$\dot{V}E$*(l/min)*:		
Rest	8.3 ± 2.6	9.0 ± 3.5
Maximum exercise	36.1 ± 13.6	35.4 ± 18.8
Breathing reserve (%)	62.8 ± 24.7	65.1 ± 29.3
Oxygen saturation (%):		
Rest	96.7 ± 1.1	96.7 + 1.1
Maximum exercise	93 + 3.2	95.6 ± 1.8*

Values are mean ± SD
$\dot{V}O_2$, oxygen consumption; AT, anaerobic threshold; $\dot{V}E$, minute ventilation; *P<0.05 compared to pre- treatment

Effect of treatment on exercise performance: With ATT, mean body weight and body mass index (BMI, kg/m^2) improved significantly (P<0.05) (Table III). The mean haemoglobin was similar before and after treatment (Table I).

There was significant improvement in the duration of exercise and work load and a significant reduction in the resting tachycardia after treatment (P<0.05). However, there was no statistically significant difference in the mean heart rate at maximum exercise and the mean heart rate reserve (P=0.17) before and after ATT (Table III). ATT resulted in a significant (P<0.05) reduction in the $\dot{V}O_2$ at rest. However, $\dot{V}O_2$ at maximum exercise was similar before and after treatment. The AT was also similar before and after treatment. There was no change in rest and maximum exercise values for oxygen pulse after treatment. The pattern of O_2 pulse response to incremental exercise before and after treatment was similar (Table III).

There was a statistically significant improvement in the resting respiratory rate and a reduction in the respiratory rate at maximum exercise (P<0.05) with ATT. The mean $\dot{V}E$ at rest and maximal exercise, mean breathing reserve and mean oxygen saturation at rest were similar before and after treatment. Mean oxygen saturation (%) at maximum exercise significantly improved after ATT (P<0.05) (Table III).

Post-treatment MTB patients and healthy subjects: The mean body weight and BMI of post-treatment MTB patients were similar to the observations in healthy subjects. However, the duration of exercise

($P<0.05$) and work load ($P<0.05$) were significantly less in MTB patients after treatment compared with healthy subjects. The resting heart rate was similar in treated MTB patients and healthy subjects. At maximum exercise, the heart rate achieved by post-treatment MTB patients was significantly lower as compared to healthy subjects ($P<0.05$). Moreover, post-treatment MTB patients achieved a significantly higher heart rate reserve as compared to healthy subjects ($P<0.05$) (Table II).

$\dot{V}O_2$ at rest, AT and maximum exercise in treated MTB patients was significantly lower than healthy subjects. The resting oxygen pulse was also lower in post-treatment MTB patients as compared to healthy subjects. Moreover, the treated patients interrupted exercise with a higher breathing reserve as compared to healthy subjects. After treatment, the resting respiratory rate and respiratory rate at maximal exercise was comparable to healthy subjects. There was a significant improvement in the oxygen saturation during maximum exercise in MTB patients after ATT, but was still lower as compared to healthy subjects (Table II).

Discussion

We appreciate the limitations imposed by the relatively small sample size of our study. In fact, to the best of our knowledge the pathophysiology of exercise limitation in MTB patients has not been reported earlier in the literature. Moreover, MTB patients constitute less than 1 per cent of the TB burden in the community and these patients are relatively sick also. Therefore, the enormous logistical constraints of a similar longitudinal study with a large sample size in India also need to be taken into consideration. Our study is a preliminary contribution in this direction.

The changes in pulmonary function tests have been studied earlier in MTB patients[2]. In the present study, anaemia does not appear to be a confounding factor in the interpretation of cardiopulmonary abnormalities as patients with MTB (before and after treatment) and healthy subjects had similar normal haemoglobin values.

Though MTB patients showed significant improvement in exercise duration after ATT, it was still less as compared to healthy subjects. However, the significant improvement in their body weight and the fact that post-treatment mean body weight and BMI of MTB patients were almost the same as in healthy subjects suggests that weight is also not a confounding factor in the interpretation of cardiopulmonary abnormalities.

