Cardiorespiratory Fitness as a Predictor of Mortality and Health Outcomes in Varied Patient Populations

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FRANKLIN: ***Cardiorespiratory Fitness as a Predictor of Mortality and Health Outcomes in Varied Patient Populations.*** *Epidemiologic studies suggest that habitually sedentary individuals, as compared with their physically active counterparts, are more likely to develop coronary artery disease. In addition, a low level of cardiorespiratory fitness appears to be an independent risk factor for all-cause and cardiovascular mortality in persons with and without heart disease and/or other co-morbid conditions (e.g., overweight/obesity, systemic hypertension, type 2 diabetes, metabolic syndrome). Recent preliminary data suggest that exercise capacity, expressed as metabolic equivalents, more accurately predicts mortality than does left ventricular ejection fraction in patients with ST-elevation myocardial infarction treated with percutaneous coronary intervention. Also, there appears to be an inverse relationship between cardiorespiratory fitness and complications after bariatric surgery among morbidly obese adults. Other provocative data support the hypothesis that exercise capacity is inversely associated with health-care costs. Accordingly, sedentary and/or unfit men and women should be encouraged to increase their daily physical activity, initiate a moderate intensity exercise program, or both. Moreover, patients should be counseled to augment their cardiorespiratory fitness by progressing to more vigorous exercise, which appears to convey greater cardioprotective benefits, provided that the higher exercise intensities can be accomplished without adverse signs or symptoms. (J HK Coll Cardiol 2006;14(Suppl 2):B13-B19)*

Fitness, health outcomes, mortality, physical activity

摘要

流行病學調查顯示對比好動的人群，習慣於安靜就坐的人們更容易得冠心病。除此之外，低水平的心肺系統適應度對於有無心臟疾患、有無伴隨疾病（如：體重超標／肥胖、高血壓、II型糖尿病、代謝綜合症）的病人，是發生各類死亡或因心血管疾病而死亡是一個獨立的危險因素。最近的初步研究表示，用代謝指數表達的運動能力比左心室射血分數，能更好地預測經冠脈介入治療的ST 段抬高的心肌梗塞病人的死亡率。同時心肺適應度和病態肥胖病人減肥手術後併發症呈現反比關係。其他更具煽動性的資料支持運動能力和健康支出存在反向關係的假設。因此，應該鼓勵慣於久坐的和／或感到不適的人增加他們每天的活動量，或者同時啓動一項中等強度的訓練計劃。此外，患者應當通過諮詢進行強度更大的運動來提高心肺系統的適應性，它能夠帶來更大的心臟保護的益處，提示高強度的運動能夠在不產生嚴重症狀下施行。

關鍵詞：適應性　健康預後　死亡率　運動能力

Introduction

Although regular physical activity and improved cardiorespiratory fitness are widely believed to be cardioprotective, Williams[1] reported that these variables had significantly different relationships to cardiovascular disease. As shown in Figure 1, the risks of coronary heart disease and cardiovascular disease decreased linearly in association with increasing percentiles of physical activity. In contrast, there was a precipitous drop in risk as one moved from the lowest to the next-lowest category for aerobic capacity. Moreover, individuals with the highest levels of aerobic capacity demonstrated more than twice the reduction in risk. Collectively, these data suggest that being unfit

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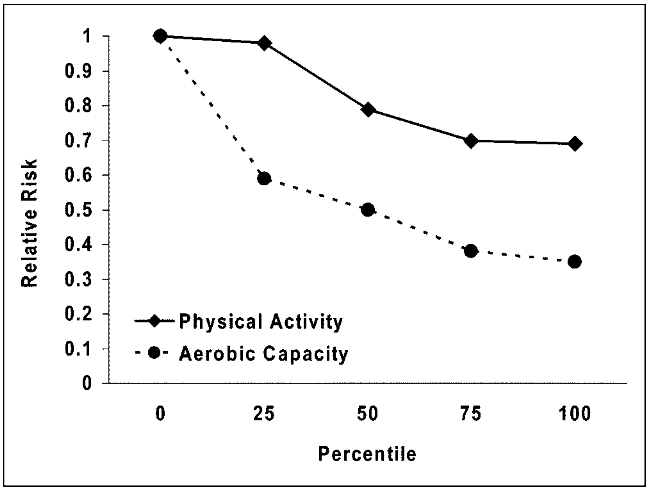

