PROCEEDINGS REPORT

Is new science driving practice improvements and better patient outcomes? Applications for cardiac rehabilitation

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Abstract

Evidence from many clinical trials in recent years suggests that a large “treatment gap” exists between recommended therapies and the care that patients actually receive. This gap has been particularly apparent in the area of primary and secondary prevention of cardiovascular disease. In this article, three areas are discussed in which new scientific advances have not been adequately translated to clinical practice. These include: 1) the most appropriate measures to define the risks associated with obesity; 2) the under-diagnosis of obstructive sleep apnea and its relation to cardiovascular risk; and 3) the use and misuse of the exercise test and other functional status tools to predict health outcomes. Each is discussed in terms of how they should be quantified, their contribution to the estimation of cardiovascular disease risk, their response to interventions, and implications for cardiac rehabilitation. Clinical cardiac rehabilitation programs can benefit from routinely including these measures, both for their value in stratifying risk and for their importance in quantifying program efficacy. Physicians and allied health professionals should expand their routine medical evaluations and coronary risk factor profiling to include these measures.

The growing worldwide burden of cardiovascular disease (CVD) mandates the development and implementation of effective population-based interventions for primary and secondary prevention. Unfortunately, the treatment of coronary artery disease has evolved from simple lifestyle modification in the mid-to-late 1960s, largely focused on early ambulation, exercise training, and a prudent diet, to an array of costly and palliative coronary revascularization procedures that are not without risk and, concomitantly, fail to aggressively address the underlying causes of disease.

Aggressive risk-factor reduction and adjunctive pharmacotherapy, however, can stabilize and even reverse the otherwise inexorable progression of atherosclerotic coronary artery disease. Guidelines and recommendations for conventional coronary risk factors (e.g., hyper-cholesterolemia, hypertension, cigarette smoking, diabetes) are widely available, as are clinically relevant threshold values for their favourable

modification.¹⁻³ However, recent reports suggest that assessment of other clinical conditions/modulators, most notably, body composition, obstructive sleep apnea, and functional capacity, can provide independent and additive prognostic information to these traditional risk factors and other widely accepted markers of cardiovascular risk (e.g., left ventricular ejection fraction).

Beyond body fatness: Combining anthropometrics with other measures to estimate cardiovascular risk

Ominous global trends in diabetes

The United States and the Western world are in the midst of an obesity and diabetes epidemic that shows no sign of abatement and is expected to continue well into the 21st century. The prevalence of diagnosed diabetes among US adults is estimated to increase by 165% between 2000 and 2050, with the fastest increases occurring in older and minority subpopulations.⁴ Unless this trend is reversed, the associated escalating co-morbidities threaten to disrupt our economy and health care system.

Clinical guidelines are not followed

A treatment gap exists between published guidelines and clinical care across all diseases and disorders, not only in the US but throughout the world. Bramlage et al⁵ report that optimal blood pressure control rates are poor and range between only 19 to 54% in patients treated worldwide. Shea and colleagues⁶ cite the disparity between guidelines and their applications among internal medicine physicians for secondary prevention of CVD and application of these guidelines in clinical practice. These and other studies reveal a long history of poor adherence to clinical guidelines and the failure to provide adequate treatment is compounded by the knowledge that patients often fail to comply with physician recommendations, including prescribed medications.

Body mass index (BMI) insufficient to detect risks

BMI is the most common measure to estimate the degree of overweight or obesity. The major flaw in the use of BMI is that it does not discriminate between bone, muscle, and fat as components of the tissue mass per unit of height. Accordingly, it may serve as a misleading measure of body composition and health status. Theoretically, two individuals of identical BMI = 30 kg/m² (height @ 72 in. and weight @ 220 lbs.) could either be lean (15% body fat) or obese (30% body fat). Further, even absolute measures of fat mass or fat percent have not been shown to be predictive of health outcomes because they fail to identify the location of the fat mass.

