Editorials

Boosting the Effectiveness of Rehabilitative Exercise Training

> Good researchers design important studies. Great researchers design easy studies.

Pulmonary rehabilitation is an important component of care for the patient with chronic obstructive pulmonary disease (COPD) (1). Exercise training is an essential (probably *the* essential) component of a rehabilitative program. Having decided that exercise training is important, the question becomes, How can its effectiveness be improved? Easier asked than answered, it turns out.

Comparing training strategies requires that randomized trials be conducted in patient groups in which only the feature in question differs between training regimens. Because patients with COPD differ in many respects that may influence training responses, and because crossover trials are not generally appropriate (bringing the patient back to the pretraining state before applying the second training period is not practical), the sample size required to discern modest differences between training strategies is likely to be large. Because training interventions are lengthy (perhaps 3 sessions/wk for 8 wk), comparing training strategies is a major undertaking.

Choosing the most relevant outcomes for study on training interventions can be problematic. Tolerated exercise duration seems a reasonable outcome, but which test to choose? Furthermore, exercise duration is clearly motivation and effort dependent. Selecting non–effort-dependent outcomes might overcome this problem, but changes in variables such as lactic acidosis threshold or isotime pulmonary ventilation might be questioned as to their clinical relevance. Discerning differences in quality of life or survival between training strategies might be attempted (and might be considered important), but sample sizes would need to be very large and/or duration of observation would have to be very long.

A sterling example of how training interventions are compared is shown in the work of Pollack and his colleagues, whose studies in healthy subjects in the 1970s informs our strategies for patients with COPD (2, 3). Wondering how long training sessions had to be and how many times a week subjects had to exercise, Pollack assigned subjects to a matrix of training programs and compared their effects on peak oxygen uptake. From his studies, and the studies of others, it has been concluded that exercise sessions of at least 30 minutes' duration held at least three times a week are advisable (4). It has been assumed that these findings apply to COPD training programs; it would be prohibitively difficult to reproduce them in the COPD population. Greater inherent variability among subjects implies that very large study groups would be required to adequately make these distinctions.

Studies have started to appear in which rehabilitative training strategies are compared. An early study showed that higher intensity exercise was more effective than lower intensity exercise, even when total work per session was the same (5). In a high-intensity training program, supplemental oxygen increased tolerated training intensities and resulted in superior exercise tolerance improvement in patients with COPD without clinically appreciable exercise desaturation (6). Testosterone was shown to have an additive effect on strength improvements elicited by a strength-training program (7). The bronchodilator tiotropium had additive effects on exercise tolerance gains from a rehabilitative training program (8). It is remarkable that the study groups in these investigations were rather small. The sole exception is the bronchodilator trial (supported by pharmaceutical industry funding) in which 91 subjects were studied. The success of these studies in demonstrating significant effects despite small study groups speaks either to a large effect size or perhaps, dare I say, to a little good luck!

Not all such attempts have been successful. Interval training (alternation of high- and low-intensity periods during a training session) has not been shown to yield superior results as compared with constant intensity training in patients with COPD (9, 10). Heliox breathing has been shown to increase exercise tolerance, but has failed to improve rehabilitative training benefits (11). Proportional assist ventilation, by unloading the respiratory muscles, has the potential to improve exercise tolerance, but so far has not been shown to improve enhance exercise training (12).

The study of Collins and colleagues (13) in this issue of the *Journal* (pp. 844–852) is a worthy addition to this literature. It is posited that a slower–deeper ventilatory pattern has the potential to decrease dynamic hyperinflation and thereby improve exercise tolerance in COPD. These investigators sought to determine whether incorporating sessions in which subjects received feedback that encouraged a slower–deeper breathing pattern improved exercise tolerance gains of an endurance training program. In the key comparison, constant work rate exercise endurance gains of 16 subjects who completed endurance training were compared with 17 subjects who used ventilation feedback during their training. The difference in the increase in exercise endurance between the two groups failed to achieve the prespecified level of statistical significance. Yet the results are quite encouraging. The key comparison would have been statistically significant had only these two groups been compared (a third group that underwent ventilation feedback training alone was included). Also, the way in which the primary outcome measure was incorporated may have decreased the likelihood of demonstrating a significant result.

