Advisory Board on Toxic Substances and Worker Health

Responses to Department of Labor Questions Regarding Use of the Six Minute Walk Test

The Department of Labor has requested assistance in answering the following questions:

> 1. What are the permissible testing mythologies that a physician may use in assigning a VO_2max for application in Table 5-12 of the *Guides*?
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> 2. If the 6MWT is a valid methodology for assigning a VO_2max for application in Table 5-12, should the evidence document that the test conforms with any particular medical standard in validating the test outcome, and what are acceptable methods for calculating the VO_2max from a validated 6MWT result?

We revised the questions very slightly and provide the following responses.

1. What are the permissible testing methodologies that a physician may use in assigning a VO_2max for application in Table 5-12 of the Guides?

In the opinion of the Board, the permissible testing methodologies that a physician may use to assign a VO_2max to an individual patient for application in Table 5-12 of the Guides include two types:

a. Direct measurement of VO_2max or VO_2peak, a satisfactory estimate of VO_2max, in a pulmonary function laboratory that is experienced in performing Cardio-Pulmonary Exercise Tests (CPET) using a treadmill or cycle ergometer.

b. The 6 Minute Walk Test (6MWT) along with a regression equation to estimate VO_2peak for application in Table 5-12 of the Guides.

A. <u>CPET</u>

Direct measurement of VO_2max, or in many cases VO_2peak, is the preferred method if the following conditions are met: a) an appropriately equipped and experienced exercise testing laboratory is readily available, b) the patient meets the pre-CPET medical clearance requirements (i.e., is well enough to undergo such testing and there are no medical contraindications), c)

payment for the CPET (which is expensive) is covered. These conditions may or may not be achievable in practice.

CPET-based measurement of VO2max is considered the "gold standard" of aerobic capacity and cardiorespiratory and pulmonary fitness assessment (American Thoracic Society; American College of Chest Physicians, 2003). The direct measurement of VO_2max by CPET has also been proposed as a gold standard for measurement of impairment due to pulmonary disorders (Sood, 2014) and for that purpose, it is complementary to, but better than, at-rest pulmonary function testing including DLCO. In his review, Sood noted that resting PFTs and CPET for evaluating impairment due to occupational lung diseases often yield discrepant results. One of the classic textbooks of exercise testing, Wasserman and Whipp's Principles of Exercise Testing and Interpretation, 6th edition (Sietsema, 2021) concurs with this and provides more details, emphasizing the high frequency of indeterminate and inaccurate impairment decisions based on PFTs alone. In a study of 348 asbestos-exposed shipyard workers (Oren, 1987), the combination of history, physical examination, chest X-ray, resting electrocardiogram, and resting PFTs (including DLCO), performed poorly in predicting dichotomous work capacity status (impaired vs not impaired) using those variables plus CPET. The initial work capacity determination without CPET was indeterminate in 134/348 subjects, 39% of the total group. Among the remaining 214 subjects, it was erroneous for 22/66 (33%) of cases initially classified as impaired and for 44/148 (30%) of cases who were initially classified as not impaired. Of the indeterminate group, 49/134 (37%) were ultimately found to be impaired by CPET, and 81/134 (60%) were unimpaired. Only 5 (1.4%) of the total group remained as indeterminate impairment status after the CPET. The authors concluded that exercise testing was advantageous for accurate assessment of work capacity in impairment evaluations.

In that study, impairment was due to cardiovascular disease in 69% of those found to be impaired, though the assessment of cardiovascular disease was not confirmed by measurements of ejection fraction or other additional cardiovascular testing. This explains some of the inaccuracy of the PFTs in predicting impairment since some of the subjects with impairment due to cardiovascular disease would have had normal PFTs. It does not explain the high frequency of indeterminate impairment status based on PFTs, especially the 60% of the indeterminate group found to be unimpaired by CPET. It is important to note that the CPET, ideally a maximal effort test, would yield a VO_2peak rather than a VO_2max in most or all patients with significant lung disease since they can rarely achieve the maximal anaerobic level of exertion needed to generate a true VO_2max.