Central obesity is the culprit and a simple algorithm is the key

Over 50 years ago a French physician, Dr. Jean Vague, noted that complications in his obese patients had more to do with **where** the fat was deposited than **how much** was deposited.⁷ Vague is credited with developing the terms “android” and “gynoid” obesity. More recently, Després and colleagues⁸ provided convincing evidence for adding waist circumference (WC) to standard screening measures because excess visceral adipose tissue is the culprit, rather than simply being overweight. Visceral obesity is closely related to the development of type 2 diabetes, primarily through the mechanisms of insulin resistance and glucose intolerance that result in hyperinsulinemia and hyperglycemia. Thus, the most valid measure of health-related body composition is the amount of fat located in the visceral region, which can be estimated by a very simple measure: WC. As the mass of visceral adipose tissue increases, there is a proportional increase in the variables comprising the metabolic syndrome, which is highly correlated to risk of CVD and is characterized by a cluster of abnormal measures: Central obesity (WC > 102 cm in men and > 88 cm in women), hypertension (SBP ≥ 130 mm Hg /DBP ≥ 85 mm Hg), dyslipidemia (triglycerides ≥ 150 mg/dL (1.7 mM/L);

and/or HDL < 40 mg/dL (1.1 mM/L) in men and < 50 mg/dL in women) and hyperglycemia (fasting blood glucose $\geq$ 110 mg/dl; 5.5 mM/L).

Clinical guidelines must be adopted

Being overweight as determined by higher BMI or skinfolds does not necessarily predict/project future health problems. It is essential to know both the composition (bone/muscle/fat) of the excess weight and the region(s) of the body where the excess weight is distributed. In 1998, the United States NHLBI published their Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report, which provided an algorithm where WC was added to the BMI to estimate health risk. Unfortunately, there is little evidence that these guidelines have been adopted by physicians in clinical practice in the United States. Recently, a new set of clinical practice guidelines has been published in Canada that also incorporates WC for the management and prevention of obesity in adults and children.⁹ It remains unclear, however, whether the medical profession in Canada will adopt these guidelines in the future.

Conclusion

If the BMI is elevated due to heavier bone and muscle, as in an athlete, and the WC is within normal range, then a higher BMI does not represent a health risk. If the BMI is elevated and the excess fat is distributed peripherally in the subcutaneous areas, especially the hips, thighs, and buttocks, while the waist/hip (WHR) ratio is within the normal range, then the individual is not considered to be at high risk for future metabolic/cardiovascular problems. However, an individual with an elevated BMI accompanied by an elevated WC and WHR is most likely at risk for the metabolic syndrome due to central obesity.

Obstructive sleep apnea (OSA) – A hidden comorbidity that impedes cardiovascular disease prevention & rehabilitation

Obstructive Sleep Apnea (OSA) is an under-diagnosed sleep disorder with substantial implications for CVD risk. In OSA, the upper airway collapses, causing repetitive inspiratory obstruction and acute effects, from hypoxemia to sympathetic activation, gasping to re-establish breathing, and arousals from sleep. Event frequency may exceed 100/hour in severe cases. Excessive Daytime Sleepiness (EDS), impaired cognitive function, and increased vehicular accidents are all direct consequences. Acute hypoxia/reoxygenation, sympathetic activation, and sleep fragmentation arising from these events mediate autonomic imbalance, inflammation, reperfusion injury, endothelial dysfunction, and metabolic dysregulation. Intermediate clinical consequences include increased risks of hypertension and Metabolic Syndrome (MetSyn),¹⁰ with later increased risks of type-2 diabetes, myocardial ischemia, cardiac dysrhythmias, congestive heart failure and cardiovascular events.¹¹

Prevalence of OSA has been estimated to be 24% and 9% for men and women,¹² respectively, but recent findings suggest that as many as 30% of primary care patients are at risk.¹³ Clinicians in CVD Prevention and Rehabilitation (P&R) should consider that 1/3 of their patients may have some degree of occult OSA. Not only may untreated OSA potentially exacerbate CVD risk factors that are targets of P&R interventions, but as the severity of OSA inevitably progresses, it independently adds to composite risk of CVD events for affected patients.

