Preventing Exercise-Related Cardiovascular Events:

Is a Medical Examination More Urgent for Physical Activity or Inactivity?

Running title: Franklin; Preventing Exercise-Related Cardiovascular Events

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Physical inactivity is a serious health problem worldwide, contributing to early development of obesity, diabetes, hypertension, and cardiovascular diseases (CVD). In fact, our hypokinetic lifestyle is now widely recognized among the most proximal risk factors for heart disease (Figure 1), along with poor dietary habits and cigarette smoking. To address these concerns, public health strategies commonly incorporate the goal of safely increasing physical levels in the populations of industrialized societies. Accordingly, the number of health/fitness facilities and members is expected to increase exponentially over the next decade. Current market research indicates that the fastest growing user subsets are those aged 35 to 54 years and those ≥55 years of age. These data, coupled with the recent finding that regular exercise prevents cellular senescence, have led an increasing number of adults, many of whom have known or occult chronic disease, to the conclusion that “more exercise is better.” Marathon running, for example, has increased in popularity over the last 3 decades, with participation increasing from 25,000 runners in 1976 to approximately 2 million in 2010. Thus, we have a population paradox in which there is an expansion in the number of habitually sedentary individuals paralleling a concomitant increase in those taking part in unprecedented hours of vigorous exercise.

Although numerous epidemiologic studies suggest that regular physical activity and/or moderate-to-high levels of cardiorespiratory fitness, expressed as metabolic equivalents (METs; 1 MET = 3.5 mL O₂/kg/min), may protect against the development of CVD, considerable evidence now indicates that cardiovascular events, including acute myocardial infarction (AMI), sudden cardiac death (SCD), stroke, and aortic dissection, can be triggered by vigorous physical activity. To a large extent, the major cause of exertion-related cardiovascular events is the combination of vigorous physical exertion and known or occult CVD, rather than the activity per se. Thus, efforts to identify adults at increased risk generally focus on medical history, including
symptomatology, cardiovascular risk factors and/or diagnostic testing to identify underlying CVD.

Because “do no harm” remains a cardinal tenet of the Hippocratic Oath, professional organizations have increasingly championed preparticipation self-screenings to identify ‘at risk’ individuals who should seek medical clearance, specially qualified supervisory staff/facilities, or both, prior to embarking on an exercise program. The ingenious study by Whitfield et al,6 published in the current issue of Circulation, evaluated 2 commonly recommended self-screening exercise preparticipation questionnaires, the American Heart Association (AHA)/American College of Sports Medicine (ACSM) Preparticipation Questionnaire (AAPQ) and the Physical Activity Readiness Questionnaire (PAR-Q), to clarify the utility of these screening tools in a systematic manner.

Using relevant responses from the combined 2001-2004 National Health and Nutrition Examination Survey (NHANES) database, including 6,785 adults (3,326 men and 3,459 women) aged ≥40 years, the investigators calculated the gender- and age-specific proportions of adult participants who would receive a recommendation for physician consultation before starting an exercise program based on AAPQ and PAR-Q referral criteria. Due to the depth and breadth of topics covered by the AAPQ, as well as the number of “yes” responses required to flag a respondent for referral to a physician, a relatively high rate of physician referral would have been anticipated in this population. Nevertheless, the present findings were sobering, to say the least: across all age groups ≥40 years, 95.5% (94.3–96.8%) of women and 93.5% (92.2–94.7%) of men would be advised to consult a physician before exercise. For both genders, the proportion referred increased with age and prescription medication use and decreased for those meeting national physical activity guidelines; however, no age- or activity-group exhibited a referral
proportion <75%. Compared with the results from the AAPQ, the PAR-Q, a previously validated tool, yielded lower referral proportions for the sample as a whole, 68.4% versus 94.5% for the AAPQ. The authors concluded that, in its present form, widespread use of the AAPQ would result in excessive medical referrals, potentially placing an unnecessary burden on the healthcare system, and present needless barriers to exercise adoption.6