Measuring VO_2max requires achieving a plateau in oxygen intake vs work rate graph, i.e., a maximal anaerobic level of effort beyond which even with a further increase in power output the muscles cannot metabolize more oxygen and rely on anaerobic ATP-based metabolism. This is often clinically contraindicated or unachievable in patients with lung disease or other comorbidities like heart disease. In these common situations, VO_2peak measurement has been shown to be a valid index of VO_2max (Day, 2003) and is often used interchangeably (Singh, 2014).

The CPET laboratory requires personnel trained specifically in CPET, which is beyond the routine training of pulmonary function laboratory technicians. The American College of

Sports Medicine (ACSM) lists cognitive skills required of personnel supervising the test as well as medical contraindications to the CPET and conditions requiring physician supervision. The American College of Cardiology/American Heart Association recommended in 2000 that the person doing the test has performed at least 50 (Rodgers, 2000) tests in the past and continues to perform at least 25 tests per year to maintain competency. Their more recent recommendation in 2014 is a minimum of 200 tests in the past and 50 tests per year to maintain competency.(Myers, 2014). It is our impression, without hard data, that many otherwise accessible and competent PFT laboratories near where claimants live may not meet these minimal criteria, and, therefore, CPET may not be readily accessible for some claimants without requiring substantial travel and lodging arrangements. Therefore, there is a need for a more accessible but acceptably accurate second line test to estimate VO_2max for the purpose of classifying impairment in patients with lung disease.

B. Six Minute Walk Test

If CPET is not available or feasible for a given claimant, in the opinion of the Board, the Six Minute Walk Test (6MWT) is the best available method for estimating VO_2max in patients with medical impairment due to pulmonary disease, such as those applying for compensation. The 6MWT has been well studied for patients with a variety of lung disorders and is reported to have acceptable repeatability, reproducibility, safety and precision to predict mean VO_2max of a group (Singh, 2014; Sood, 2014; Ross, 2010; Cahalin, 1995). The evidence was systematically reviewed by the European Respiratory Society / American Thoracic Society (ERS/ATS) in 2014 (Singh 2014). These same Societies also published an official Technical Standard on how the 6MWT should be performed in patients with chronic respiratory disease (Holland 2014).

The ERS/ATS systematic review concluded that the 6MWT is a valid, reliable, and "robust test of functional exercise capacity in adults with chronic respiratory disease." The review also concluded that the relationship between 6MWD and either VO2peak or peak work on a progressive incremental Cardiopulmonary Exercise Testing (CPET) was moderate to strong and was consistent across patient groups with chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD). Seven out of eight studies of patients with COPD or ILD compared the VO2 peak as estimated by the 6MWT versus the CPET and found no significant differences between the two testing techniques. Review of 35 studies of people with chronic lung disease showed a consistent association between results of the 6MWT and mortality and hospitalization. 6MWT results are associated with oxygen desaturation in many patients, and several studies showed that it was more sensitive than CPET in detecting such exercise-associated desaturation. The authors conclude that "The 6MWT has historically been considered to be a test of submaximal exercise capacity, however, direct comparisons of the physiological demands of the 6MWT and CPET reveal that, in patients with chronic respiratory disease, measures of peak exercise performance are similar between the tests." (Singh, 2014, p. 1469).

The 6MWT measures peak VO_2 (VO_2peak), which provides acceptable estimates of VO_2max when VO_2max is not clinically advisable or achievable. Both the CPET and the 6MWT would generally yield a VO_2peak rather than a VO_2max in most or all of these patients since individuals with significant lung disease can rarely achieve the maximal anaerobic level of exertion needed to generate a true VO_2max on the CPET. Dale and colleagues studied the

6MWT versus the incremental cycle test in 25 people with asbestos-related pleural disease and found that 6MWD correlated with peak work rate (r=0.58, p=0.002). They concluded that "6MWT may be a useful surrogate measure of peak exercise capacity and physical activity levels in the absence of cardiopulmonary exercise testing" (Dale, 2013).