Figure 1. *The risks of coronary heart disease and cardiovascular disease decrease linearly in association with increasing percentiles of physical activity. In contrast, there is a precipitous drop in risk when comparing the lowest to the next-lowest category for aerobic capacity. Beyond this demarcation, the reductions in risk parallel those observed with increasing physical activity, but are essentially twice as great for aerobic capacity. (Adapted from reference #1)*

warrants consideration as an independent risk factor, and that a low cardiorespiratory fitness or aerobic capacity increases the risk of cardiovascular disease to a greater extent than merely being physically inactive. This article briefly summarizes the inverse relationship between physical activity and/or aerobic fitness and cardiovascular and all-cause mortality in varied patient populations, with specific reference to short-term complications after bariatric surgery, health care costs, and high risk and cardioprotective fitness levels.

Apparently Healthy Individuals

One of the landmark, epidemiologic studies to examine the relationship between cardiorespiratory fitness and all-cause mortality involved 10,224 apparently healthy men and 3,120 women who were given a medical examination and a maximal treadmill test to estimate aerobic capacity, expressed as metabolic equivalents or METs (1 MET=3.5 ml O_2/kg/min).[2] During an average follow-up period of slightly more than 8 years, 240 men and 43 women died. In general, the higher the initial level of fitness, the lower was the subsequent death rate from cancer and heart disease (Figure 2), even after statistical adjustments were made for age, coronary risk factors, and family history of heart disease. Interestingly, there appeared to be no additional decrease in mortality associated with fitness levels higher than 9 to 10 METs. Moreover, the greatest reduction in age-adjusted mortality for men occurred as one progressed from the lowest level of aerobic fitness (≤6 METs) to the next lowest level (7 METs).

Blair et al[3] examined the relative risk for all-cause mortality for several major risk factors (Table 1), including low fitness (20% least fit), in 25,341 men and 7,080 women who underwent preventive medical examinations. The average follow-up interval from

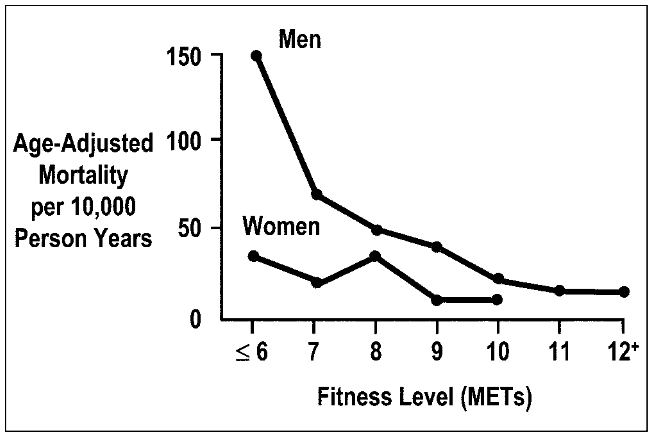

Figure 2. *Age-adjusted, all-cause mortality rates per 10,000 person-years of follow-up by cardiorespiratory fitness (METs) estimated during maximal treadmill exercise testing. (Adapted from reference #2)*

Table 1. Relative risk for all-cause mortality for selected mortality predictors, men and women, Aerobics Center Longitudinal Study, 1970 through 1989

Mortality predictor	Relative risk* Men	Women
Low fitness (20% least fit)	2.03	2.23
Current or recent cigarette smoker	1.89	2.12
Systolic hypertension (≥140 mmHg)	1.67	0.89
Cholesterol (≥240 mg/dL)	1.45	1.16
Body mass index (≥27 kg/m^2)	1.33	1.18

*Adjusted for age and examination year. Source: Blair et al.[3]

baseline examination to date of death was 8.4 years. Unfit men and women were more than twice as likely to die during the follow-up, as compared with their fit counterparts. Two provocative findings emerged: first, moderate fitness seemed to protect against the influence of the other risk factors on mortality; and second, the protective effect of fitness held for smokers and nonsmokers, as well as those with and without hypercholesterolemia or hypertension.

More recently, Myers et al[4] reported on 6,213 consecutive men referred for treadmill exercise testing, including a subset without a history of cardiovascular disease (n=2,534). Exercise capacity data were estimated on the basis of the speed and grade of the treadmill. The average follow-up was 6.2 ± 3.7 years. Normal subjects with the highest relative risk of death (4.5) had an estimated aerobic capacity ≤5.9 METs. In contrast, those with the lowest relative risk (1.0) had the highest cardiorespiratory fitness (≥13.0 METs). Similarly, Gulati et al[5] studied a cohort of 5,721 asymptomatic women (mean ± SD age at baseline was 52 ± 11 years) who were followed for approximately 8 years. After adjusting for age and traditional cardiac risk factors using the Framingham Risk Score, the risk of death doubled and tripled for those in the lowest fitness category (<5 METs) when compared with the subgroup with the highest exercise capacity (>8 METs; Figure 3).

