

Thorax

Editorials

Thorax with extra "e"

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¹ About HighWire Press. Highwire.stanford.edu/about.shtml

² Knox AJ, Britton JR. Rising impact, fast review: Annual Report October 1997 to September 1998. *Thorax* 1999;54:5-6.

Exercise training as an adjunct to asthma management?

N Carroll, P Sly

Whether the mechanism is respiratory heat loss¹ or increased osmolarity due to respiratory water loss,² exercise is a potent stimulus for provoking asthma symptoms in children. For this reason children with asthma may avoid exercise which may in turn be detrimental to their physical and social conditioning. On this background the efficacy of exercise training in children with asthma has generated continued interest over the years. The use of exercise training programmes in the clinical management of children with asthma is at best controversial. While a number of studies have reported an improvement in lung function, aerobic capacity/conditioning, psychosocial behaviour, and a reduced incidence and severity of exercise induced bronchoconstriction,^{3–11} the findings in these studies have been variable and have not addressed the clinical efficacy of such programmes. The quality of the studies has varied and assessing the efficacy of such programmes depends on which outcomes are assessed and how these outcomes are measured.

It is widely recognised that suitable training regimens increase exercise tolerance and capacity in healthy individuals, with greater improvements usually being seen in the more sedentary subjects.¹² This is generally due to a greater capacity for improvement in non-trained individuals. Improvements in exercise capacity are usually accompanied by a number of physiological adaptations including increased oxygen uptake ($\dot{V}O_2$), reduced ventilatory requirements, reduced cardiac frequency, and a reduction in lactic acid production at any given work load.¹³ Anatomical and metabolic changes such as increased mitochondrial density, increased capillarisation of trained muscles, and changes in muscle fibre type and density generally accompany these physiological changes.¹³ Along with these physiological changes in response to training, improved psychosocial outcomes such as improved sense of self-worth and well being as well as improved concentration and decreased stress levels have been reported. These changes in response to appropriate modes, duration, frequency, and intensity of exercise training programmes should apply equally well to children with and without asthma, provided they have no other physical limitations. It therefore comes as no surprise when demonstrable physiological and psychosocial improvements are observed in studies of children with asthma following suitable exercise training regimens. The qualitative and quantitative differences between published studies^{3–11} is likely to be due, at least in part, to variations in subject selection, both in terms of severity of disease (that is, the amount and type of airway inflammation likely to be present and the degree of bronchial responsiveness), medication usage, age, and training status. Differences in the methodology used and interpretation of the results also contribute to the reported differences in outcome.

At rest, compromised respiratory function has been reported in young asthmatic patients including decreased flows, increased residual volume, increased ratio of physiological dead space to tidal volume (V_D/V_T), increased alveolar–arterial oxygen tension difference ($A-aPO_2$), and mild arterial hypoxaemia and desaturation.¹⁴ During exercise these physiological variables return to normal and exercise tolerance is not limited by these factors. Provided that a child's asthma is well managed and

there is no significant degree of fixed airflow obstruction, there are few physiological reasons why they would not tolerate and, indeed, significantly improve their aerobic capacity following an aerobic training regimen. However, the clinical benefit of such a training regimen to the patient may not be comparable to the physical improvements. There is no consistent evidence that exercise training decreases the incidence of exercise induced bronchoconstriction or improves peak expiratory flows (PEF). It is likely that in patients with airway pathology there is a threshold ventilatory rate (which may be modulated by inspired air conditions) at which exercise induced bronchoconstriction is triggered.¹⁵ When patients are challenged at or above this ventilatory threshold, exercise induced bronchoconstriction is likely to occur regardless of the fitness level of the subject. This would mean that exercise challenges performed after a period of aerobic training need to be conducted at the same relative loads—that is, the same ventilatory equivalent—rather than at the same absolute load, and with the same inspired air conditions. This would allow valid comparisons of the incidence of exercise induced bronchoconstriction after a period of exercise training. However, if exercise training allows a patient to exercise more before reaching the threshold for triggering exercise induced bronchoconstriction, that patient may report an increased exercise capacity without experiencing exercise induced bronchoconstriction.

Two publications in this issue of *Thorax* describe similar improvements in aerobic exercise capacity after swimming and cycle ergometry training in children with asthma. The study by Matsumoto and colleagues¹⁶ showed that, when asthmatic children were assessed at the same relative work loads before and after an aerobic training programme, the fall in FEV₁ following exercise was reduced. This occurred despite finding no change in the PC₂₀ to histamine, which suggests minimal change in airway structure/inflammation. The authors did not report medication usage during the training phase and this may also have affected the results. Interestingly, the lack of change in airway responsiveness to histamine suggests that airway structure may be a more important determinant of in vivo airway responsiveness to exercise than inflammatory stimuli.

