The authors should be commended for running this trial in such challenging times, the substance of the biological plausibility, and the willingness to provide further data on an important topic. Methodological issues from the trial, especially on analyses, preclude more conclusive findings. Although neither safety nor efficacy can be clearly concluded from a trial with such a small sample size and interpretation should be approached with appropriate skepticism, the necessity of a larger trial, perhaps on acute respiratory distress syndrome *lato sensu,* is fully justified by present data. ■

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Disconcerting and Counterintuitive Findings from a Trial of Exercise in Cystic Fibrosis

Can Exercise Make Our Patients Worse?

Physical activity is an integral component of a comprehensive treatment plan for people living with cystic fibrosis (CF) (1, 2), and exercise is universally recommended based on evidence for its positive benefits on the lung health of people with CF (3). However, the evidence supporting physical activity is of limited quality, and there is little to guide physicians on prescription of the optimal form of exercise (aerobic vs. resistance vs. high intensity) and its duration and frequency (3). In this issue of the *Journal*, the authors of the ACTIVATE-CF trial (pp. 330–339) (4) have endeavored to provide such evidence. We applaud the authors for investigating such an important component of CF care and successfully implementing this complex intervention. To date, this is the largest randomized controlled trial investigating the effects of exercise on the health of patients with CF.

ACTIVATE-CF was a randomized controlled trial that included 117 patients with CF aged 12 years or older with an FEV_1 of at least 35% who were performing less than 4 hours of physical activity per week. Participants were included from 27 centers in 8 countries across North America and Western Europe and followed over a 12-month period. The intervention group was asked to add at least 3 hours of vigorous physical activity per week (including 30 minutes of strength-building exercises and 2 hours of aerobic activity), whereas the control group was asked to continue their current activity level. The intervention group also received structured motivational interviews, exercise intensity prescriptions, activity counseling, and monitoring of their training (4).

Paradoxically and unexpectedly, after 6 months, the control group had a statistically significant 2.7% higher improvement in their FEV_1 when compared with the intervention group ($P = 0.04$). This despite the fact that the intervention group reported more vigorous physical activity levels and had a higher exercise capacity ($\dot{V}O_2$peak) at 6 and 12 months. There were no differences between the two groups in the time to first exacerbation or number of exacerbations or hospitalizations (4).

There may be several reasons for the counterintuitive results of this study. One significant limitation to this study was its inability to recruit and randomize the target sample size. The study recruited only 40% of its target population, and this meant that assessment of the secondary outcomes was hindered by a lack of power and β-error.

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Other potential issues included an insufficient difference in physical activity between the two groups. The intervention group had relatively low adherence to their exercise prescription (58% at 6 mo and 50% at 12 mo), whereas some in the control group increased their physical activity. Despite this, there was a clear difference in the objective measures of physical activity favoring the intervention arm, including improvement in exercise capacity and aerobic steps measured with a pedometer.

We know that treatment plans in CF carry a high time burden (5) and the addition of 3 hours of exercise per week to an already busy schedule full of treatments and life events may result in decreased adherence to other therapies, such as nebulized antibiotics and/or mucolytics. Finally, as there was no way to blind participants or the healthcare team to their group allocation, there may have been a contribution of the Hawthorne effect, whereby participants in the control group may have shown improved adherence to their other therapies. Of note, adherence to other CF therapies was not recorded and may have been differentially distributed between the two trial groups.

As in other studies investigating treatment effects of CFTR modulators and inhaled antibiotics in CF (6, 7), the authors chose lung function as their primary outcome, with a difference of 3% deemed significant. Although this study found that a 2.7% difference in FEV_1 between the control and intervention groups was statistically significant, such a small change is unlikely to be clinically relevant. Perhaps in light of the improved health of patients with CF, and more patients maintaining their FEV_1 in the normal range, FEV_1 may no longer be the most appropriate primary endpoint for many studies (8, 9). And although there is evidence showing that exercise can improve lung function in CF at 6 months (4), and it has been used as a substitute for chest physiotherapy (10), is there a good physiologic reason to think it will increase FEV_1? Given the significance of $\dot{V}O_2$peak as a prognostic factor for survival in CF (11, 12), cardiopulmonary exercise testing might be a better choice of outcome for studies examining the effects of exercise and exercise programs. Cardiopulmonary exercise testing has been shown to be more tightly correlated to lung structural abnormalities, dead space ventilation, and ventilation inhomogeneity compared with FEV_1 or other spirometric measures (9), and studies suggest $\dot{V}O_2$peak correlates with survival, which would be the ultimate clinical trial endpoint for any study of patients with CF.

A somewhat understated finding of this study is that the investigators were able to show a significant behavioral change in the participants with the combination of partial exercise supervision and motivational interviewing. This is a unique aspect of this study that has been minimally studied but is important, given the challenges with adherence to medications in CF (13).

Despite the counterintuitive results, we think all CF clinicians would agree that exercise is still a valuable component of a comprehensive treatment plan for people living with CF. It is incumbent upon clinicians to better understand which treatments give patients the most bang for their buck in terms of time commitment, convenience, and outcome. Of course, exercise prescriptions would ideally be personalized, based on an individual's needs (14). However, until we have a better understanding of the optimal form, duration, and frequency of exercise, and how to balance the time commitment with other components of a comprehensive CF care plan, we suggest that patients pick some form of exercise that they enjoy and that makes them feel empowered. Finally, future studies that investigate the role of exercise should consider whether primary outcomes other than FEV_1 might be more relevant. ■

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