Persons with Coronary Artery Disease

To examine the relationship between aerobic fitness and mortality in patients with documented cardiovascular disease, Vanhees et al[6] studied 527 men who were referred to an outpatient cardiac rehabilitation program. Peak oxygen uptake on a cycle ergometer was directly measured 12.9 ± 2.7 weeks after myocardial infarction (n=312) or coronary artery bypass surgery (n=215). During the average follow-up duration of 6.1 years, 33 and 20 patients died of cardiovascular and noncardiovascular causes, respectively. Those with the highest cardiovascular and all-cause mortality averaged ≤4.4 METs. In contrast, there were no deaths among patients who averaged ≥9.2 METs. Figure 4 shows the inverse relationship between peak oxygen uptake, expressed as mL/kg/min, and all-cause and cardiovascular mortality.

In the cohort of men (n=6,213) reported by Myers et al,[4] 3,679 with an abnormal exercise-test result and/or known cardiovascular disease were referred for treadmill exercise testing. Those with an exercise capacity of ≤4.9 METs had the highest relative risk of death, whereas those with a fitness level ≥10.7 METs had the lowest relative risk of death (4.1 and 1.0, respectively). For the total group, every 1-MET increase in exercise capacity conferred a 12% improvement in survival. Similarly, long-term findings from the National

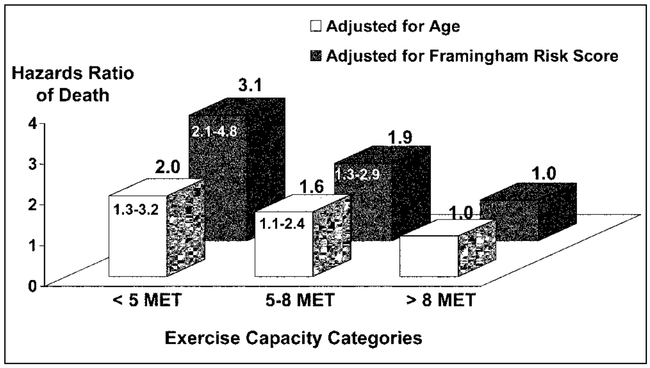

Figure 3. *Hazard ratios of all-cause death when adjusted for age and Framingham Risk Score for each of the exercise capacity categories (in METs) <5, 5 to 8, and >8. The highest exercise capacity category (>8 METs) was the reference category. Hazard ratios are listed above the bars; 95% confidence intervals are shown within the bars. (Adapted from reference #5)*

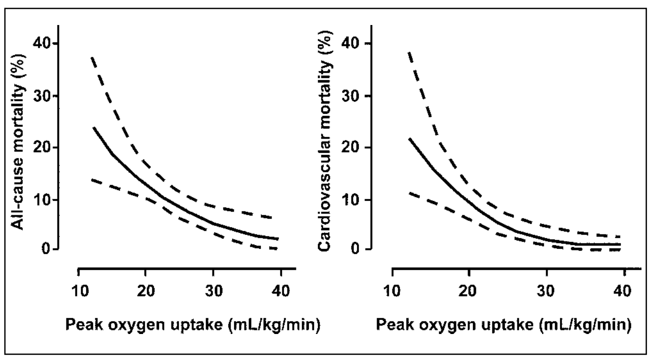

Figure 4. *Relation between peak oxygen uptake with all-cause mortality (left) and cardiovascular mortality (right) in patients with coronary artery disease. Shaded area represents 95% confidence limits. (Adapted from reference #6)*

Exercise and Heart Disease Project among post-myocardial infarction patients demonstrated that every 1-MET increase in exercise capacity after a training period was associated with a reduction in mortality from any cause that ranged from 8% to 14% over the course of 19 years of follow-up.[7]

Kavanagh and associates evaluated the predictive value of cardiopulmonary exercise testing in 12,169 men (55.0 ± 9.6 years) and 2,380 women (59.7 ± 9.5 years) with known coronary heart disease who were referred for exercise-based cardiac rehabilitation.[8,9] The men and women were followed for an average of 7.9 and 6.1 years, respectively. Directly measured peak oxygen uptake on a cycle ergometer at program entry proved to be a powerful predictor of cardiovascular and all-cause mortality. The cutoff point above which there was a marked benefit in prognosis was 13 mL/kg/min (3.7 METs) in women and 15 mL/kg/min (4.3 METs) in men. For each 1 mL/kg/min increase in exercise capacity, there was a 10% reduction of cardiac mortality in women versus 9% in men.