Oga and coworkers demonstrated that, for a given intervention, fractional exercise tolerance increases were larger when assessed by constant work rate duration than with incremental exercise testing or with the six-minute-walk test (14). However, a disadvantage of this test is that, if the intervention is very effective, a work rate that is above critical power before the intervention will be below the critical power after the intervention. In this case, the postintervention test will have a duration that is essentially infinite. This becomes more problematic if preintervention constant work rate test duration is long (i.e., it is only a little above critical power). A target constant work rate duration in the 4- to 7-minute range has been proposed (15). Because, in Collins and colleagues' study, pretraining duration averaged about 10 minutes, it seems plausible that, post-training, exercise duration may have been limited by boredom rather than physiologic factors in some subjects.

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Nonetheless, the results obtained by Collins and coworkers are quite promising. A larger trial of this strategy would seem to be a priority. Furthermore, pulmonary rehabilitation practitioners should, I think, start to consider incorporating selected strategies with the goal of boosting the effectiveness of this important therapy.

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To Be or Not to Be

Light at the End of the Tunnel of Career Counseling for Atopics

Workers in the field of asthma and allergies are well aware that occupational asthma is the leading cause of occupational respiratory disease in industrialized countries; recent estimates indicate that 10–25% of adult asthma can be attributed to work-related factors (1). Among the more than 250 substances that may cause occupational and work-aggravated asthma animal allergens, flour and grain dust as well as latex are the high-molecular-weight agents with the highest relevance (2). At the same time, up to half of the adolescent population in high-income countries is atopic, with up to 30% reporting wheezing and up to 20% suffering from allergic rhinoconjunctivitis (3). What should the physician tell these individuals when it comes to career counseling? Should an atopic teenager be a baker or a laboratory animal worker?

Current guidelines state that the "positive predictive values of screening criteria are too poorly discriminating for screening out potentially susceptible individuals" (2). While it might be reasonable to prevent those with severe or moderately severe asthma from potential employment in jobs with exposure to asthmagens (4), the positive predictive value of atopy has been reported to be as low as 23% (laboratory animal workers) to 33% (bakers) (5, 6). In this context, the article by Gautrin and colleagues (7) in this issue of the *Journal* (pp. 871–879) might help to bring some light to the end of the tunnel. They have comprehensively followed almost 400 young adults from the start of apprenticeship for an average of 8 years after the end of training. During apprenticeship, all participants were occupationally exposed to one of the high-molecular-weight agents known to be most relevant in the causation of occupational asthma (animals, flour, or latex) (2). From the end of training until follow-up, only 18% had changed their job.

The numbers lost to follow-up may give some indication about the effort Gautrin and colleagues had to put into this study: After thorough follow-up procedures, 50% of the original cohort (8) could not be studied because they had either moved or even left the country without letting the researchers know, cancelled their appointment more than once, or simply did not answer without telling why. All of us face this challenge if we want to do an epidemiologic study among young adults (9)—and the challenge is even greater in a prospective cohort study. Nevertheless, the findings by Gautrin and coworkers encourage us doing such surveys as they show that the effort is worth the trouble.

Several important public health messages can be deduced from the article (7). The majority of those who developed job-specific sensitization or rhinoconjunctivitis symptoms had already done so during training, and only a few developed sensitization or symptoms later on. The difference in the incidence of bronchial hyperresponsiveness (BHR) was not as impressive (6 per 100 person-years during training as compared with 2 per 100 person-years during follow-up). This finding is in accordance with other studies. For example, a recent population-based cohort study indicated that upper respiratory symptoms mainly develop