First-line treatment for most OSA patients is nightly use of nasal continuous positive airway pressure therapy (nCPAP). Alternative treatments involve use of oral appliances worn during sleep to advance the mandible and, in severe OSA, surgical interventions to reduce redundant soft tissue masses and/or advance the mandible and maxilla. With nCPAP therapy, a mask connected to a small bedside device is

TABLE 1. Risk factors for obstructive sleep apnea in patients enrolled in cardiovascular disease prevention & rehabilitation programs

Identifying High Risk Clients

Screen with modified Berlin Questionnaire: Queries topography of sleepiness, fatigue, snoring, history of HTN, plus witnessed breathing pauses or choking during sleep.¹⁵

Gender & Anthropometrics: Male gender, large neck circumference and indices of central adiposity, such as large waist or WHR, are better predictors of OSA risk than BMI.¹⁶

Treatment-Resistant Cardiometabolic Risks: OSA was acknowledged in JNC 7 as one cause of treatment-resistant HTN.¹¹ Interactively with obesity, OSA seems to potentiate both dyslipidemia and insulin resistance.¹² Thus, any patient with several components of the MetSyn may also be considered at increased risk for OSA.

Impaired Post-Exercise CV Recovery: Patients with undiagnosed OSA have delayed SBP recovery following maximal aerobic exercise testing.⁷ Elevated SBP persisting up to 5 minutes during a physically active recovery following a vigorous aerobic exercise bout may be a helpful marker of increased OSA risk.

OSA=Obstructive Sleep Apnea; EDS=Excessive Daytime Sleepiness, HTN=Hypertension; WHR=Waist-to-Hip Ratio; CV=Cardiovascular; nCPAP=nasal Continuous Positive Airway Pressure; MetSyn=Metabolic Syndrome; SBP=Systolic Blood Pressure.

worn which introduces a jet of air to reduce negative pressure generated in the throat during an obstructed inspiration. This acts as a “pneumatic splint”, pushing the soft palate and tongue forward, away from the posterior oropharyngeal wall, thereby restoring ventilation. Sleep continues and apnea-induced physiological events abate. Adherence is often problematic with nCPAP, but clearly it can reduce EDS and daytime hypertension for many patients.¹⁴

Identifying patients at risk for OSA

P&R practice guidelines, such as those of the American Association for Cardiovascular and Pulmonary Rehabilitation, are surprisingly silent on this disorder. Fortunately, simple screening tools are available for risk stratifying these patients (Table 1). We recommend the Berlin Questionnaire,¹⁵ because of its high predictive accuracy. The Berlin integrates perceptions of EDS and fatigue, overweight, history of hypertension, and witnessed snoring/breathing pauses during sleep; up to 81% of patients may thus be correctly classified with respect to OSA risk.¹⁵ In addition, male gender, central adiposity, medication-resistant hypertension, and presence of multiple MetSyn components may further point to likelihood of OSA (Table 1). Finally, we have found that blunted post-exercise systolic blood pressure recovery (SBPR), following maximal ramping cycle ergometer testing, to be espe-

cially useful in differentiating the OSA patient from other overweight adults.¹⁶ Since P&R clinicians use cycle training in their circuit exercise protocols, it would be easy to systematically monitor this SBPR, after ~10 minutes of moderate-vigorous stationary cycling. Certainly, the SBPR response may be influenced by various comorbidities and therapeutic medications. However, in addition to demonstrating this response in a controlled study,¹⁶ we have observed the same response pattern in selected P&R clinic patients with OSA who were not treatment adherent with nCPAP – even under conditions where they were receiving β -blocker therapy.

Thus, P&R clinicians may easily inventory OSA risk markers, identify high risk individuals, and encourage them to seek physician advice concerning referral to sleep specialists. Effective OSA treatment should reap substantial rewards, particularly when obesity is a fundamental contributor to the increased risks of both OSA and CVD. Obesity occurs in 70-80% of OSA patients and explains ~50% of the severity of their disorder. When the OSA is effectively treated and coupled with behavioral interventions to reduce excess fat mass, not only may the CVD risk parameters be more dramatically improved, but the severity of OSA may be markedly diminished. Attention to this disorder is an opportunity to better serve the health needs of the P&R patient with OSA.

