MAYO CLINIC

Quantitating the Dose of Physical Activity in Secondary Prevention: Relation of Exercise Intensity to Survival

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With the enormous current and projected economic burden of cardiovascular disease (CVD), which is expected to triple in the next 20 years,[1] therapeutic strategies to improve cardiovascular outcomes and reduce cardiovascular mortality are urgently needed. Accordingly, interventions that may reduce the risk of recurrent cardiovascular events and/or the need for repeated coronary revascularization procedures, including aggressive lifestyle modification and complementary cardioprotective medications, collectively referred to as secondary prevention (Figure 1), are critically important.[3,4] Structured exercise training, increased lifestyle physical activity (PA), or both have been reported in numerous randomized controlled trials and meta-analyses to reduce the overall mortality associated with atherosclerotic coronary artery disease (CAD). One systematic review and meta-analysis of 33 PA studies, including 883,372 participants, reported risk reductions of 30% to 50% for cardiovascular mortality and 20% to 50% for all-cause mortality, with pooled risk reductions of 35% and 33%, respectively.[5] These epidemiologic analyses, when combined with adjunctive experimental and clinical investigations providing biologic plausibility,[6,7] and other relevant reports,[8-12] support a cause-and-effect relation between increased levels of PA and cardiorespiratory fitness (CRF) and reduced cardiovascular mortality, rather than merely associations between these variables.[13,14] Progressive exercise after an acute cardiovascular event and/or coronary revascularization procedure is often prescribed as an integral component of a secondary prevention program in outpatient cardiac rehabilitation. Nevertheless, delineating the optimal cardioprotective dosage, including the modulating impact of variations in the associated frequency, intensity, and duration on subsequent mortality in patients with known CAD, has remained controversial and elusive.

Recently, researchers developed a new fitness metric, using the frequency, duration, and intensity of PA, the latter estimated from continuous heart rate (HR) monitoring in the Nord-Trøndelag Health Study (HUNT) Fitness Study cohort, to clarify the relation between exercise dose and health outcomes.[15] Termed the personalized activity intelligence (PAI) score, it is derived from the cumulative 7-day modulations in activity HR over time, and gives more credit (ie, a higher PAI score) for vigorous exercise than for mild-to-moderate PA. For example, when compared with an hour-long 3-mile walk, a 30-minute strenuous bike ride earns 8 times the PAI score, 7 vs 56, respectively.[16]

According to a recently published investigation regarding the prevention of CVD in the general population, using the HUNT study database over an average follow-up of 26.2 years, men and women achieving a weekly PAI score of greater than or equal to 100 had a 20% ± 3% reduced risk of CVD mortality, compared with an inactive control group.[15] The findings indicated that this exercise dosage could potentially increase the lifespan by up to 10 years for persons younger than 50 years. In aggregate, these data, and other relevant investigations,[17,18] suggest that large daily fluctuations in HR and associated energy expenditure, which can be assessed using the PAI score, appear to confer not only increased survival but decreased health care costs as well. The study by Kieffer et al[19] published in the current issue of *Mayo Clinic Proceedings* extends these analyses to a large cohort of patients with self-reported CVD, defined as angina pectoris, previous myocardial infarction, stroke, or combinations thereof, in the HUNT database, with specific reference to selected subgroups of coronary patients, regardless of whether contemporary PA recommendations were simultaneously being met.

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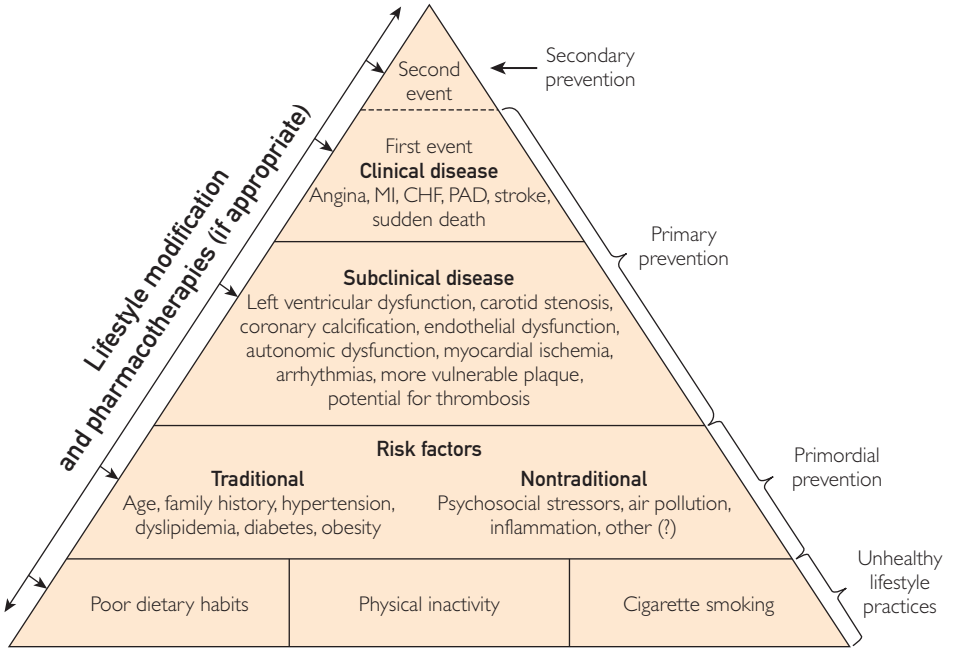