More recently, Dutcher et al,[10] using the well-described primary angioplasty in acute myocardial infarction (PAMI-2) database, reported that exercise capacity more accurately predicts 2- and 5-year mortality than does left ventricular ejection fraction in patients with ST-elevation myocardial infarction treated with percutaneous coronary intervention. Those who had an exercise capacity ≥4 METs had excellent long-term survival, regardless of their ejection fraction. In contrast, those with an exercise capacity <4 METs were at a substantially increased risk of mortality, which was exacerbated in the presence of left ventricular dysfunction (ejection fraction <40%). Accordingly, these data have important implications for the medical management and triaging of post-myocardial infarction patients who may benefit the most from an exercise-based cardiac rehabilitation program.

Fitness, Fatness and Mortality

Over the past decade, several studies have examined the relationship between cardiorespiratory fitness and/or habitual physical activity and mortality in normal-weight, overweight, and obese men and women. A landmark study of over 25,000 men who were followed-up for an average of 8.5 years reported that moderate-to-high fit men with a body mass index (BMI) >30 kg/m^2 had approximately one third the age-adjusted death rate of lean (<27 kg/m^2), low-fit men.[11] The age-adjusted mortality rates for these cohorts were 18.0 and 52.1 deaths per 10,000 man-years, respectively. The investigators concluded that although physical activity or exercise training may not make all people lean, it appears that an active way of life may have important health benefits, even for those who remain overweight. Similarly, Wei et al[12] demonstrated that low fitness is an independent predictor of mortality in normal-weight, overweight, and obese men; the relative risk of all-cause mortality for these respective cohorts was approximately 3, 4.5, and 5 when unfit versus fit subjects were compared.

More recently, Meyers et al[4] reported that the relative risk of death over a 6.2 ± 3.7 year follow-up for obese men (BMI ≥30 kg/m^2) achieving an estimated functional capacity of <5 METs and 5 to 8 METs was 2.35 and 1.6 as compared with the fittest subjects (those achieving >8 METs). Hu et al[13] examined whether higher levels of physical activity (i.e., time spent exercising per week) can counter the elevated risk of death associated with excess adiposity. During a 24-year follow-up of 116,564 women who, in 1976, were 30 to 55 years of age and free of known cardiovascular disease and cancer, there were 10,282 deaths. The relative risk of death of lean (BMI <25 kg/m^2)-active, lean-inactive, obese (BMI ≥30 kg/m^2)-active, and obese-inactive was 1.00, 1.55, 1.91, and 2.42, respectively. It was concluded that both increased adiposity and reduced physical activity (<3.5 hours of exercise per week) are strong and independent predictors of death.

Does Improved Fitness/Physical Activity Decrease Mortality?

It has been suggested that genetic factors, undetected preexisting disease, or other population-specific confounding variables could account, at least in part, for the inverse relationship between cardiorespiratory fitness and mortality. To clarify these issues, Blair and associates[14] followed 9,777 men

(20 to 82 years of age) who underwent two treadmill tests about 5 years apart. Approximately 5 years after the second stress test, deaths from all causes were determined. The highest death rate occurred in men who were unfit at both examinations (122.0/10,000 man-years); the lowest death rate was in men who were physically fit at both examinations (39.6/10,000 man-years). Men who improved from the unfit to the fit category between the first and second examinations had an intermediate death rate (67.7/10,000 man-years), even after adjustments were made for age, health status, and other risk factors. Other investigators have reported that each 1-MET increase in exercise capacity appears to confer an 8% to 17% reduction in mortality.[4,5,7] On the other hand, Myers et al[15] found that an approximate 1,000-kcal/week increase in activity energy expenditure, a modest amount achievable by most adults, confers a survival benefit of 20%. Collectively, these and other data[16] suggest that individuals can reduce their risk of mortality by increasing physical activity, improving cardiorespiratory fitness, or both.