Several study limitations were acknowledged by the investigators, including the fact that 5 items for the AAPQ did not have matching items in NHANES 2001-2004, and 3 notable deviations were present in the matrix of PAR-Q items and their NHANES equivalents. Nevertheless, these were appropriately accounted for in the data analyses. Additional limitations included insufficient information regarding how commonly the AAPQ is used (and followed), reliability of the AAPQ using NHANES data, and whether respondents would answer AAPQ items with the same accuracy as their NHANES interviews. Despite these limitations, the authors focus was to clarify, for the first time, the utility of the AAPQ, a self-screening tool that is endorsed by 2 professional organizations, the AHA and the ACSM, relative to the proportion of adults ≥40 years of age who would be advised to consult a physician before starting an exercise program. It is in this clinical sphere where delineating the limitations of the current self-screening tool, appears to be an important advance in our effort to more accurately identify individuals at risk for exertion-related cardiovascular events.

The Risk-Protection Paradox of Exercise

The incidence of cardiovascular events during very light-to-moderate intensity activities is extremely low and similar to that expected at rest. However, vigorous physical exertion, especially when it is sudden, unaccustomed, or involving high levels of anaerobic metabolism, appears to transiently increase the risk of AMI and SCD in susceptible individuals. Thompson et
al, reported 1 jogging death per year for every 7,620 joggers in Rhode Island, or approximately 1 death per 396,000 hours of jogging. This rate was 7.6 times the hourly death rate during sedentary activities. Vander et al, in a retrospective review of recreational physical activity, documented 1 nonfatal event per 1,124,200 hours and 1 fatal event per 887,526 hours of participation. Malinow et al, conducted a retrospective survey of the incidence of cardiovascular events among participants at YMCA sports centers and found an even lower rate, 1 death per 2,897,057 person-hours. Collectively, these and other recent studies suggest that the absolute risk of exercise-related SCD in the general population is very low, approximating 1/565,000 person-hours.

To clarify the risk of cardiac arrest and SCD associated with marathon and half-marathons in the US from January 1, 2000 to May 31, 2010, investigators recently reported on the incidences and outcomes of cardiovascular events among 10.9 million registered marathon runners. Of the 59 cases of cardiac arrest (mean ± SD age: 42±13 years; 51 men), 42 (71%) were fatal. The overall incidence of cardiac arrest was 1 per 184,000 participants, and that of SCD was 1 per 259,000 participants, which translates to 0.2 cardiac arrests and 0.14 SCDs per 100,000 estimated runner-hours. Sufficient information was available to suggest the cause of cardiac arrest in only 31 of the 59 cases. The most frequent clinical and autopsy findings were hypertrophic cardiomyopathy and atherosclerotic CVD, respectively.

To place the risks of exercise into perspective, it is important to consider that the absolute risk associated with each bout of exercise is extremely low, the relative risk is inversely related to the habitual level of activity, and the long-term cardioprotective effect of regular physical activity is substantial. Using data from the Onset study, the risk of AMI associated with each bout of physical activity is approximately doubled for an individual who engages in vigorous
exercise ≥5 times per week for approximately 1 hour per session. However, during or soon after
an acute bout of vigorous exercise, the risk of AMI would be approximately 50 times higher for
the least active than for the most active cohort (Figure 2).13 Because regular exercise has been
reported to reduce the overall risk of CVD,14 during the remaining 23 hours of the day, the
habitually active individual’s risk would be up to 50% lower, highlighting the clear net benefit of
exercise.

Identifying the Individual at Risk: Limitations of Exercise Testing

Because of the vagaries of the atherosclerotic process, the accuracy of predicting who will
experience an exercise-related cardiovascular event remains imperfect. Neither superior athletic
ability nor regular physical training, nor the absence of coronary risk factors, guarantees
protection against an exercise death. One important clue, however, has emerged. Individuals
who experience nonfatal or fatal cardiovascular complications during or soon after exercise often
had prodromal symptoms in the days or weeks before the event.5 Thus, physicians and allied
health professionals should promote education of exertion-related signs/symptoms in the patients
they counsel.