The 6MWT is a field test that is widely available, does not require specialized equipment, and can be performed safely in a typical medical office setting by most patients with pulmonary or cardiac compromise. The accuracy of estimation of VO_2max provided by the VO_2peak from the 6MWT is adequate for the determination of medical impairment. It is important to note that both the 6MWT and the CPET reflect a number of different functional domains, including respiratory, cardiac, peripheral vascular, neurologic and musculoskeletal functionality. For this reason, determination of whether impairment is due to chronic respiratory disease versus other causes requires a clinical decision by the examining physician that impairment is not due to significant disease of other organ systems.

Eaton et al tested 30 people with pulmonary fibrosis with the 6MWT and incremental exercise treadmill testing and found an excellent and highly significant ("striking") correlation (r=0.78, p<0.0001) between treadmill VO2max and results of the 6MWT (Eaton, 2005). Within-subject-reproducibility on repeat testing was far better for the 6MWT distance (r=0.98, SD/mean=0.042) than for the VO2max (r=0.88, SD/mean=.105). They concluded that the 6MWT is superior to maximal exercise testing based on the former's higher reproducibility.

The ERS/ATS Technical Standard published by Holland et al. (2014) provides standardized instructions and quality assurance procedures for 3 field walking tests in chronic respiratory diseases, the 6MWT, the Incremental Shuttle Walk Test (ISWT) and the Endurance Shuttle Walk test (ESWT). All 3 tests produce results similar to those from the CPET; however, in the view of the Board, the 6MWT is more feasible to perform in typical medical settings than the other field walking tests reviewed. The ESWT requires the ISWT as a prerequisite and the ISWT requires much more detailed monitoring and technician training during the test than the 6MWT. As discussed in the next section, a reasonable equation is available to estimate VO_2peak from the 6MWT but not from the ISWT or ESWT.

In the opinion of the Board, if the CPET is not available, affordable or suitable, the 6MWT as described in the ERS/ATS official technical standard (Holland, 2014) is a permissible testing methodology that a physician may use in assigning a VO_2max for application in Table 5-12 of the Guides.

2. If the 6MWT is a valid methodology for assigning a VO_2max for application in Table 5-12, should the evidence document that the test conforms with any particular medical standard in validating the test outcome? Also, what are acceptable methods for calculating the VO_2max from a validated 6MWT result?

In the opinion of the Board, yes, the evidence should document that the 6MWT was performed according to the ERS/ATS official Technical Standard (Holland, 2014). The authors of that standard reported that the 6MWT demonstrates good construct validity as a test of functional exercise performance, has good test-retest reliability with evidence of a learning effect

between first and second test, elicits a VO_2peak that is similar to that produced by a CPET, and has similar precautions and contraindications to the CPET. They note that the test is sensitive to variations in methodology including use of encouragement, provision of supplemental oxygen, changes in track layout and length, and use of wheeled walkers and recommended strict adherence to the recommended protocol for performing the 6MWT. They also recommended that clinically significant heart disease and musculoskeletal limitations be factored into the results of the 6MWT for assessment of respiratory status. The recommendation to perform two 6MWT because of the learning effect is for use of the test in serial assessment of change over time, for example, to assess progress during a program of pulmonary rehabilitation. On p. 1431, Holland et al state, however, that, "Where the 6MWD is used as a one-off measure to stage disease or assess risk (e.g. likelihood of hospitalization or mortality), the magnitude of the learning effect may be less important and one test may be sufficient." Performing the test twice would require sequential 6MWT tests on different days and, given the statement in the Holland review, may not be necessary for a one time use of the 6MWT to assess impairment after maximal medical improvement.

To estimate VO_2max from the 6MWT requires a statistical methodology derived from study of a large number of subjects. In the opinion of the Board, the best available method which is medically acceptable is to use the equation published by Ross et al in 2010 to estimate the VO_2peak in an individual patient. This equation is stated in the article as:

Mean Peak VO2 (ml / kg /min) = 4.948 + 0.023*Mean 6MWD (meters)