Fitness and Complications After Bariatric Surgery

In recent years, bariatric surgery has become an increasingly utilized treatment option for obese patients, especially those with BMIs >40 kg/m^2. In a just-published report, McCullough et al[17] examined the relationship between measures of cardiorespiratory fitness, including peak oxygen consumption (VO_2 peak), and postoperative complications after bariatric surgery in 82 patients (75% women) whose mean BMI was 48.7 ± 7.2 (range, 36.0 to 90.0 kg/m^2). The major complication rate, defined as death, unstable angina, myocardial infarction, venous thromboembolism, renal failure, or stroke, occurred in 6 of 37 patients (16.6%) and 2 of 78 patients (2.8%) with VO_2 peak levels <4.5 METs or >4.5 METs, respectively. Thus, reduced cardiorespiratory fitness levels were associated with increased, short-term complications after bariatric surgery. It was concluded that cardiorespiratory fitness in patients with morbid obesity should be optimized prior to laparoscopic Roux-en-Y gastric bypass surgery to potentially reduce postoperative complications.

Fitness and Health-care Costs

Weiss et al[18] studied the relationship between exercise capacity, expressed as METs, and 1-year total health care costs following a standard exercise test, using 881 consecutive patients (mean age = 59 years, 95% men) who were referred for clinical reasons for treadmill testing at the Palo Alto Veteran Affairs Health Care System. In unadjusted analysis, health care costs were incrementally lower by an average of 5.4% per MET increase ($p<0.001$). Moreover, after adjusting for demographic and clinical variables, peak METs were found to be the most significant predictor of cost. The investigators concluded that the estimated METs, as calculated from peak treadmill speed, grade, and duration, is inversely associated with health-care costs.

High Risk and Cardioprotective Fitness Levels

The Aerobics Center Longitudinal Study (ACLS) represents the most comprehensive database regarding fitness and mortality. Tables 2 and 3 illustrate low, moderate, and high fitness levels (METs) for men and women, respectively, expressed as a function of age. The "low fitness" groups are at an increased mortality risk, whereas the "high fit" groups generally have an excellent prognosis, regardless of existing co-morbidities or underlying coronary disease.[19] For example, a 55-year-old man who achieves only 5 minutes on the conventional Bruce treadmill protocol, corresponding to an estimated exercise capacity of 6.6 METs, would be classified in the "low fit" category, which is associated with an increased mortality rate. An initial goal for him would be to increase his exercise capacity to the moderate category (8.9-10.9 METs) and higher (>10.9 METs), if possible, thereafter. On the other hand, a 65-year-old woman who achieves 6 minutes on the conventional Bruce treadmill protocol, would have an estimated cardiorespiratory fitness level of 7.0 METs, corresponding to the average or moderate fitness category. A goal for her would be to achieve "high" fitness or >7.5 METs, which is associated with the greatest survival benefit.

Table 2. Fitness and mortality in men, ACLS, fitness categories*

Fitness group	**Age groups (years)** 20-39	**40-49**	**50-59**	**60+**
Low	≤10.5	≤9.9	≤8.8	≤7.5
Moderate	10.6-12.7	10.0-12.1	8.9-10.9	7.6-9.7
High	>12.7	>12.1	>10.9	>9.7

*Courtesy of the Cooper Institute for Aerobics Research, Dallas, Texas, with permission.

Table values are maximal METs attained during treadmill exercise testing.

Table 3. Fitness and mortality in women, ACLS, fitness categories*

Fitness group	**Age groups (years)** 20-39	**40-49**	**50-59**	**60+**
Low	≤8.1	≤7.5	≤6.5	≤5.7
Moderate	8.2-10.5	7.6-9.5	6.6-8.3	5.7-7.5
High	>10.5	>9.5	>8.3	>7.5

*Courtesy of the Cooper Institute for Aerobics Research, Dallas, Texas, with permission.

Table values are maximal METs attained during treadmill exercise testing.

Conclusions

Exercise tolerance or, more specifically, aerobic capacity, is one of the strongest and most consistent prognostic markers in persons with and without heart disease and/or other co-morbid conditions (e.g., overweight/obesity, systemic hypertension, type 2 diabetes, metabolic syndrome).[20-23] Accordingly, physicians and allied health professionals should encourage sedentary men and women to become more physically active and/or fit by starting a moderate-intensity exercise program, increasing lifestyle physical activity, or both. When previously sedentary individuals can adopt this regimen comfortably, they should strive for the goal of more vigorous exercise, which appears to convey greater cardioprotective benefits,[24,25] provided there are no contraindications.