The study by Neder and colleagues¹⁷ reported a short term decrease in the daily use of inhaled and oral steroids in a group of children with severe asthma following a two month cycle ergometry training programme, with no change in the number of positive exercise challenges. The authors attributed the decrease in medication usage to improved psychosocial factors related to exercise training. The interpretation of these data requires a cautious approach. The authors provide no evidence of longer term treatment requirements. Also, it is possible that the reported decrease in medication use was a “trial” effect or that the subjects did not require the dose of inhaled steroids initially prescribed.

Because exercise induced bronchoconstriction may itself limit the maximum aerobic work capacity, adequate asthma control is required during any aerobic training regimens. This may involve an increase in preventative medication usage and/or pre-exercise use of a bronchodilating agent. The observation that the severity of exercise induced bronchoconstriction is reduced but airway responsiveness to

inhaled bronchoconstricting stimuli remains the same following aerobic exercise training¹⁶ raises an interesting possibility that aerobic conditioning may reduce the airway response to specific stimuli. This hypothesis has not been examined and warrants further investigation. From the point of view that exercise training in children with asthma demonstrates a beneficial effect on aerobic conditioning and psychosocial behaviour, it warrants consideration from a general health perspective. If aerobic conditioning reduces the likelihood of provoking an asthma attack due to decreased ventilatory requirements for any given task, then increased participation in physical activity by children with asthma is desirable. In terms of clinical management of children with asthma, the evidence is still not strong enough to support modifications in conventional therapeutic treatment even in well trained children with asthma. We encourage researchers in this field to conduct well designed studies to address the important issue of whether exercise training programmes can improve asthma control and decrease medication requirements in asthmatic children.

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Field tests in pulmonary disease

N Ambrosino

Proper evaluation of potential patients is the keystone to a successful pulmonary rehabilitation programme.¹ The so-called functional approach which relates to *impairment* (the physiological deficit), *disability* (total effect of impairment on the patient's life), and *handicap* (the social disadvantages) as part of the comprehensive programme of care is one approach. It is useful not only for monitoring the patient's functional status, but it enables the rehabilitation team to set and to achieve goals to improve the quality of the patient's life.

Although an exercise test may help to uncover other coexisting diseases, it is generally necessary to assess the patient's exercise tolerance and to evaluate possible blood gas changes which cannot be predicted from baseline lung function tests.² The exercise test is also used to establish a safe and appropriate prescription for subsequent training. Cardiopulmonary exercise testing has been found to be useful in the evaluation of exercise tolerance in patients with dyspnoea and cardiopulmonary diseases. Compared with a clinical laboratory approach, it allows the detection of an underestimated circulatory component causing exercise limitation.³ Graded exercise testing has been shown to be useful in diagnosing patients with chronic unexplained dyspnoea although it was not sensitive in distinguishing a cardiac disease from deconditioning.⁴ Variables measured and/or monitored during testing should include workload, heart rate, electrocardiogram, arterial oxygenation, and symptoms. Blood gas sampling during exercise adds a sig-

nificant degree of complexity to testing. Non-invasive techniques such as cutaneous oximetry of arterial oxygen saturation are useful for continuous monitoring but should not be relied on for precise assessment of arterial oxygenation because of their limited accuracy.⁵ Other measurements such as analysis of expired gas to calculate variables such as oxygen consumption ($\dot{V}O_2$) may be performed, depending on the interest and expertise of the referring physician, laboratory personnel, and programme staff. Assessment of exercise is best made using the type of exercise that will be employed in training—for example, treadmill testing for a walking exercise training programme; however, results from one type of exercise test can be translated to similar forms of exercise.⁶ Indeed, although regular bicycle exercise was unfamiliar and generated the greatest lactate response in patients with chronic obstructive pulmonary disease (COPD), peak $\dot{V}O_2$ was the same during cycle and treadmill exercise.⁷