There is controversy regarding the value and utility of medical screening procedures,
including peak or symptom-limited exercise testing, prior to initiating exercise programs. The
ACSM suggests that neither a medical examination nor exercise testing are needed in low risk
individuals (asymptomatic, <2 risk factors) embarking on a moderate intensity (40% - < 60%
VO₂ reserve; 3 - <6 METs) or vigorous (≥60% VO₂ reserve; ≥6 METs) exercise program.15 On
the other hand, it recommends a medical examination in moderate risk individuals
(asymptomatic, ≥2 risk factors) before vigorous exercise as well as in high risk individuals
(symptomatic, or known cardiovascular, pulmonary, renal, or metabolic disease [ie, diabetes
mellitus) starting moderate or vigorous exercise regimens. Symptom-limited exercise testing is also recommended in high risk individuals initiating either a moderate or vigorous exercise program. Although the AHA/ACC have discouraged the use of exercise testing as a routine screening procedure, their guidelines recommend exercise testing before vigorous exercise in persons with known CVD. These guidelines further acknowledge the possible value of exercise testing in persons with diabetes who are contemplating an exercise program and in men >45 years and women >55 years who plan to start vigorous exercise programs. However, few data are available to substantiate these screening recommendations or that physician consultation improves exercise safety. The US Preventive Services Task Force found insufficient evidence to support the use of exercise testing before exercise programs in low risk, asymptomatic adults. Similarly, a systematic review of the evidence supporting the benefits and risks of physical activity and structured exercise in older adults argued that any policy (ie, the need for routine exercise testing) that deters a large number of people from participating in an exercise program may cause more harm than good.

Although exercise testing may be helpful in identifying exertional angina or threatening ventricular arrhythmias, a truly “positive” exercise test requires the presence of a flow-limiting coronary lesion, whereas most acute coronary events evolve from vulnerable plaque rupture at mild-to-moderate stenoses. These findings, coupled with the extremely low incidence of exercise-related cardiovascular complications in physically active asymptomatic persons, the high rate of false-positive responses in some populations, the costs of routine exercise testing and follow-up of abnormal results with expensive noninvasive/invasive studies, and the uncertainties associated with abnormal exercise electrocardiographic (ECG) responses in persons with a low
pre-test risk of coronary disease, suggest that it is impractical to use exercise testing to prevent cardiovascular events in asymptomatic exercisers.9

Exercise: Who Benefits the Most?

The risk of coronary heart disease and CVD decrease linearly in association with increasing levels of physical activity and aerobic capacity. However, there is a precipitous drop in risk when comparing the lowest to the next lowest category for aerobic capacity (cardiorespiratory fitness). Beyond this point, the reductions in risk parallel those observed with increasing physical activity but are essentially twice as great for aerobic capacity.19

Numerous epidemiologic studies have now shown that the risk for all-cause and cardiovascular mortality is markedly increased in persons unable to achieve 5 METs during peak or symptom-limited exercise testing. Other reports suggest that this fitness demarcation also renders an important indicator of heightened short-term perioperative complications, perhaps providing an index of the patient’s physiologic capacity to cope with the metabolic demands created by the trauma of major surgery.20

To clarify the question, “Should we be advising our patients to walk or run?,” researchers used a meta-analysis to evaluate the effect of physical activity with different intensities on all-cause mortality.21 The results showed a dose-response curve from sedentary subjects to those with low-to-moderate exercise intensities, with only a minor additional mortality reduction with vigorous physical activity. Collectively, these data suggest that habitually sedentary patients should be regularly counseled to initiate and maintain a walking program, so as to move them out of the least fit, least active, “high-risk” cohort (bottom 20%).22 Slow walking, even at 1 to 2 mph, approximates 2.0 to 2.5 METs and can constitute a sufficient training stimulus for this patient subset. Avoidance of the lowest category of fitness/physical activity may be among the
easiest interventions to introduce, and most likely to maintain, to favorably modify cardiovascular and other related health outcomes. Thus, from a public health perspective, the primary beneficiaries are those at the bottom of the fitness/activity continuum.

Although there appears to be an inverse relationship between peak METs and mortality, Blair et al\(^2^3\) reported an “asymptote of gain” beyond which further improvements in cardiorespiratory fitness conveyed no additional survival benefit. This asymptote was estimated to be about 9 METs for women and 10 METs for men, approximate cut points that have been substantiated by others.\(^2^4\) Blair et al\(^2^3\) concluded that the aerobic capacity values associated with the lowest death rates are attainable by most adults who engage regularly in moderate exercise (eg, a brisk walk of 30 to 60 min each day). These data, and other recent reports, suggest that patients need not become endurance athletes or, for that matter, marathon runners, to achieve the survival benefits of exercise.