Functional and health status measures: Applications for health outcomes in cardiovascular disease

Accurately estimating prognosis is important in the treatment of patients with CVD, both to identify patients for whom interventions might improve outcomes, and to answer patients' questions regarding the probable outcome of their illness. Estimating prognosis is commonly done by applying one of many tools designed to quantify functional or health status. These include exercise duration, cardiopulmonary exercise testing (CPX), submaximal walking tests, symptom and health status questionnaires, and various functional classifications. What is the optimal measure of functional or health status when assessing outcomes? In the current section, each of the following positions will be taken and briefly addressed: 1) exercise capacity is an underappreciated but powerful predictor of health outcomes; 2) the CPX provides the strongest prediction of health risk; and 3) submaximal functional tests and health status measures provide useful but less precise information related to health outcomes.

Exercise capacity is an underappreciated but powerful predictor of health outcomes

A considerable volume of data has recently been published demonstrating the importance of exercise capacity in predicting risk for adverse health outcomes.^{17,18} A consistent observation in these studies is that, after adjustment for age and other risk factors, exercise capacity is a stronger marker of risk for cardiovascular or all-cause mortality than established risk factors such as hypertension, smoking, hyperlipidemia, diabetes, and obesity. In addition, exercise capacity has been shown to be a more powerful predictor of risk than other exercise test variables, including ST-depression, symptoms, and hemodynamic responses. On the other hand, lower levels of fitness in these studies did not appear to be associated with subclinical disease. A number of recent studies has expressed exercise capacity in the context of survival

benefit per metabolic equivalent (MET; 1 MET = 3.5 mL O₂/kg/min) achieved; some of these studies are presented in Table 2. These observations are noteworthy in that each 1-MET increase in exercise capacity was associated with large (8 to 35%) improvements in survival. The importance of exercise capacity in the risk paradigm has historically received inadequate attention because of the tendency for clinicians to focus on the ST-segment.¹⁸

The CPX test provides the strongest prediction of health risk

Given the value of exercise capacity as a marker of health outcomes, it follows that measuring exercise capacity directly using CPX would provide even more precise information on stratifying risk. For this reason, the CPX has become an established tool in the risk paradigm among patients with chronic heart failure.¹⁹ Studies have shown that directly measured peak VO₂ more powerfully predicts risk for cardiovascular and all-cause mortality than exercise capacity estimated from treadmill or cycle ergometer work rate in both chronic heart failure and CVD. This test also has advantages in that, relative to the standard exercise test, it is more reproducible, and it provides a broader yield of information regarding cardiopulmonary function and the pathophysiology of disease.¹⁹

In recent years, there has been increasing interest in CPX responses other than peak VO₂ in estimating risk. Some of these responses are listed in Table 3. In particular, indices related to ventilatory inefficiency have supplanted peak VO₂ as the most powerful predictors of risk.²⁰ The slope of the linear relationship between ventilation and CO₂ production throughout exercise, commonly termed the *VE/VCO₂ slope*, has been the most widely studied response. The VE/VCO₂ slope has been repeatedly shown to provide information for predicting risk that is independent from, and superior to, peak VO₂.²⁰ Studies have also shown that risk is most accurately classified by the application of multivariate models which include peak VO₂, ventila-

TABLE 2. Studies expressing exercise capacity as an incremental survival benefit per MET

