Cardiopulmonary Stress Testing in Patients With Pulmonary Artery Hypertension

To the Editor: We read with interest and applaud the recent article by Taichman et al[1] that examined the limitations of subjectively determining functional class in patients with pulmonary artery hypertension (PAH). As with heart failure (HF), PAH often leads to a substantial reduction in exercise tolerance. Thus, assessing the degree to which functional capacity is limited becomes an important aspect of examination of patients with PAH. The authors appropriately state that the modified New York Heart Association (NYHA) functional classification system, adopted by the World Health Organization (WHO), is frequently used for the following: (1) to describe patients enrolled in clinical trials, (2) to gauge their treatment response to a given intervention, and (3) to guide treatment in clinical practice. Of the participating clinicians in the study by Taichman et al, 96% indicated that they "use the NYHA/WHO functional classification as part of their evaluation when selecting therapy for their patients." Because an interclass correlation coefficient failed to reach 0.70 in any analytic scenario and often fell well below this value, the poor NYHA/WHO functional class agreement among experienced clinicians for an individual patient clearly illustrates the need for a more objective, reliable, and valid measure of physical capacity in patients with PAH.

Cardiopulmonary exercise testing (CPX) is considered the criterion standard for determining both submaximal exercise tolerance (ie, ventilatory anaerobic threshold) and maximal aerobic capacity.[2] This technique is well established in patients diagnosed as having HF and provides an objective quantification of disease severity that prognostically outperforms the NYHA classification.[3-6] Moreover, several CPX variables favorably respond to numerous lifestyle, pharmacological, and surgical interventions in patients with HF.[7]

Our group has recently summarized the evidence (>20 original research investigations) that shows the potential clinical and research value of CPX in patients with PAH.[8] Both peak oxygen consumption and measures of pulmonary gas exchange efficiency ($\dot{V}E/\dot{V}CO_2$ and $PETCO_2$) are highly reflective of disease severity (ie, the degree of PAH and functional limitation), favorably respond to several pharmacological interventions, and may provide valuable prognostic insight. The use of CPX in patients with PAH allows clinicians and researchers to eliminate interrater variation of functional classification, accurately quantify the effect of the disease state on maximal and submaximal exercise tolerance, and have more confidence in attributing improvements after a given intervention to a true physiologic adaptation as opposed to poor measurement reliability (ie, NYHA/WHO class).

However, use of CPX to objectively quantify functional status requires an increased cost, additional equipment, and personnel properly trained in conducting this exercise assessment. Other scientific guideline statements provide a detailed description of the essential components required for conducting CPX in a safe, reliable, and valid manner.[9] Given the attention functional classification is afforded in both the clinical and the research settings, the importance of its accurate quantification in patients with PAH supersedes the additional cost, equipment, and personnel requirements.

Taichman et al[1] eloquently illustrated the limitations of subjective functional classification in patients with PAH. The next step is to augment the implementation of a more objective, reliable, and valid measure of functional status in this patient population. On the basis of our recent literature review,[8] there appears to be an evidence-based rationale for use of CPX in patients with PAH in both the clinical and the research settings.

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In reply: We thank Drs Arena and Lavie for their thoughtful comments regarding our study. We share their conclusion that development of more reliable means of assessing the functional status of patients with PAH would be beneficial. Doing so will likely require refinements in our tools to assess both functional capacity and functional performance.