This regression equation was derived from pooled data taken from 11 studies conducted between 1996 and 2006 including a total of 1,083 patients with diverse cardiopulmonary disorders. The equation is presented to calculate the mean VO_2peak in a group from the mean 6MWD in that group. Although the structure of the equation is the same as would be used to calculate the VO_2peak for an individual from that individual's 6MWD, the authors reported that the Standard Error of the Estimate (SEE) for the individual calculation was 3.82 ml/kg/min and that is too large, i.e., would produce an estimate with relatively wide confidence intervals for an individual. Examining the plots of the regression equations for the whole data set and several of the component sub-studies, we have not, however, found evidence that using the equation for individual patients would systematically overestimate or systematically underestimate the VO_2peak values calculated from the 6MWD values for those patients. So we do not expect that the point estimates of VO_2peak produced by using this equation would be biased, just that the confidence intervals would be larger than we would like. This is the largest pooled dataset available to derive such a regression equation. The use of at-rest PFTs (including DLCO) in conjunction with history, physical, CXR and electrocardiogram without any field or laboratory exercise testing, on the other hand, would be expected to generate very substantial rates of indeterminate results as well as overestimates and underestimates of level of impairment.

The regression equation from Ross, et al, is more appropriate for this use than the equation from the 2014 ACSM 9th edition (p. 173) that was provided by DOL along with a table of values of 6MWD and VO_2. The ACSM equation, in spite of the footnote that it is best for patients with walking speeds 1.9 to 3.7 mph (equivalent to VO_2 of 8.6 to 13.7 ml kg^{-1} min^{-1}), appears to have been derived from data on very small numbers of young and athletic subjects,

and thus may be more appropriate for use in sports medicine than impairment evaluations. The equation appears unchanged in the ACSM text from the 7th edition through the current 11th edition (Liguori, 2021, Table D.1, p. 488, released this month). The convoluted cross references in the various ACSM editions 7, 9 and 11 that we had access to did not allow us to clearly identify the exact derivation of the equation they propose; however it appears to be based on just two older studies (Dill, 1965; Nagle, 1971) of 3 and 10 young (<45 years old) athletic (VO_2max 35-58 ml kg^{-1} min^{-1}) subjects. Neither of these studies performed a formal 6MWT, which had not been developed at the time of the studies, but rather correlated steady state walking with oxygen consumption. One of the 3 subjects in the first study (Dill, 1965) was a world class marathon runner, the other 2 were healthy athletes. In contrast, the Ross study combined data points from a total of 1,083 subjects with pulmonary and cardiac disease in 11 separate studies of actual 6 minute walk tests compared with CPET for each subject using cycle or treadmill ergometers to derive the equation given above. Aside from the Ross et al review, we have not identified any other quantitative review of the use of the 6MWT to estimate VO_2peak in patients with pulmonary disease, using pooled data or meta-analysis. In the opinion of the Board, if the 6MWT is used, the VO_2peak should be calculated from the 6MWD using the equation adapted from that in Ross et al:

$$VO_2\text{peak (ml per minute per kg)} = 4.948 + 0.023 * \text{6MWD (meters)}$$

Conclusion and Board Advice

In conclusion, the preferred method of assigning VO_2max to an individual claimant with pulmonary disease for application in Table 5-12 of the Guides is direct measurement of VO_2max or, more likely, VO_2peak using the CPET. If CPET is not available, the 6MWT is the next best method and is entirely acceptable. For this purpose, compared with using at-rest clinical information and PFTs alone, it is more reliable, less likely to generate indeterminate results, and more likely to accurately classify impairment. The valid methods of performing the 6MWT are those described in the ERS/ATS standard paper (Holland, 2014) and it is important to follow this standardized protocol. In addition, it is important to confirm the respiratory disease diagnosis using PFTs and other clinical information. A clinical judgment will be required to rule out or properly apportion the contribution of cardiac, musculoskeletal or neurologic causes of impairment as determined with either the CPET or 6MWT. The best valid and available method to estimate a value of VO_2max from the 6MWD for application in Table 5-12 is to use the equation derived by Ross et al provided above. Although less precise for use in individual claimants than we would like, this equation appears to be valid, meaning it does not systematically overstate or understate the level of impairment. Compared with the ACSM equation, the Ross equation is far better supported with research data when used for the purpose of estimating the VO2max from the 6MWD in people with respiratory disease.

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