Author	Population	Survival Benefit Per MET	Comment
Blair et al. <i>JAMA</i> 1995	9,777 men completing 2 health evaluations 5±4 years apart	16%	Survival† in subjects who improved exercise capacity with serial testing
Dorn et al. <i>Circulation</i> 1999	315 post-MI men randomized to a 6-month exercise program	8 to 14%	Increase in exercise capacity during cardiac rehabilitation had sustained benefits up to 19 years
Goraya et al. <i>Ann Int Med</i> 2000	Elderly (514) vs. younger (2,593) subjects referred for exercise testing	14 and 18%	14 and 18% survival benefit per MET for younger and elderly subjects, respectively
Myers et al. <i>New Engl J Med</i> 2002	6,213 clinically-referred subjects	12%	Exercise capacity most powerful predictor of mortality
Gulati et al. <i>Circulation</i> 2003	5,721 asymptomatic women in the St. James Women Take Heart Project	17%	Exercise capacity an independent predictor of mortality in women, higher than previously established in men
Mora et al. <i>JAMA</i> 2003	2,994 asymptomatic women from the Lipid Research Clinics Prevalence Study	20%	Fitness-related variables more strongly associated with survival than other exercise test variables
Kavanagh et al. <i>J Am Coll Cardiol.</i> 2003	2,300 women referred for rehabilitation; followed for >6 years	35%	Peak VO ₂ increase during cardiac rehabilitation
Balady et al. <i>Circulation</i> 2004	3,043 asymptomatic men and women from the Framingham offspring study	13%	Reduction in risk of events per MET among high risk men in Framingham Offspring Study
Myers et al. <i>Am J Med</i> 2004	6,213 clinically referred subjects for exercise testing; subgroup of 842 assessed for physical activity patterns	20%	1-MET increment in exercise capacity roughly equivalent to 1,000 kcal/week adulthood activity

tory inefficiency, and clinical and hemodynamic responses.^{19,20}

Submaximal functional tests and health status measures provide useful but less precise information related to health outcomes

Because time, costs, and availability of equipment can preclude the use of the exercise test, particularly in multicentre clinical trials, submaximal walking tests, health status instruments, and symptom questionnaires are often employed in lieu of exercise testing. Advantages of these tools include their simplicity, and the

fact that they are readily accessible, inexpensive, and safe. Although it has been suggested that these instruments can be unreliable because they may provide incomplete or misleading information, some of them have also been shown to be sensitive to changes in clinical status.²¹ An underlying assumption is that these tools will yield similar information in regard to functional status. However, the extent to which the commonly-used estimates of functional status are associated with clinical status measures, quality of life (Q of L), or directly measured exercise capacity varies widely. For example, although Q of L is usually as-

TABLE 3. CPX predictors of risk other than peak VO₂

- VE/VO₂ slope
- Oxygen uptake efficiency slope (OUES)
- VO₂ kinetics
- Ventilatory threshold
- End-tidal CO₂ pressure at rest and exercise
- VO₂ in recovery
- Exercise periodic (oscillatory) breathing during exercise
- Multivariate scores – including historical, pre-test, cardiopulmonary, and hemodynamic data

sumed to be closely related to one's exercise capabilities, correlation coefficients between various Q of L domains and exercise tolerance have ranged in the order of 0.20 to 0.60.²¹ Similarly, while it might be expected that 6-minute walk performance, as a sub-maximal measure, would be closely associated with questionnaires designed to reflect symptom limitations during daily activities, correlation coefficients between 6-minute walk performance and these instruments have ranged between 0.40 to 0.70. Moreover, in the few prognostic studies that have compared the 6-minute walk test multivariately with CPX responses, the former was only weakly associated with future risk. Collectively, the implications of these studies are that: 1) each test or instrument targets a specific aspect of clinical status and, as such, they should not be considered interchangeable; and 2) none of these measures alone is a reliable surrogate for peak VO₂.

In summary, health status measures, including functional capabilities, symptoms associated with daily activities, and physical or psychological well-being, are important indices that are widely used in the assessment of interventions for patients with CVD. However, tools commonly used to assess health and functional status in CVD have only modest associations with peak VO₂ and with one-another. In practical terms, this suggests that: 1) laboratory exercise tolerance is not necessarily a good reflection of how patients perceive their capacity to undertake daily activities; and 2) CPX, non-exercise test estimates of physical function, and Q of L measures reflect different facets of health status and one should not be con-

sidered a surrogate for another. Similarly, considerable variation exists in terms of the ability of exercise and non-exercise tools to predict outcomes. The variance between indices widely used for the assessment functional and health status should be considered in the design and interpretation of clinical trials in which surrogates of exercise tolerance are used as efficacy parameters in patients with CVD.

