

# Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



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*Circulation* 2005;112:771-776; originally published online Jul 5, 2005;

DOI: 10.1161/CIRCULATIONAHA.105.166543

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214

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## Exercise Testing in Asymptomatic Adults

### A Statement for Professionals From the American Heart Association Council on Clinical Cardiology, Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention

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**Abstract**—Along with coronary artery calcium scanning, ankle-brachial index measurement, and carotid artery ultrasound, exercise electrocardiography has been proposed as a screening tool for asymptomatic subjects thought to be at intermediate risk for developing clinical coronary disease. A wealth of data indicate that exercise testing can be used to assess and refine prognosis, particularly when emphasis is placed on nonelectrocardiographic measures such as exercise capacity, chronotropic response, heart rate recovery, and ventricular ectopy. Nevertheless, randomized trial data on the clinical value of screening exercise testing are absent; that is, it is not known whether a strategy of routine screening exercise testing in selected subjects reduces the risk for premature mortality or major cardiac morbidity. The writing group believes that a large-scale randomized trial of such a strategy should be performed. (*Circulation*. 2005; 112:771-776.)

**Key Words:** AHA Scientific Statements ■ exercise test ■ imaging ■ coronary disease ■ heart rate

Coronary artery disease is the leading cause of death in the developed world<sup>1</sup> and may become the leading cause of death in the entire world<sup>2</sup>; however, many patients with prognostically significant coronary artery disease are asymptomatic.<sup>1</sup> Consequently, there has been enormous interest during the past 10 to 15 years in developing screening techniques by which important but asymptomatic disease can be diagnosed at an early stage.<sup>3</sup>

Screening for serious chronic diseases is a complex topic. Outside the realm of large randomized trials, it is arguably impossible to definitively determine whether screening has any real benefit.<sup>4</sup> Although it makes intuitive sense to diagnose disease at a stage before it causes major clinical events, screening may actually be harmful.<sup>5</sup> Thus, new screening techniques that have become available during the past 5 to 10 years have engendered a great deal of controversy, given the absence of randomized trial data demonstrating that the use of screening results in improved clinical outcomes.<sup>6,7</sup> The purpose of this scientific statement is to consider, on the basis of existing evidence, what role—if any—exercise testing plays in risk stratification in asymptomatic subjects.

We pay particular attention to the value of non-ST-segment measures, including functional capacity, chronotropic response, heart rate (HR) recovery, and ventricular ectopy.

#### Appropriateness of Exercise Testing in Asymptomatic Subjects

The exercise test historically has been considered a potential useful modality for coronary disease screening.<sup>3</sup> It is simple to administer, inexpensive, and safe. Nonetheless, the relatively poor accuracy of exercise electrocardiography for diagnosing hemodynamically significant coronary disease, even in symptomatic subjects,<sup>8</sup> has led to recommendations against the use of exercise testing as a screening tool, as is well documented by a recent report from the US Preventive Services Task Force.<sup>9</sup> These recommendations have been largely based on an extensive body of literature documenting the limitations of the ST segment for diagnosing coronary disease in asymptomatic subjects. Indeed, when used as a purely diagnostic test, it must be realized that false-positive tests are common among asymptomatic adults, especially

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This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on April 22, 2005. A single reprint is available by calling 800-242-8721 (US only) or writing the American Heart Association, Public Information, 7272 Greenville Ave, Dallas, TX 75231-4596. Ask for reprint No. 71-0326. To purchase additional reprints: up to 999 copies, call 800-611-6083 (US only) or fax 413-665-2671; 1000 or more copies, call 410-528-4121, fax 410-528-4264, or e-mail kgray@lww.com. To make photocopies for personal or educational use, call the Copyright Clearance Center, 978-750-8400.

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DOI: 10.1161/CIRCULATIONAHA.105.166543

women, and may lead to unnecessary testing, overtreatment, and labeling.<sup>9</sup> Still, reports on modifications to ST-segment interpretation,<sup>10</sup> consideration of non-ST-segment measures,<sup>11</sup> and evaluation of the exercise test as a prognostic<sup>11</sup> rather than a diagnostic test suggest that the prognostic value of the screening exercise test may have been underestimated.