FIGURE 1. Unhealthy lifestyle habits lead to traditional risk factors, the progression of cardiovascular disease, and ultimately, adverse outcomes or clinical end points, with specific reference to the types of prevention interventions: primordial (prevention of risk factors), primary (treatment of risk factors), and secondary (prevention of recurrent cardiovascular events). Bona fide interventions include lifestyle modification, pharmacotherapies (eg, aspirin, β-adrenergic blockers, statins, angiotensin-converting enzyme inhibitors), and emergent or elective coronary revascularization, when clinically indicated. CHF = congestive heart failure; MI = myocardial infarction; PAD = peripheral arterial disease. From *Circulation*, with permission.[2]

Using a study population of 3133 patients with CVD (mean age, 67.6±10.3 years; 64% men) with complete baseline data on PAI, based on directly monitored HR fluctuations, habitual PA, and pertinent demographic and clinical characteristics, the investigators divided participants into 4 groups to further clarify the association between PAI and subsequent risk of mortality.[19] These groups included the following: those with a PAI score of 0 (inactive, reference group); those with a PAI score of 50 or less; those with a PAI score of 51 to 99; and those with a PAI score of 100 or more. Over an average follow-up of 12.5 years, after adjusting for potential confounders in a multiadjusted model, participants attaining a weekly PAI score of 100 or more had a 36% and 24% lower risk of cardiovascular and all-cause mortality, respectively, as compared with the inactive group, irrespective of whether they were following contemporary PA guidelines.[20] After adjusting for sex, those attaining a PAI score of less than 100 demonstrated an average of 4.7 years of life lost as compared with their counterparts achieving a PAI score of 100 or more. Relative to younger (≤70 years) vs older (>70 years) participants, the corresponding years of life lost were 4.3 and 3.3, respectively. In contrast to the reverse J-shaped hypothesis regarding exercise,[21] there were no further reductions or loss of survival benefit beyond obtaining a weekly PAI score of 100 or more. Moreover, achieving a PAI score of 100 or more was associated with similar mortality risk reductions for both sexes and different age groups. Subgroup analyses were, for the most part, unremarkable.

Despite several acknowledged observational study limitations (eg, cannot imply cause and effect, self-reported data, PA and PAI assessed at baseline only, no information

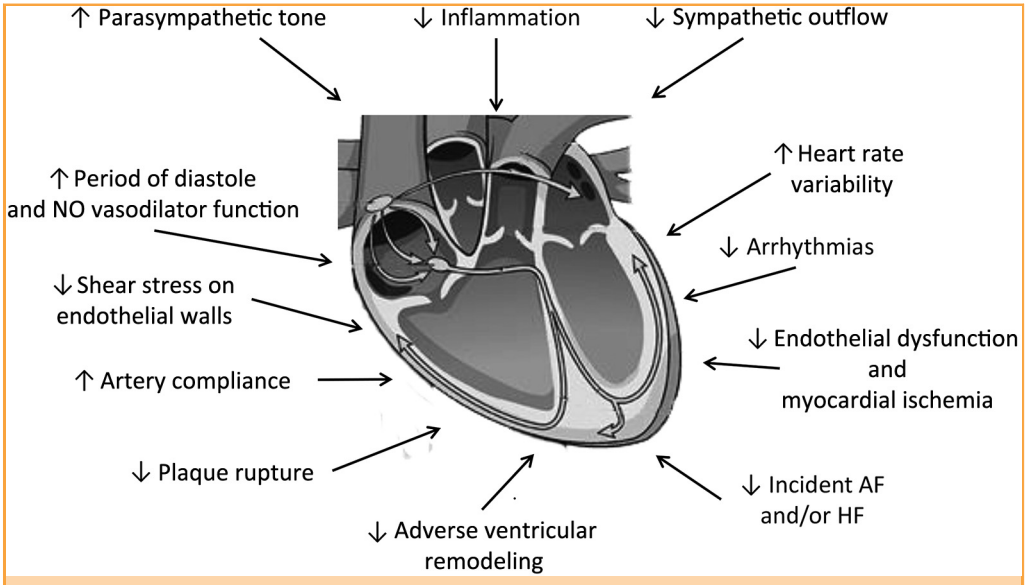

FIGURE 2. Multiple mechanisms by which vigorous-intensity exercise training may be more effective than moderate-intensity exercise at reducing cardiovascular risk. AF = atrial fibrillation; HF = heart failure; NO = nitric oxide.