Functional capacity measures a patient's potential for physical activity and has most often been assessed in patients with PAH by a 6-minute walk test. Although this test is simple and inexpensive, its reliability can vary substantially, "ceiling" effects have been noted, and a clinically relevant change in patients with PAH has not been defined.[1] Cardiopulmonary exercise testing also has been used to evaluate functional capacity and, as noted by Arena and Lavie, may provide a more sensitive assessment than does the 6-minute walk test. Indeed, others have also noted its potential as a prognostic indicator in patients with PAH.[2] We agree that further study is required to determine whether the additional expense and inconvenience associated with cardiopulmonary exercise testing (compared with the 6-minute walk test) will be justified by improved utility in research and patient care. Functional performance encompasses both physical and emotional aspects of a patient's day-to-day well-being and includes domains often measured in health-related quality-of-life tools. The difference between capacity and performance is a patient's "reserve."[3]

Functional classification may be viewed as the interplay among functional capacity, performance, and reserve. Therefore, measurement of functional classification requires attention to all these factors. We applaud efforts such as those described by Arena and Lavie to improve accurate measurement of individual contributing components of functional class (eg, functional capacity). We hope these and efforts focused on other aspects of functional class will together help better standardize patient evaluations, research reporting, and ultimately patient care.

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Ergo-anthropometric Assessment

To the Editor: The association between obesity and cardiovascular disease is controversial and was not recognized as a major independent cardiovascular risk factor by the American Heart Association until 1998. One explanation could be the high degree of comorbidity and limitations in the clinical assessment of obese patients.[1] A potentially better way to define obesity is by assessing body fat, in which obesity could be defined as greater than 25% body fat in men and greater than 35% in women.[2] A practical alternative could be a combined assessment of the main anthropometric measures and the degree of physical activity or fitness (ergo-anthropometric classification), which allows identification of sedentary obese (or unfit-obese) individuals, a subgroup with greater cardiovascular risk and theoretically more body fat.

Evidence supporting the superiority of ergo-anthropometric assessment[1] vs isolated anthropometric assessment includes the following:

1. The INTERHEART study found that obesity and physical activity were 2 of the 9 factors that can explain 90% of the risk of acute myocardial infarction.[3]

2. In the Nurses' Health Study (cohort of 88,393 women), combined assessment of body weight and physical activity showed that cardiovascular risk increases progressively in active-normal weight (relative risk [RR], 1), sedentary-normal weight (RR, 1.48), active-obese (RR, 2.48), and sedentary-obese (RR, 3.44) subgroups.[4]

3. In the Women's Health Study (cohort of 38,987 women), the increased risk was as follows: active-normal weight (hazard ratio [HR], 1), sedentary-normal weight (HR, 1.08), active-overweight (HR, 1.54), active-obese (HR, 1.87), sedentary-overweight (HR, 1.88) and sedentary obese women (HR, 2.53).[5]

4. In the Framingham study, moderate and high physical activity increased life expectancy similarly in men and women.[6]

5. In a cohort of 18,892 Finnish people (8928 men), combined assessment of physical activity and obesity by any of the main indices (body mass index [BMI] calculated as weight in kilograms divided by height in meters squared, waist circumference, and waist-hip ratio) improved the predictive value of cardiovascular risk, especially in men.[7]

6. In the Lipid Research Clinics Study (2506 women and 2860 men), the combined assessment of fitness and fatness stratified cardiovascular risk in equivalent subgroups: unfit-not fat (HR: men, 1.25; women, 1.30), fit-fat (HR: men, 1.44; women, 1.32), and unfit-fat (HR: men, 1.49; women, 1.57).[8]

7. In a meta-analysis, better cardiorespiratory fitness was associated with lower risk of all-cause mortality and cardiovascular events in healthy men and women.[9]

These results support the validity of the new ergo-anthropometric classification,[1] which includes assessment of waist circumference and physical fitness, in addition to BMI. It has the following advantages compared with the American National Heart, Lung, and Blood Institute classification: (1) the risk score it assigns is modified if lifestyle is sedentary or unfit; (2) it allows identification of sedentary-normal weight, active-overweight, active-obese, sedentary-overweight, and sedentary-obese subgroups who have an increased risk[4,5]; (3) it includes the waist-hip ratio in the abdominal obesity assessment because there is no consistent evidence for which of the main anthropometric measures is best[10]; and (4) it takes into consideration that underweight (BMI, <18.5 kg/m^2) is an increased risk (especially in secondary prevention).

