The 6-Min Walk Test in Pulmonary Arterial Hypertension: Only for Bad News?

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In the present issue of *Respiration*, Huang et al. [1] show that an early *decline* in the 6-min walk distance predicts clinical worsening in pulmonary arterial hypertension (PAH). The 6-min walk distance was measured at the time of diagnosis and after 6 months of the initiation of PAH-targeted therapies in a population of 100 idiopathic PAH patients. Both the 6-min walk distance at baseline and its decline by more than 35 m after 6 months were predictive of clinical worsening defined by clinical features of right heart failure, admission to hospital for PAH-related respiratory or cardiac causes, initiation of intravenous prostanoids after failing oral therapy, and lung transplantation or death [1]. The fact that the 6-min walk distance predicts survival in pulmonary hypertension is no new finding, but it has been subject to controversy in recent years, though probably wrongly so [2].

The 6-min walk test is a test of aerobic exercise capacity which is based on the linear relationship between maximum oxygen consumption (VO_2max) and maximal averaged speed of running/walking in healthy subjects [3] or heart failure patients [4]. The correlation may not be very tight because of differences between the subjects' walking skills, mechanical efficiency or neuromuscular coordination [2]. Because VO_2 is linearly related to cardiac output, the 6-min walk distance may be considered as an indirect measure of the ability of the heart to in-

crease cardiac output (i.e. the cardiac reserve) [2, 5]. The 6-min walk distance has been repeatedly shown to be one of the strongest independent predictors of outcome in PAH, at initial evaluation as well as during follow-up after the institution of targeted therapies [6, 7]. Meta-analyses of randomized controlled trials which reported a significant improvement in the 6-min walk distance achieved by 3–4 months of targeted therapies showed that this was associated with an almost 50% decrease in mortality [8]. Hence the simple concept that a better 6-min walk test reflects less severe disease. So, what is the controversy about?

Systematic meta-analyses on the effect of PAH-specific therapies have shown that *changes* in the 6-min walk distance from baseline are not related to outcome [8–10]. A recent monocentric study also showed no relation between prognosis and *change* in the 6-min walk distance after initiation of PAH-targeted therapy [11]. In another meta-analysis on 10 trials which had recruited 2,404 patients, placebo-corrected *change* in the 6-min walk distance was related to clinical outcome but only explained 22% of the drug effect [12]. These reports casted doubt on the ability of the 6-min walk test to assess response to treatment and to be a reliable index of disease progression in pulmonary hypertension.

Why is the absolute 6-min walk distance measured at baseline and after specific PAH therapies predictive of outcome, whereas *change* following these treatments is not? Targeted therapies stabilize rather than reverse the course of the disease [8]. Changes under treatment are small in regard to the absolute distance walked. Consider a randomized controlled trial of an intervention associated with a significant increase in the 6-min walk distance from 360 ± 40 to 400 ± 40 m. The *change*, here, is hardly over the threshold of 30–40 m associated with better clinical condition in PAH. With a standard deviation of the magnitude of the increase, the effect may be not significant because the signal would be too feeble in regard to background noise. This may be the reason why meta-analyses of randomized controlled trials of targeted therapies in PAH also could not find any relevance in the *change* in cardiac output, pulmonary vascular resistance or right atrial pressure, which are also robust predictors of outcome in PAH patients at initial evaluation or during follow-up [13].

PAH is an aggressive disease of rapid evolution. Huang et al. [1] show, as Farber et al. [14] already did in a recent study derived from the US Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL), that the *decrease*, not the *increase*, in the 6-min walk distance is associated with survival. Prognosis under treatment stays poor in PAH with rapid degradation of patients undergoing progression of the disease. Accordingly, the magnitude of negative changes is proportionally greater, and so are the signal to noise ratio and the likelihood of $p < 0.05$ levels of significance.

Huang et al. [1] are to be commended for their elegant study which rehabilitates the 6-min walk test as clinically meaningful in the initial evaluation and also follow-up of PAH patients. Like any other clinical test, it has limitations and must be integrated in a clinical context. The 6-min walk test is not only for bad news.

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