Because no large-scale randomized trials have been performed to demonstrate a clinical benefit, recent American Heart Association/American College of Cardiology and US Preventive Services Task Force guidelines<sup>9</sup> have discouraged the use of exercise testing as a screening modality for routine use (Class III; see Table 1).<sup>12–14</sup> The guidelines acknowledge the possible value of exercise testing in people with diabetes who are contemplating an exercise program (Class IIa); in patients with multiple risk factors for whom risk-reduction therapy needs to be guided (Class IIb); and in men >45 years old and women >55 years old who plan to start vigorous exercise programs, are involved in high-risk occupations, and are at risk for coronary disease because of other diseases such as peripheral atherosclerosis and chronic renal failure (all Class IIb).<sup>12</sup> The US Preventive Services Task Force found that screening exercise testing had no value in low-risk subjects and found insufficient evidence for or against testing in subjects at higher risk.<sup>9</sup>

A recent article by Greenland et al in *Circulation*<sup>3</sup> recommended that all subjects undergo global risk assessment based on office tools such as the Framingham Risk Score.<sup>15,16</sup> Subjects who are deemed to be at low risk for a cardiac event (<0.6% per year) need not undergo any further evaluation, whereas those deemed to be at high risk for such events (>2% per year) deserve to undergo aggressive treatment. There may be a role for screening in patients who are at intermediate risk of events (0.6% to 2.0% per year). Greenland et al<sup>3</sup> noted 4 tests that may be of value: exercise electrocardiography, carotid ultrasound, coronary artery calcium scanning, and ankle-brachial indexes.<sup>3</sup>

### Relation of Predictive Value to Test Performance Characteristics

Recommendations against screening asymptomatic subjects by exercise testing are rooted in a well-established bayesian argument. Given the limited sensitivity and imperfect specificity of standard ST-segment depression criteria for the identification of coronary artery disease, the positive predictive value of the exercise test in populations with a low prevalence of disease must be low.<sup>12</sup> Even if positive predictive value is improved by altering test criteria to improve specificity, sensitivity must be reduced, meaning that a number of people with significant disease will be missed.

### Limitations of ST-Segment Depression in Asymptomatic Subjects

The diagnostic value of ST-segment depression in asymptomatic subjects is difficult to assess because few asymptomatic patients undergo coronary angiography. There are conflicting data with regard to its value for prognosis.<sup>8,17–20</sup> This may be due to the inability of standard ST-segment changes to reflect the workload and degree of myocardial ischemia present.<sup>10,21–23</sup> Another important issue that affects the predictive

value of the exercise test is verification bias.<sup>8,24</sup> Nearly all of the studies in the literature have been based on cohorts of patients in whom the decision to perform the “gold standard” test of coronary angiography was at least in part related to the result of the exercise ECG. Because physicians believe that the exercise ECG may be of value in identifying patients with and without coronary disease, populations of patients undergoing coronary angiography are heavily influenced by a selection bias. This selection bias, or more correctly “verification bias,” results in an inflated sensitivity and deflated specificity.<sup>8,24</sup> One large recent study of a clinical population in which patients underwent coronary angiography largely independent of the exercise ECG result showed that a poor sensitivity of <50% was associated with a relatively high specificity of >80%.<sup>8</sup> Because one can assume that asymptomatic patients are even less likely to be referred to coronary angiography than are symptomatic patients unless marked ST-segment depression is noted (eg, at a very low workload in the absence of left ventricular hypertrophy), the problem with workup bias may be even worse.

Another problem with ST-segment interpretation is the use of coronary angiography as the gold standard. Coronary angiography represents an incomplete look at disease within the coronary vessel wall,<sup>25</sup> which does not enable clinicians to determine the physiological response of a diseased endothelium under conditions of stress.<sup>26</sup> Thus, a noninvasive test that demonstrates stress-induced ischemia may well be associated with a coronary angiogram showing only mild disease.<sup>27</sup> If stress leads to a paradoxical vasoconstriction, then ischemia may be present, despite a benign-appearing resting coronary angiogram.<sup>27</sup> Thus, the apparent lack of correlation between a noninvasive exercise test finding and coronary angiogram findings may be caused more by the inadequacy of the coronary angiogram to best describe severity of atherosclerosis than by an inherent problem in the exercise test itself.

### Consideration of the Exercise Test as a Screening Tool

Consideration of the exercise test as a screening tool in asymptomatic patients involves several issues for investigation and development. First, improvement in the sensitivity and specificity of electrocardiographic criteria for the identification of ischemia may improve the positive and negative predictive values of the test in populations with any prevalence of disease. Second, recognition of the predictive value of nonelectrocardiographic exercise test findings for coronary and noncoronary events suggests that these may be incorporated productively into combined exercise test scores. Third, risk as a predictive end point of the exercise test requires distinguishing between the identification of any disease and the identification of prognostically important disease.