In MTB patients, resting tachycardia and tachypnoea improved following treatment and were similar to the observations in healthy subjects. Moreover, after ATT, there was improvement in hypoxaemia during exercise in patients with MTB. However, treated MTB patients had reduced AT compared to healthy subjects. The lower AT in patients with lung disease may be due to reduced oxygen transfer because of diffusion abnormalities in the lungs resulting in reduced oxygen carrying capacity and lower oxygen availability at the tissue mitochondria level. Though lung diseases classically do not have decreased AT, the reduced AT in MTB patients may also be due to a low cardiac output state[6]. Since clinically no patient had any cardiac abnormality, cardiac evaluation with echocardiography was not included in the protocol of our study. It can be postulated that low cardiac output in MTB patients may be due to early cor-pulmonale due to extensive miliary involvement of lung or direct involvement of heart due to TB. A low AT may be an important compensatory mechanism and the relative contribution to energy output in MTB patients by anaerobic mechanisms may be greater.

On exercise, post-treatment MTB patients had significantly reduced oxygen consumption as

compared to healthy subjects. The reduced $\dot{V}O_2$max may be the result of reduced oxygen carrying capacity in MTB patients due to the diffusion abnormalities in the lungs. The fact that oxygen consumption did not improve with treatment may be due to poor exercise tolerance as well as subtle changes in the alveolocapillary membrane and/or ventilation perfusion mismatching and/or factors related to capillary blood flow.

The oxygen pulse plateau was significantly less steep in MTB patients before and after treatment as compared to healthy subjects. Before ATT, lower oxygen pulse at rest and maximum exercise may be due to the marked resting tachycardia. Since the tachycardia settled after ATT, this does not seem to be the plausible explanation as there is no improvement in the oxygen pulse after therapy. The low oxygen pulse may again signify lower stroke volume in these patients. However, it is also important to appreciate that a low oxygen pulse at maximum exercise in MTB patients before and after treatment might be the result of the patient interrupting the exercise before the cardiovascular system was maximally stressed rather than compromised O_2 transport. The importance of deconditioning of muscles due to lack of exercise when these subjects are ill also needs to be taken into consideration.

Though $\dot{V}E$ max was reduced in treated MTB patients as compared to healthy subjects, but when compared with similar work rate, they had a higher $\dot{V}E$ than the healthy subjects. This implies that there is a higher ventilatory requirement to accomplish the same work in MTB patients as compared to healthy subjects and this does not become normal even after ATT therapy. The breathing reserve was higher in MTB patients suggesting that they did not stop exercise due to exhaustion of ventilatory capacity. It possibly indicates that MTB patients stopped exercise at a comparatively lower level of ventilation possibly due to fatigability or these patients were cardiovascular-limited as also suggested by low oxygen pulse. The patients with MTB had a higher heart rate reserve as compared to healthy subjects, suggesting that they stopped exercise probably due to poor muscle conditioning.

Interestingly, an earlier study by Sharma *et al*[7] had demonstrated subtle 'air trapping' in MTB patients not only at the time of diagnosis, but it also persisted on follow up, when these patients had clinically become asymptomatic after nine to twelve months of ATT. The subtle air trapping findings were not appreciated on a plain chest radiograph but observed only on computed tomography. These air trapping lesions were not typical of classical emphysema. The authors had postulated that the clinical significance of these subtle air trappings needs to be studied in patients of MTB who were otherwise 'asymptomatic' after treatment[7]. The current study possibly explains the clinical significance of the earlier observations.

In conclusion, though simple clinical parameters like duration of exercise, resting tachycardia, tachypnoea and oxygen saturation showed improvement after anti-TB therapy, there were significant functional abnormalities on the cardiopulmonary exercise test. This indicates that MTB patients, though "clinically" normal following treatment, have underlying residual cardiopulmonary limitations, which are unmasked on exercise. As most patients with TB are young and economically active, our observations have long-term implications for these individuals. We believe that exercise studies at regular intervals after completion of ATT in MTB patients which also includes simultaneous cardiac evaluation would clarify further as to whether these functional abnormalities are static or improve after a period of time. The issue of exercise training and muscle deconditioning in MTB patients also needs critical evaluation and research.

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