Conclusion

Physicians and allied health professionals should expand their medical evaluations and coronary risk factor profiling to include objective data regarding their patients' central obesity, signs and/or symptoms of obstructive sleep apnea, and exercise capacity, expressed relative to age and gender norms. The above-referenced findings and other recent reports suggest that these complementary data have enormous implications for risk stratification and health care cost containment.

References

1. Pearson TA, Blair SN, Daniels SR, et al. AHA guidelines for primary prevention of cardiovascular disease and stroke: 2002 Update. *Circulation*. 2002;106:388-91.
2. Smith SC, Allen J, Blair SN, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update. *Circulation*. 2006;113:2363-72.
3. American College of Sports Medicine. ACSM's Guidelines for Exercise Testing and Prescription. 7th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2006.
4. Boyle JP, Honeycutt AA, Narayan KM et al. Projection of diabetes burden through 2050. *Diabetes Care*. 2001;24:1936-40.
5. Bramlage P, Thoenes M, Kirch W, Lenfant C. Clinical practice and recent recommendations in hypertension management--reporting a gap in a global survey of 1259 primary care physicians in 17 countries. *Curr Med Res Opin*. 2007;23:783-91.
6. Shea AM et al. DePuy V, Allen JM, Weinfurt KP. Use and perceptions of clinical practice guidelines by inter-

- nal medicine physicians. *Am J Med Qual*. 2007;22:170-6.
7. Vague J. The degree of masculine differentiation of obesities: a factor determining predisposition to diabetes, atherosclerosis, gout, and uric calculous disease. *Am J Clin Nutr*. 1956;4:20-34.
8. Després JP, Lemieux I. Abdominal obesity and metabolic syndrome. *Nature*. 2006;444:881-7.
9. Lau DCW, Douketis JD, Morrison K, et al; Obesity Canada Clinical Practice Guidelines Expert Panel. 2006 Canadian clinical practice guidelines on the management and prevention of obesity in adults and children [summary]. *CMAJ*. 2007;176 (8 Suppl):S1-13.
10. Wolk R, Somers VK. Sleep and the metabolic syndrome. *Exp Physiol* 2007;92:67-78.
11. Caples SM, Garcia-Touchard A, Somers VK. Sleep-disordered breathing and cardiovascular risk. *Sleep* 2007;30:291-303.
12. Young T, Palta M, Dempsey J, et al. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993;328:1230-5.
13. Netzer NC, Hoegel JJ, Loube D, et al. Prevalence of symptoms and risk of sleep apnea in primary care. *Chest* 2003;124:1406-14.
14. Loube DI. Technologic advances in the treatment of obstructive sleep apnea syndrome. *Chest* 1999;116:1426-33.
15. Sharma SK, Vasudev C, Sinha S, et al. Validation of the modified Berlin questionnaire to identify patients at risk for the obstructive sleep apnoea syndrome. *Indian J Med Res* 2006; 124:281-90.
16. Kaleth AS, Chittenden TW, Hawkins BJ, et al. Unique cardiopulmonary exercise test responses in overweight middle-aged adults with obstructive sleep apnea. *Sleep Med* 2007; 8:160-8.
17. Myers JN, Prakash M, Froelicher VF, et al: Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med* 2002;346:793-801.
18. Myers J. Beyond ST-segment displacement: newer diagnostic and prognostic markers from the exercise test. *Am J Med Sports* 2003;5:332-6.
19. Myers J. Applications of cardiopulmonary exercise testing in the management of cardiovascular and pulmonary disease. *Int J Sports Med* 2005;26:S49-S55.
20. Arena R, Guazzi M, Myers J. Ventilatory abnormalities during exercise in heart failure: A mini review. *Curr Resp Med Reviews* 2007;3:179-87.
21. Myers J, Zaheer N, Quaglietti S, Madhavan R, et al. Association of functional and health status measures in heart failure. *J Cardiac Fail* 2006;12:439-45.

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