Laboratory tests are the gold standard measurements. However, "field tests" can provide a useful assessment of task performance when laboratory facilities are unavailable. Timed walking tests can be used to measure exercise capacity indirectly following rehabilitation, particularly when limited resources are available. Measuring the distance covered during a walking test is considered a simple and reproducible way to determine exercise tolerance in patients with chronic lung disease. The first test proposed involved measuring the distance covered over 12

minutes (12MWD, 12 minute walking distance). It was shown that the distance walked was related to peak $\dot{V}O_2$. The test has been progressively shortened to the now most frequently used 6MWD and, more recently, a 2MWD test has been proposed.⁸⁻¹⁰ The 6MWD has been shown to predict survival in patients with COPD and heart failure.^{11,12} It has been shown that, in patients with stable COPD, the smallest difference in 6MWD distances that was associated with a noticeable difference in patients' subjective comparison ratings of their walking ability was 54 m.¹³ The main advantages of walking tests are simplicity, minimal resource requirements (a corridor and a supervisor), and general applicability. The main disadvantages of these tests are patient and supervisor susceptibility to motivation, their non-standardised nature, and their dependence on a single quantitative measure of distance covered. Although walking tests are capable of meeting stringent test-retest criteria, the plethora of circumstances in which testing takes place limits comparison of the magnitude of various rehabilitation treatment results from different centres. Where facilities are limited the timed walking test remains a simple method for assessing exercise capacity in individual patients provided that reproducibility of the measurement is demonstrated. The effects of learning on initial walks need to be taken into account.^{14,15} Furthermore, the lack of control of the workload in the 6MWD does not define the type of activity in any individual.

The basic function of walking is one of the five major life activities (with breathing, hearing, seeing, and speaking). Significant impairment in at least one of these would constitute a disability. For walking to be impaired and considered a disability with regard to independent ambulation, qualitative (dynamic balance sufficient for safety to prevent falls) and quantitative (velocity and distance tolerated) parameters need to be described and compared with realistic functional demands in the community. A review of the literature reports a normal walking velocity of 83 m/min.¹⁶ These velocity values are comparable to the functional velocity needed (79 m/min) to cross a traffic intersection from kerb to kerb with the crossing signal lit, and to the velocity determined for urban pedestrians. In addition, 600 m was the longest distance found necessary for a person to walk to visit a common commercial destination in the community.¹⁷ Thus distance and velocity criteria for walking both require consideration for arriving at or defining a person's level of independence regarding functional mobility. A review of the literature shows that the distances walked in 12 minutes by patients with COPD with different degrees of airflow obstruction ranged from 315 to 1215 m. Nevertheless, studies do not usually report the number of rest stops or the total rest time taken during performance of the walking tests, so it is difficult to interpret accurately the degree to which the major life activity of walking is significantly impaired for independent community ambulation.

The recent Pulmonary Rehabilitation Joint ACCP/AACVPR evidence based guidelines¹⁸ recommend that patients with COPD who undergo a programme of lower extremity exercise training consistently improve measures of exercise tolerance without evidence of adverse outcome. This recommendation is based on the results of 14 randomised controlled trials that have appeared in the peer reviewed literature. Outcome measures in these studies included timed walking tests, incremental treadmill and stationary bicycle protocols, and constant work rate treadmill or cycle studies. Effort dependent outcome measures in such studies may be influenced by the motivation of participants. Of the nine studies that employed timed walking tests, all but one reported significant increases. Although it has been recommended that timed walking

tests should be repeated up to three times at baseline to achieve reproducible results, none of these eight studies followed this procedure. In the five studies that used incremental treadmill protocols only one reported an increased peak $\dot{V}O_2$, and in the six studies in which incremental cycle ergometer protocols were used again only one reported an increase in peak $\dot{V}O_2$. Seven studies reported the responses to submaximal treadmill or cycle ergometer exercise. In three of these studies the duration of exercise tolerated was increased. The overall conclusion of these guidelines was that timed walking distances and treadmill walking protocols are dependent on effort, motivation, and strategy. Improvement in these measures can be due to the psychological effects of a training programme and cannot be taken as clear evidence of a physiological training effect.