on objectively measured CRF, left ventricular ejection fraction, or beta-blocker usage), and the fact that the study population was predominantly white, the present[19] and previous findings[15] suggest that the PAI metric applies to men and women with and without established CVD. The prognostic implications of higher PAI values (ie, ≥100) being associated with a reduced risk of mortality in patients with self-reported CVD are compatible with previous reports,[22,23] and may be explained, at least in part, by higher levels of CRF.[9,10,12-14]

CARDIOPROTECTIVE BENEFITS OF VIGOROUS- VS MODERATE-INTENSITY PA

Although a key attribute of the PAI method is the classification of relative exercise intensity (ie, specific to the individual), in clinical practice it is more common to use absolute intensity where vigorous is considered as 6 or more metabolic equivalents (METs; 1 MET = 3.5 mL O_2/kg/min) and moderate is 3.0 to 5.9 METs. To clarify whether vigorous- or moderate-intensity exercise has disparate effects on cardiovascular outcomes, specifically on the risk factors for and incidence of CAD, we previously reviewed relevant epidemiologic and clinical studies that evaluated the impact of varying intensity levels while controlling for total energy expenditure.[22] Risk factors included resting blood pressure, blood lipids, glucose control, CRF, and body fatness. Relevant studies consistently found a greater reduction in the risk of atherosclerotic CVD and more cardioprotective risk factor profiles for individuals engaged in vigorous, as opposed to moderate-intensity PA, including more favorable changes in diastolic blood pressure, glucose control, and CRF, whereas improvements in systolic blood pressure, blood lipids, and body fatness were comparable. Collectively, our analysis suggested that if the total energy expenditure of exercise is held constant, regular vigorous-intensity exercise appears to be superior to moderate-intensity exercise in eliciting beneficial cardiovascular adaptations.

Why vigorous-intensity exercise provides greater cardiovascular benefits than moderate-intensity PA,[24] even when the energy expenditure is equated,[22] may be due to several mechanisms. Vigorous exercise intensities are more effective than moderate intensities at increasing CRF,[25] especially for individuals with higher baseline CRF.[26] Each 1-MET increase in CRF is associated with an average

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(median) reduction of 16% (range, 8%-35%) in mortality,[27] which compares favorably with the survival benefit conferred by low-dose aspirin, statins, β-blockers, and angiotensin-converting enzyme inhibitors after acute myocardial infarction.[28] Other possible mechanisms associated with vigorous-intensity exercise training may include autonomic adaptations, specifically decreased sympathetic outflow and increased vagal tone, increased or maintained HR variability and endothelial function, decreased vascular stiffness, platelet adhesiveness, fibrinogen, and blood viscosity, increased diastolic filling time, augmenting coronary flow, and enhanced nitric oxide vasodilator function.[6,7] In addition, escalating reliance on carbohydrate use over fat metabolism evoked by increased adrenergic stimulation at higher exercise intensities may be the mechanism underlying improvements in insulin sensitivity after vigorous-intensity training in obese individuals, with and without diabetes mellitus.[29] A summary of these and other potential physiologic, antiischemic, and antiarrhythmic cardioprotective mechanisms associated with vigorous-intensity exercise is shown in Figure 2.

IMPLICATIONS FOR HEALTH CARE PROFESSIONALS

"Wicks et al[30] reported a simple method for the prediction of activity METs in patients with and without CAD, including those taking β-blockers, using the HR Index equation: METs = (6 × HR Index) − 5, where the HR Index equals the activity HR divided by the resting HR. For example, a tennis player's resting HR of 60 beats per minute (bpm) is increased to approximately 120 bpm during a match. His MET level is estimated as (6 × 120/60) − 5 = 7 METs.[31]"

The larger the increase between the resting HR and the HR during PA, the greater the estimated MET level.