**Clinical Implications**

Exercise may protect against and provoke acute cardiac events. The risk of cardiovascular complications appears to increase transiently during strenuous physical exertion compared with the risk at other times. This seems to be particularly true among inactive persons with occult or known CVD who engage in unaccustomed vigorous physical activity. However, the net effect of regular physical activity is a *lower overall risk* of mortality from CVD.

Considering the cardiovascular benefits and risks of exercise, the former outweighs the latter for the vast majority of adults, especially if one adopts a light-to-moderate exercise intensity. Asymptomatic men and women who plan to be physically active at these levels do not need to consult with a physician or health care provider unless they have specific medical questions. Although exercise testing is recommended in coronary patients initiating either a
moderate or vigorous exercise program,\textsuperscript{15,16} our empiric experience and previous studies have demonstrated the safety and effectiveness of early outpatient medically supervised exercise rehabilitation in selected cardiac patients, using adjunctive intensity modulators (eg, rating of perceived and/or the patient’s resting heart rate plus 20-30 beats/min) and continuous ECG monitoring, without a preliminary exercise test.\textsuperscript{25}

In conclusion, numerous epidemiologic studies have shown that low-fit individuals are approximately 2 to 5 times more likely to die during follow-up as compared with their more fit counterparts, regardless of the presence or absence of coronary disease and/or associated risk factors (eg, overweight/obesity, diabetes).\textsuperscript{22} Perhaps Per-Olof Åstrand, MD, summed it up best when he stated: “As a general rule, moderate activity is less harmful to health than inactivity. You could also put it this way: a medical evaluation is more urgent for those who plan to remain inactive than for those who intend to get into good physical shape.”

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**References:**


**Figure Legends:**

**Figure 1.** The evolutionary CVD pyramid. Unhealthy lifestyle practices lead to risk factors, the progression of CVD, and, ultimately, adverse outcomes or clinical endpoints. The first-line strategy to prevent initial or recurrent cardiac events is to favorably modify unhealthy lifestyle habits, including cigarette smoking and poor dietary habits and physical inactivity. In 2000,
these habits were responsible for an estimated 435,000 and 365,000 deaths, respectively. CVD signifies cardiovascular disease; MI indicates myocardial infarction; CHF, congestive heart failure; and PAD, peripheral arterial disease. Adapted for Mozaffarian D, et al and Franklin BA and Cushman M.

**Figure 2.** Relative risk of acute myocardial infarction at rest and during vigorous physical exertion (≥6 METs) in sedentary and physically active individuals, with specific reference to the habitual frequency of vigorous exertion (days/week). Adapted from Mittleman MA, et al.
Figure 1

Clinical disease
- Angina, MI, CHF, PAD, stroke, sudden death

Subclinical disease
- Left ventricular dysfunction, carotid stenosis, coronary calcification, endothelial dysfunction, autonomic dysfunction, myocardial ischemia, arrhythmias, more vulnerable plaque, potential for thrombosis

Risk factors
- Traditional: Age, family history, hypertension, dyslipidemia, diabetes, obesity
- Nontraditional: Psychosocial stressors, air pollution, inflammation, other (?)

Unhealthy lifestyle practices

Poor Dietary Habits | Physical Inactivity | Cigarette Smoking

Lifestyle Modification (if appropriate)

Secondary prevention

Primary prevention

Primordial prevention
Figure 2

Graph showing the relative risk of AMI for active and sedentary subjects. The x-axis represents the habitual frequency of vigorous physical activity in days per week, ranging from 0 to 5+. The y-axis represents the relative risk of AMI, ranging from 0 to 200.

- **Active Subject**: Blue line with asterisks indicating a higher relative risk for certain days per week.
- **Sedentary Subject**: Red dashed line with a lower relative risk for all days per week.

*Vigorous exercise bout*

**Baseline Risk**
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