In this issue of *Thorax* Revill *et al*¹⁹ introduce the endurance shuttle walk test (ESWT) which is a standardised, constant work load, field walking test. It is derived from and complements the incremental shuttle walk test (ISWT).²⁰ It is reasonable to view these tests as the field equivalents of the symptom limited laboratory exercise test and a constant workload laboratory examination. The ISWT measures maximal capacity (potential) while the ESWT examines the ability to use that capacity. The rationale for development is that changes in maximal capacity are unlikely to be demonstrated by therapeutic interventions with chronic lung disease. However, changes in submaximal utilisation of maximal capacity are more likely to be seen but currently cannot be assessed in a standardised and reproducible way. The work rate of the ESWT is set at 85% of maximal capacity which is obtained from a prior ISWT. This workload is apparently high, but in keeping with the recognised ability of patients with COPD to achieve high relative workloads. The chosen workload is also a compromise between intensity and the duration of the test which is open ended. This aspect may be a potential disadvantage since an endurance test may go on for too long unless the intensity is sufficiently high. The need for a prior ISWT is another disadvantage but may obviate the requirement for a second practice ESWT. According to their proposers, both types of shuttle walk tests are simple in concept and easy to conduct in practice; the subjects usually have no difficulty in understanding what is required and the end point is quite clear. Like other walking tests, the ESWT may be particularly suited to patients with chronic lung or cardiac disease in whom disability is evident. It will not be appropriate for normal subjects since the required walking speeds will be too high. The value of the ESWT lies in the sensitivity with which it can detect the effect of rehabilitation. The effect size is many times greater than a symptom limited test of capacity and is more likely to reflect real life improvements in activity. The ESWT also has the potential to form a standardised but sensitive instrument to examine the effect of other interventions on functional capacity such as drugs, oxygen, and pressure support.

However, standardised maximal and submaximal exercise tests and related endurance tests (treadmill, cycloergometer, measurement of exhaled gas, etc) already exist and it is hard to prefer these field tests when an exercise laboratory is available. The use of this proposed test involves the use of cassettes and appears to be more complex than previously used field tests. Revill *et al*¹⁹ imposed a 20 minute time limit for the faster endurance speed; with this limitation 40% of the patients reached the 20 minute limit of the 75% ESWT. Following a rehabilitation programme the mean time achieved during the ESWT was 11.2 minutes, seven of the 21 patients achieving >17 minutes. This is far longer than the duration of a 6MWD. An analysis of time spent on the test and a cost/benefit ratio in com-

parison with standardised endurance tests and other field tests should therefore be undertaken in future research.

Opinion appears to be divided between those who are interested in scientific research in pulmonary rehabilitation and those who have the practical responsibility for provision of the service. Some practitioners claim that there is a need to make rehabilitation as simple and as practical as possible in order for it to develop widespread acceptance. Their concern is that it will become a barrier to widespread uptake if the measures proposed for evaluation are too demanding technically or administratively.

Measurements of ventilatory, circulatory, and metabolic adaptations to exercise during "in the field" protocols—such as walking or stair climbing or upper limb exercise—should be encouraged, particularly in severely limited patients. Abnormalities observed "in the field" are likely to reflect more closely symptoms and limitations referred by the patients during day life activities. Laboratory tests such as cycle ergometry, however, remain the gold standard to assess maximal exercise tolerance. By using an incremental exercise protocol, as currently recommended by the ERS Task Force on Clinical Exercise Testing,²¹ it is possible to have a good indicator of factors that eventually limit exercise tolerance and to identify the work rates that the subject can tolerate easily (moderate) or sustain with difficulty (heavy). The integration of information obtained with laboratory and "in the field" protocols represents the best way to address questions relative to the patient's ability to sustain specific tasks (short bouts of heavy exercise, endurance exercise, exercise that involves different muscle groups). Walking tests have been proposed for assessing exercise tolerance in severely disabled patients. The information obtainable with the shuttle test may be considered of greater value than other un paced walking tests, particularly if ventilatory and metabolic measurements are obtained.²²

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Can manifesting heterozygotes have cystic fibrosis?

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Scientific advances and the passage of time are causing us to review what constitutes a diagnosis of cystic fibrosis (CF). Over and above those with a typical presentation and laboratory findings, there have always been patients who fall in the grey area—"does she or doesn't she have CF?" Since the discovery of the CFTR gene in 1989 and the ongoing discovery of mutations associated with CF (the mutation count now stands at over 800), genetic analysis has brought a new sophistication to the area but has not solved all the problems. A consensus conference on diagnostic criteria arranged by the North American Cystic Fibrosis Foundation has published the agreed criteria.¹ In addition to those with typical features (sweat chloride levels above 60 mmol/l and the finding of two mutations of CFTR known to be associated with the disease), the consensus statement admits that approximately 2% have an atypical phenotype with chronic sinopulmonary disease, pancreatic insufficiency, and either borderline (40–60 mmol/l) or normal (<40 mmol/l) sweat chloride concentrations. The predominance of single features may still allow a diagnosis of CF if two CF mutations, or abnormal sweat electrolytes, or abnormal ion transport across the nasal epithelium are found.^{2,3} A truly borderline diagnostic situation may apply when congenital bilateral absence of the vas deferens (CBAVD) or another form of obstructive azoospermia is the sole clinical feature with one or two CFTR mutations or the incompletely penetrant mutation (5T) in intron 8.⁴ In borderline patients the persistent finding of mucoid *Pseudomonas aeruginosa* in the sputum is highly suggestive of CF, while persistent colonisation with *Staphylococcus aureus*, *Haemophilus influenzae*, and *Burkholderia cepacia* may support a diagnosis of CF.