Empiric experience has shown that although most cardiac patients initiate exercise-based rehabilitation programs at approximately 2 to 3 METs, uptitration of training intensities over time is often suboptimal, especially when direct early outpatient medical supervision and continuous electrocardiogram monitoring have ceased.[32] Because fitness levels are influenced by age and sex, and little additional survival benefit occurs when moving from "good" to "excellent" fitness, suggesting a plateau in reduced relative risk, the Table provides "good" fitness levels and recommended aerobic training requirements (METs) for middle-aged and older men and women.[33] In our experience, if

TABLE. "Good" Fitness Levels for Middle-Aged and Older Men and Women, and the Training Aerobic Requirements Associated With These Cardioprotective Fitness Levels[a,b,c]

	Age groups (y)				
	30-39	40-49	50-59	60-69	70-79
Men					
Good fitness	≥12.9	≥11.5	≥10.0	≥8.7	≥7.7
Training METs[d]	9.3-10.5	8.4-9.4	7.3-8.2	6.4-7.2	5.7-6.4
Women					
Good fitness	≥9.2	≥8.2	≥7.2	≥6.1	≥5.5
Training METs[d]	6.7-7.6	6.0-6.8	5.3-6.0	4.6-5.1	4.2-4.6

[a]MET = metabolic equivalent.
[b]Fitness levels are from the Fitness Registry and the Importance of Exercise National Database reference standards.[33]
[c]Table values represent "good" fitness levels, expressed as METs, for men and women, attained during peak or symptom-limited exercise testing, and the recommended aerobic training requirements (METs) to achieve these cardioprotective fitness levels. These training intensities are suggested as a goal, after 6 to 12 mo of slow progressive increases in exercise intensity, provided the patient remains asymptomatic, without adverse signs and/or symptoms, and perceived exertion (6-20 scale) remains below "15," signifying "fairly light" to "somewhat hard" work.
[d]70%-80% VO_2 reserve.

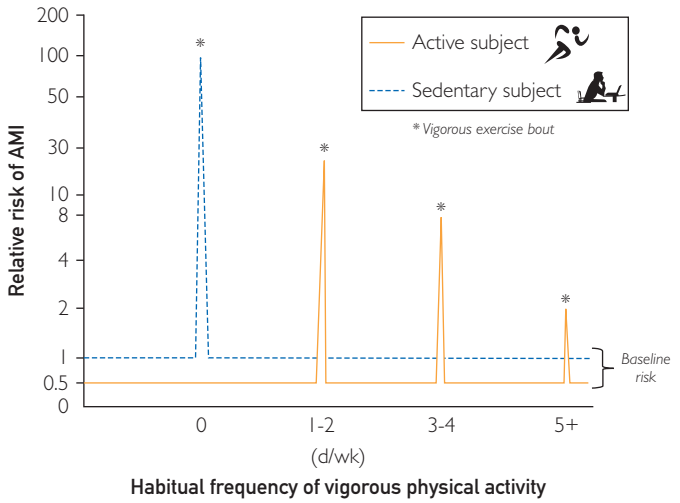

FIGURE 3. Relative risk of acute myocardial infarction during vigorous physical exertion (≥6 METs) according to activity status and exercise frequency (days/week). Baseline or overall risk for the active subject is approximately half that of their sedentary counterpart, 0.5 and 1.0, respectively. From *Circulation*, with permission.[2]

patients can progress to training levels that are 70% to 80% of VO_2 reserve, without adverse signs/symptoms or excessive ratings of perceived exertion (ie, ≥15 [hard work] on the 6-20 scale), it is likely that they can attain these fitness levels that are compatible with increased longevity. For example, "good" CRF for a 55-year-old man would be 10.0 or more METs; accordingly, a training level of 7.3 to 8.2 METs would serve as a worthwhile goal. This approach is compatible with the PAI score, where more credit is given to larger fluctuations in HR and exercise intensity, which appear to confer greater survival benefits.[15]

In our current hypokinetic society, any PA is better than none, moderate intensity is better than low intensity, and vigorous-intensity exercise appears better yet.[34] However, the risk of exertion-related acute cardiac events is highest among habitually sedentary individuals with known or occult CVD who perform unaccustomed vigorous- to high-intensity PA.[35] Accordingly, when previously sedentary patients with or without CAD initiate an exercise program, a "progressive transitional phase" should be prescribed to gradually allow improvement in their CRF, without being subjected to the large spikes in relative cardiac risk from vigorous-intensity bouts during this phase.[36] Once a vigorous exercise intensity is attained, the more frequently it is performed (ie, days/week), the lower the relative risk of each bout (Figure 3).[2] Nevertheless, because prodromal symptoms often precede exercise-related acute cardiac events,[37] patients should be strongly counseled to cease vigorous-intensity exercise at the initial onset of symptoms and seek medical evaluation before resuming training.

In summary, the study by Kieffer et al[19] provides additional evidence of the importance of regular exercise training as a key cardioprotective intervention, with an emphasis on the time efficiency and effectiveness of using vigorous-intensity exercise, when appropriate.

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