### Nonelectrocardiographic Advances in Stress Testing Applied to Asymptomatic Subjects

During the past 10 to 15 years, a number of discoveries have extended our understanding of exercise testing as a prognostic tool.<sup>11</sup> The assessment of prognosis was previously difficult because of the need for assembling and electronically

**TABLE 1. ACC/AHA Classifications**

**Class I:** Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective.

**Class II:** Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.

**IIa:** Weight of evidence/opinion is in favor of usefulness/efficacy.

**IIb:** Usefulness/efficacy is less well established by evidence/opinion.

**Class III:** Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful.

characterizing large cohorts and the need for long periods of follow-up. Several groups have successfully overcome this hurdle and have shown that measures other than those directly related to myocardial ischemia are strong predictors of mortality in cardiovascular risk (see Table 2 for descriptions and abnormal values).<sup>19,20,28–32</sup> Furthermore, although exercise testing is traditionally thought of as an appropriate modality for evaluating patients with symptoms suggestive of coronary disease,<sup>12–14</sup> clinical and population-based analyses have suggested that once risk factors and exercise test findings are accounted for, the presence or absence of symptoms is a relatively weak predictor of risk.<sup>33,34</sup>

### Functional Capacity

Perhaps the most important marker of risk yielded by the exercise test is the measure of functional capacity. Ideally, functional capacity would be measured via either direct measurement of oxygen consumption or work production as a function of oxygen consumption. In routine exercise testing, however, this is simply not practical. Despite the discrepancies between estimated exercise capacity and directly measured exercise capacity, estimations of exercise capacity have been shown to be reasonably accurate<sup>35</sup> and predictive of risk.<sup>36</sup>

Several population-based studies have looked at the ability of functional capacity to predict mortality and cardiovascular risk in asymptomatic subjects.<sup>28–31,37–39</sup> Essentially without exception, all have shown that impaired functional capacity predicts increased risk over and above demographics and standard risk factors. In fact, in a large Cooper Institute study involving >20 000 men, it was noted that the apparent

association between obesity and increased risk could be explained almost entirely by the association of obesity with impaired functional capacity.<sup>28</sup> Recently, 2 large population-based studies (St James Heart Study and Lipid Research Clinics Prevalence Study) found that exercise capacity is a strong predictor of risk in women.<sup>30,31</sup> Both population-based (Framingham Heart Study) and clinically based (Cleveland Clinic Preventive Medicine Program) studies of asymptomatic subjects have shown that exercise capacity predicts risk over and above the Framingham<sup>40</sup> and European<sup>20</sup> Risk Scores.

## HR and Rhythm

### Chronotropic Incompetence

Chronotropic incompetence refers to the inability of HR to increase appropriately during exercise. There are a number of ways of assessing chronotropic incompetence, including simply noting the peak HR, noting what proportion of age-predicted maximal HR is achieved, and noting what proportion of HR reserve is used at peak exercise (see Table for details). All 3 of these measures have been shown to be of prognostic value,<sup>11,32</sup> although a large recent report in a clinical population suggests that the proportion of HR reserve used at peak exercise is most strongly correlated with risk.<sup>41</sup>

The increase in HR during exercise is a reflection of decreased parasympathetic tone and increased sympathetic tone. An important study of normal subjects and subjects with varying degrees of heart failure demonstrated that chronotropic incompetence in cardiac disease may be caused by decreased sympathetic sensitivity of the sinus node.<sup>42</sup> As with functional capacity, population-based studies of asymptomatic subjects have demonstrated that people with an impaired chronotropic response have higher rates of death and higher rates of major cardiac events,<sup>32</sup> even after accounting for the Framingham Risk Score.<sup>40</sup>

### HR Recovery

HR recovery refers to the decline of HR after exercise. In normal asymptomatic subjects and in athletes, there is a rapid fall in HR during the first 30 seconds after exercise, followed by a shallower fall.<sup>43</sup> This rapid decline in HR can be prevented by administration of atropine, which suggests that

**TABLE 2. Nonelectrocardiographic Exercise Test Variables of Prognostic Value in Asymptomatic Subjects**

Exercise Test Variable	Method of Measurement	High-Risk Values and Remarks
Exercise capacity	Estimated according to protocol <sup>51</sup>	No widely accepted abnormal values for asymptomatic subjects Some derive abnormal values based on age and sex <sup>20,28</sup> Some advocate cutoff values of <5 METs, 5–8 METs, and >8 METs <sup>31</sup>
Chronotropic response	Peak HR Achievement of target HR based on age <sup>40</sup> Proportion of HR reserve used <sup>32</sup>	85% of (220–age) (Peak HR–resting HR)/(220–age–resting HR) Value of $\leq 0.80$ higher risk <sup>32</sup>
HR recovery	Difference between HR at peak exercise and 1 or 2 min later <sup>20,30,37</sup>	Peak HR–HR 1 or 2 min later Abnormal value of $\leq 12$ bpm after 1-min recovery based on use of a cool-down period <sup>20</sup>

All references based on studies that focused on asymptomatic subjects.

the decrease in HR early after exercise is a manifestation of vagal reactivation.<sup>43</sup>

