## EDITORIAL COMMENT

# The 6-Minute Walk Test as a Primary Endpoint in Clinical Trials for Pulmonary Hypertension*

Stuart Rich, MD

*Chicago, Illinois*

> *"Golf is a good walk spoiled."*
> —Mark Twain (1)

Walking is a basic form of locomotion that involves the coordination of numerous muscles to provide forward movement while maintaining body balance and limiting energy expenditure (2). The distance and speed that a healthy individual can walk is governed by many factors, including age, sex, height (longer legs make longer strides), weight, and motivation (3). For these reasons, it is hard to know what normal walking is. Watch people walking to work in the morning on a busy street in any large city, and you will get a sense of the variety of walking styles.

In the presence of an underlying disease, the factors that limit how quickly one can walk become more complex because an impairment of any of the participating organ systems may limit the overall ability to walk a specific distance within a specific time. Although it may seem counterintuitive, several studies have shown better correlations between exercise tolerance and peripheral abnormalities than hemodynamic abnormalities in patients with cardiopulmonary disease (4). This is because changes that occur in the periphery as a consequence of the systemic effects of heart failure often become the factors limiting exercise more than the heart dysfunction that initiated the syndrome. Consequently, you may have better results improving exercise tolerance in a patient with pulmonary arterial hypertension (PAH) if you target your treatments to

increasing blood flow to exercising muscles than if you target them to resting hemodynamics.

The first randomized controlled trial (RCT) for drug registration for PAH was initiated in 1990 to evaluate the efficacy and safety of intravenous epoprostenol (5). Although the steering committee for that study suggested hemodynamics as the primary endpoint, the Food and Drug Administration insisted (correctly) that an acceptable primary endpoint needed to either be a measure of the patient's symptoms, exercise tolerance, or survival. The sponsor (Burroughs Wellcome) was unwilling to make survival the primary endpoint because it would have required a much larger trial over a much longer period of time. The sponsor was also reluctant to use functional class as the endpoint because of its subjective nature. As a result, a measure of exercise capacity was chosen. The steering committee, which was composed of cardiologists and pulmonologists, then debated which measure of exercise to use. The cardiologists recommended a treadmill test because it was a popular test for coronary artery disease (6) and it had been used successfully in heart failure trials (7). The pulmonologists preferred the 6-min walk (6MW) test, which was just being introduced as a clinical tool in patients with lung disease (8), even though there were no data about its utility in PAH. The pulmonologists major objection was that they would have to coordinate the use of the treadmill with the cardiology division in their medical centers. Because there were more pulmonologists than cardiologists on the steering committee, the quick show of hands resulted in the 6MW test as the winner.

As is typical in clinical trials, because the 6MW test was a successful primary endpoint in the first epoprostenol trial, almost every subsequent registration trial evaluating pulmonary vasodilators in PAH has also used the 6MW test as the primary endpoint. It is not, and was never intended to be, a surrogate for pulmonary hemodynamics or a measure of the underlying pulmonary vascular disease. It is a test that reflects activities of daily living and to the extent that 6MW can be improved, it is a worthwhile metric.

Meta-analyses on the RCTs for PAH have reported that in addition to improving 6MW distance, the pulmonary vasodilators also reduce short-term mortality (9). In this issue of the *Journal*, Savarese et al. (10) sought to determine what the magnitude of change in the 6MW test represented in patients with PAH. Because the individual RCTs were not powered to detect differences in clinical events, they performed a meta-analysis on 22 published trials involving more than 3,000 patients. From the hypothesis that the patients with better improvements would have better outcomes, they were surprised to find no relationship between the change in 6MW distance and mortality, lung transplantation, hospitalization for pulmonary hypertension, or initiation of pulmonary hypertension rescue therapy. It is curious that every RCT in PAH evaluating a pulmonary vasodilator drug has resulted in similar increases in 6MW

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distance, approximately 40 m, which is less than most patients report is even noticeable (11). The following seem to make little difference in the results: patient's age, severity of symptoms, hemodynamics, type of pulmonary hypertension, drug studied, or drug dosage. Remarkably, it appears that if a pulmonary vasodilator results in any increase in 6MW distance, it will be associated with improved survival over a 4-month period (9). What we do not know is why.

There is no debate that improving exercise capacity and reducing mortality are worthwhile achievements for patients with PAH. However, the current design of RCTs in this illness has been woefully lacking with respect to identifying other important endpoints that are affected, identifying biomarkers that represent how the disease may be altered, or showing that the durability of treatment effect will last beyond 4 months. More disappointing, in my opinion, is that none of the clinical trials has yet demonstrated the mechanism of action of the treatments used in studied patients with PAH. We do not know if endothelin receptors were effectively blocked or whether endothelin receptor blockade affects the pulmonary vasculature directly. Nor do we know to what extent phosphodiesterase 5 was inhibited in the lung or myocardium. Nor do we know if the long-term benefits of prostacyclin are a result of its effects on the pulmonary circulation or the myocardial circulation. It remains a possibility that pulmonary vasodilators work primarily on the peripheral circulation (12).

We have been challenged with trying to treat a progressive and fatal illness that affects a relatively small number of people with PAH and seem to be a long way from triumph. Emerging pathology studies in patients with PAH who have died while being treated with pulmonary vasodilators have failed to show that the therapies protected the pulmonary vasculature against progressive vascular changes (13,14). For that reason, the RCTs for PAH in the future have to be designed to assure that they will always succeed, even if the treatments do not. By that I mean that we need to advance our knowledge about the disease and the therapy every time we conduct a study. This will require moving away from the outdated traditional clinical trial design to more novel trial strategies. For example, by pre-specifying an analysis of specific subgroups in the RCTs, we may identify patients with better responses, which can lead to the development of more personalized treatments. Evaluating novel biomarkers that represent our current understanding of the disease pathobiology may validate them as surrogate endpoints and allow for smaller studies in the future. And measuring the response of the biological targets of the drug in patients will lead to a better understanding of how drugs may modify disease expression. It will take a coordinated effort among the physicians, pharmaceutical companies, and regulatory agencies to make this happen, and it will not be a walk in the park. But we have the knowledge and means to do it, and our patients clearly deserve it.

**Reprint requests and correspondence:** Dr. Stuart Rich, Department of Medicine, Section of Cardiology, University of Chicago, 5841 South Maryland Avenue, Suite L 08, MC 5403, Chicago, Illinois 60637. E-mail: srich@medicine.bsd.uchicago.edu.

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