References

1. Williams PT. Physical fitness and activity as separate heart disease risk factors: a meta-analysis. Med Sci Sports Exerc 2001;33:754-61.
2. Blair SN, Kohl HW 3rd, Paffenbarger RS Jr, et al. Physical fitness and all-cause mortality. A prospective study of healthy men and women. JAMA 1989;262:2395-2401.
3. Blair SN, Kampert JB, Kohl HW 3rd, et al. Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. JAMA 1996; 276:205-10.
4. Myers J, Prakash M, Froelicher V, et al. Exercise capacity and mortality among men referred for exercise testing. N Engl J Med 2002;346:793-801.
5. Gulati M, Pandey DK, Arnsdorf MF, et al. Exercise capacity and the risk of death in women: the St James Women Take Heart Project. Circulation 2003;108:1554-9.
6. Vanhees L, Fagard R, Thijs L, et al. Prognostic significance of peak exercise capacity in patients with coronary artery disease. J Am Coll Cardiol 1994;23:358-63.
7. Dorn J, Naughton J, Imamura D, et al. Results of a multicenter randomized clinical trial of exercise and long-term survival in myocardial infarction patients: the National Exercise and Heart Disease Project (NEHDP). Circulation 1999;100:1764-9.
8. Kavanagh T, Mertens DJ, Hamm LF, et al. Prediction of long-term prognosis in 12 169 men referred for cardiac rehabilitation. Circulation 2002;106:666-71.
9. Kavanagh T, Mertens DJ, Hamm LF, et al. Peak oxygen intake and cardiac mortality in women referred for cardiac rehabilitation. J Am Coll Cardiol 2003;42:2139-43.
10. Dutcher JR, Kahn J, Grines C, et al. Comparison of left ventricular ejection fraction and exercise capacity as predictors of 2- and 5-year mortality following acute myocardial infarction. Am J Cardiol (In press).

11. Barlow CE, Kohl HW 3rd, Gibbons LW, et al. Physical fitness, mortality and obesity. Int J Obes Relat Metab Disord 1995;19 Suppl 4:S41-4.
12. Wei M, Kampert JB, Barlow CE, et al. Relationship between low cardiorespiratory fitness and mortality in normal-weight, overweight, and obese men. JAMA 1999;282(16):1547-53.
13. Hu FB, Willett WC, Li T, et al. Adiposity as compared with physical activity in predicting mortality among women. N Engl J Med 2004;351:2694-703.
14. Blair SN, Kohl HW 3rd, Barlow CE, et al. Changes in physical fitness and all-cause mortality. A prospective study of healthy and unhealthy men. JAMA 1995;273:1093-8.
15. Myers J, Kaykha A, George S, et al. Fitness versus physical activity patterns in predicting mortality in men. Am J Med 2004; 117:912-8.
16. Vanhees L, Fagard R, Thijs L, et al. Prognostic value of training-induced change in peak exercise capacity in patients with myocardial infarcts and patients with coronary bypass surgery. Am J Cardiol 1995;76:1014-9.
17. McCullough PA, Gallagher MJ, deJong AT, et al. Cardiorespiratory fitness and short-term complications after bariatric surgery. Chest 2006;130:517-25.
18. Weiss JP, Froelicher VF, Myers JN, et al. Health-care costs and exercise capacity. Chest 2004;126:608-13.
19. Franklin B. Fitness: the ultimate marker for risk stratification and health outcomes. Prev Cardiology (In press).
20. Laukkanen JA, Lakka TA, Rauramaa R, et al. Cardiovascular fitness as a predictor of mortality in men. Arch Intern Med 2001;161:825-31.
21. Wei M, Gibbons LW, Kampert JB, et al. Low cardiorespiratory fitness and physical inactivity as predictors of mortality in men with type 2 diabetes. Ann Intern Med 2000;132:605-11.
22. Church TS, Kampert JB, Gibbons LW, et al. Usefulness of cardiorespiratory fitness as a predictor of all-cause and cardiovascular disease mortality in men with systemic hypertension. Am J Cardiol 2001;88:651-6.
23. Katzmarzyk PT, Church TS, Blair SN. Cardiorespiratory fitness attenuates the effects of the metabolic syndrome on all-cause and cardiovascular disease mortality in men. Arch Intern Med 2004;164:1092-7.
24. Swain DP, Franklin BA. Comparison of cardioprotective benefits of vigorous versus moderate intensity aerobic exercise. Am J Cardiol 2006;97:141-7.
25. Swain DP. Moderate- or vigorous-intensity exercise: what should we prescribe? ACSM's Health & Fitness Journal 2006; 10:7-11.