Recent reports on the obesity paradox (overweight-obese people with established cardiovascular disease have better prognosis compared with normal-weight patients)[11] have led to doubts regarding the usefulness of anthropometric assessment and goal weight management in secondary prevention. However, unmeasured prognostic factors could be the main confounding mechanism that explains the obesity paradox.[1]

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In reply: We appreciate the opportunity to respond to the insightful comments from Drs Morales Salinas and Coca, who suggest that ergo-anthropometric assessment of obesity may be preferable to the standard body mass index (BMI) method. Along with our colleagues at Ochsner Clinic and Mayo Clinic, we have been extremely interested in the current epidemic of obesity that is profoundly affecting many aspects of health in westernized societies.[1,2]

Although BMI is the most common method to define overweightness and obesity in both epidemiological studies and major clinical trials, clearly this method does not necessarily reflect true body fatness, and BMI/body fatness may differ considerably among people of different age, sex, and race.[1,3-6] Defining obesity by other methods, including waist circumference, waist-hip ratio, and percent body fat assessment, may be more accurate.[1] In fact, researchers at Mayo Clinic recently reported that BMI performed suboptimally to predict obesity as defined by the World Health Organization criterion standard (body fat >25% in men and >35% in women)[7] in cohorts with coronary heart disease (CHD) and in the general population.[4,8] The accuracy of BMI in diagnosing obesity is limited, particularly for individuals in the intermediate BMI ranges, in men, and in the elderly. A BMI cutoff of 30 kg/m^2 or greater has good specificity but misses more than half of the people with excess body fat.

Along with the obesity epidemic, we are currently experiencing a physical inactivity epidemic in most westernized societies.[9] Although both obesity and physical inactivity/reduced cardiorespiratory fitness (CRF) increase the risk of most cardiovascular diseases (CVDs), improving CRF may markedly reduce the risk of CVD among obese people.[1,9,10] In fact, this latter point was made in a recent article that analyzed a large cohort of women with impaired fasting glucose or undiagnosed diabetes in which CRF, not BMI, predicted all-cause and CVD mortality.[11]

Researchers at both Ochsner Clinic and Mayo Clinic have also been extremely interested in the concept of the "obesity paradox."[1,12] Although clearly obesity is a major risk factor for most CVDs, numerous studies have now documented that, among cohorts with established CVD, obese cohorts surprisingly (and paradoxically) often have a better prognosis than their lean counterparts. Explaining this paradox is difficult and beyond the scope of this letter, but it has been discussed previously.[1] Certainly, selection bias may play a role in the paradox. Overweight and obese persons often develop dyslipidemia, elevated blood pressure, metabolic syndrome/diabetes, increased levels of inflammation, and structural and functional alterations of the heart and vasculature that lead to substantial CVD. In fact, without weight gain, many overweight and obese patients may not have developed CVD in the first place, whereas lean patients develop CVD from a different mechanism and have a genetic predisposition, possibly making their disease more difficult to treat effectively. Part of the explanation of the obesity paradox has been blamed on the limitations of the BMI assessment of overweightness/obesity.[12] Clearly, abdominal obesity has predicted all-cause and CVD mortality in all BMI categories in cohorts with end-stage renal disease.[13] However, researchers from Ochsner Clinic have shown that, even when obesity is defined by the World Health Organization percent body fat method, a strong obesity paradox still exists in cohorts with heart failure and CHD, ie, those with higher percent body fat have better event-free survival.[1,14,15] Despite the paradox, efforts at purposeful weight reduction have still predicted marked improvements in prognosis in cohorts with CHD.[1,15,16]

We agree with Morales Salinas and Coca that methods other than BMI may be better to detect overweightness/obesity and predict increased medical and CVD risk. Moreover, along with efforts at preventing obesity and promoting successful weight reduction, efforts to improve overall physical activity and CRF would go a long way to protect against CVD.

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