Because of the strong relationship between vagal tone and cardiac risk, investigators studying clinical populations suspected and confirmed that attenuated HR recovery, as a reflection of impaired vagal tone, would be predictive of an increased risk of death.<sup>37,38,44,45</sup> Recently, HR recovery has been evaluated in several cohorts of asymptomatic subjects or subjects undergoing stress testing as part of a population-based epidemiological study; HR recovery was found to have prognostic value in these subjects as well,<sup>20,30,37,38,46</sup> and this association persisted even after accounting for the Framingham and European Risk Scores.<sup>20</sup> An important uncertainty, however, is whether  $\beta$ -blockers affect the ability of HR recovery to predict risk. Studies that focused solely on asymptomatic subjects had few patients taking  $\beta$ -blockers.<sup>20,37</sup>

### Ventricular Ectopy

The occurrence of ventricular ectopy during and after exercise may also be a reflection of electrical instability and altered autonomic tone. A recent report on a population-based study of asymptomatic French civil servants has demonstrated that frequent ventricular ectopy during and after exercise was associated with an increased risk of death<sup>47,48</sup>; however, the prevalence of frequent ventricular ectopy was very low. In a study of a primarily clinical population, ventricular ectopy during recovery after exercise was a stronger predictor of risk than was ventricular ectopy during exercise<sup>49</sup>; whether this also applies to asymptomatic subjects is unclear. A major problem with the literature on ventricular ectopy during exercise testing is the failure to record the entire exercise test, as recording the entire test would allow for a fully objective count and description of ectopic beats.

### Conclusions and Need for Future Research

Although current data suggest that in patients who have an estimated intermediate risk of developing disease there may be value in additional noninvasive screening tests, including exercise testing,<sup>3</sup> we agree with the recent recommendations of the US Preventive Services Task Force<sup>9</sup> that there is insufficient evidence at this time to recommend exercise testing as a routine

screening modality in asymptomatic adults. Although nonelectrocardiographic measures, including functional capacity,<sup>28,29,31</sup> chronotropic response,<sup>32</sup> HR recovery,<sup>37</sup> and ventricular ectopy,<sup>48</sup> have been shown to predict adverse events in asymptomatic subjects, and although exercise testing measures have been shown to improve the prediction of coronary heart disease events over and above the Framingham Risk Score,<sup>40</sup> there is no evidence that gaining this knowledge improves outcomes. It is not known whether some of the nonischemic measures, such as HR recovery and ventricular ectopy, are modifiable in a clinically meaningful way. It is not even known whether pursuing more intensive risk factor modification or obtaining imaging data in this clinical setting produces real clinical benefits for individual patients.

Given the strong evidence linking exercise test findings with risk in asymptomatic subjects, we believe that the next major priority is the design and implementation of large-scale randomized trials to determine whether an exercise screening strategy leads to an improvement in outcomes. These trials would provide much-needed evidence about the cost-effectiveness of exercise testing as well as its clinical value in asymptomatic women, older adults, and members of minority groups. Because of the current data showing that exercise testing provides maximal prognostic information in people with preexisting risk markers,<sup>20,39</sup> it might be reasonable to target trials accordingly. Trials also would provide a context for other research—for example, an examination of the genetic links between exercise capacity and cardiovascular risk. Recently reported animal model work has shown that rats with genetically bred poor exercise capacity have abnormalities of mitochondrial function that may contribute to atherosclerotic risk.<sup>50</sup>

Although the prognostic capability of screening exercise testing is established, its clinical value for improving long-term outcome is not, as is well documented by the US Preventive Services Task Force.<sup>9</sup> Discussion and policy about screening techniques like exercise testing should engender controversy, given the absence of randomized trials demonstrating improved clinical outcomes with their application.<sup>6,51</sup>

### Writing Group Disclosures

Writing Group Member	Employment	Research Grant	Other		Speakers Bureau/Honoraria	Ownership Interest	Consultant/Advisory Board	
			Research Support	Other			Other	Other
Michael Lauer	The Cleveland Clinic Foundation	None	None	None	None	None	None	None
Erika Sivarajan Froelicher	University of California, San Francisco	None	None	None	None	None	None	None
Mark Williams	Creighton University School of Medicine	None	None	None	None	None	None	None
Paul Kligfield	Weill Medical College of Cornell University	None	Equipment donations from Quinton, GE, Mortara, Philips	None	None	GE	Philips Medical; GE; Mortara	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit.

## Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers Bureau/Honoraria	Ownership Interest	Consultant/Advisory Board	Other
Dr Gary Balady	Boston University Medical Center	None	None	None	None	None	None
Dr Bernard R. Chaitman	Saint Louis University	None	None	None	None	None	None
Dr Raymond J. Gibbons	Mayo Clinic	None	None	None	None	CV Therapeutics; Molecular Insight Pharm; Cardiovascular Clinical Studies; Consumers Union	None
Dr Victor Froelicher	Stanford University	None	None	None	None	None	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Reviewer Disclosure Questionnaire, which all reviewers are required to complete and submit.

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