The interesting case described on page 278 of this issue of *Thorax* raises a number of points.⁵ The authors claim that their patient, born to consanguineous parents and with a history of having lost two infant siblings with CF, is a manifesting heterozygote—that is, is someone with only one CF mutation but showing the phenotype of the disease. While single system heterozygote effects are accepted as occurring in cases of CBAVD,⁶ disseminated bronchiectasis,⁷ allergic bronchopulmonary aspergillosis,⁸ and chronic pancreatitis,⁹ in these patients other features or abnormal tests that would allow a diagnosis of CF are absent. One could consider them as having CFTR disease but not CF. The degree of chest disease likely in the heterozygotes in whom the lung is involved would generally not approach that found in adults with CF. In this patient with a history of recurrent nasal polyps and severe sinopulmonary disease with clubbing and chronic *Staphylococcus aureus* infection a diagnostically abnormal nasal potential difference test allows a diagnosis of CF, even with a normal sweat test and normal pancreatic function.¹ The authors' claim is that, on the basis of parental consanguinity, adverse homozygosity at a number of alleles has resulted in a reduction in CFTR production as coded for by the patient's "normal" CFTR gene. Thus, for one set of intragenic polymorphisms TG₁₂T₇ from intron 8 they quote from the literature that 30% of exon 9 transcript would not mature. One would have been more impressed had the finding been homozygosity of 5T rather than 7T, for with the smaller polyT tract there is abundant evidence of underproduction of CFTR due to inefficient splicing of exon 9.⁴ No CFTR mRNA data from the patient are presented. The

authors have gone to considerable trouble to search for CFTR mutations by single stranded conformational polymorphism (SSCP) which included the promoter region and exon flanking intron regions and they also searched for deletions. One still cannot entirely exclude a functionally active intron mutation away from exon flanking region; the accepted CF mutation 3849+10 kb C>T⁹ is an example of such a mutation (incidentally giving CF with a normal sweat test, as in this patient). Similarly, denaturing gradient gel electrophoresis (DGGE) may reveal some mutations missed by SSCP. Thus, the claim by the authors of a manifesting heterozygote with CF can only remain theoretical.

Is there anything more which the authors could do to strengthen our belief in their hypothesis? What of the family history, of two infant siblings dying of severe early onset disease and necroscopic examinations having been carried out in at least one? At a clinical level the occurrence of meconium ileus and thus, by definition, pancreatic insufficiency had the child survived provides some support with the patient pancreatic sufficient. If tissue blocks are still available from the necroscopy then DNA extraction could permit a mutation search, starting first by testing for homozygosity for the single rare mutation, 1898+3 AG found in the study patient. However, it might be simpler to trace the consanguineous parents to check their mutation status. The occurrence of both mutations in the necroscopic tissue or of a CF mutation in each parent would provide strong supportive evidence for the hypothesis. On the other hand, if the fetal tissues revealed CFTR genetic identity to the case reported or a CF mutation could only be shown in one parent, this would support the existence of a second as yet undiscovered mutation in this patient. Even if only one parent were available for testing, the exercise would be worthwhile; if that person proved negative on a mutation search again an undiscovered mutation would become the more likely explanation, despite the rigour of the search by the authors for a mutation.

The hypothesis proposed by the authors could provide a possible explanation for the poor outlook of Pakistani children with CF in Britain¹¹ whose parents are often consanguineous. Homozygosity of adverse polymorphisms, either within or outside the CF gene, such as the loci described on chromosome 19 could be playing a role.¹²

The finding of recurrent nasal polyps together with significant chest disease would have caused many physicians, especially those from CF centres, to have regarded this patient as having atypical CF worthy of an active therapeutic approach. Regardless of the test results, the clinical picture remains the most important guide in this respect. An extra responsibility is devolving onto paediatricians to try to detect those patients with an atypical picture in childhood who are going to run an adverse course, as in the case described. Mutation analysis will help in this respect but full measurement of nasal potential difference^{2,3,13} should be developed to the standards of a reliable test in CF centres so that the full diagnostic armamentarium is available.

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