Cardiovascular Screening in Asymptomatic Adults: Lessons for the Diving World*

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At the broadest level, consensus preparticipation recommendations for athletes of all ages focus on performance of a history and physical examination, with the additional performance of a screening test being more controversial. Depending upon athlete age and the associated prevalence of etiologies of cardiac death, differences exist regarding specific targets for the history and physical and for the type of testing considered. This paper provides a summary of the estimated relative value of the components of a screening program for both younger and older athletes.

Introduction

Unexpected death is always a tragedy but is perhaps more poignant when it occurs during sport. Athletes, even recreational ones, are felt to be "healthier" than the rest of the population, and exercise is often prescribed to improve cardiovascular health. Yet it is clear that exercise itself is a cardiovascular stressor and that the majority of nontraumatic deaths during exercise are cardiac in origin.

Many organizations have sought to define principles for the early detection of those who might be at risk, with the hope that these individuals can then undergo further evaluation, treatment to reduce risk or limitation of risk by reducing exposure to exercise. Recent data indicating that about one-quarter of diving deaths are related to cardiovascular disease (Denoble, Caruso et al. 2008; Denoble, Pollock et al. 2008) has provided the impetus to examine whether more could be done to prevent cardiovascular events in divers. This review will address the principles of screening in asymptomatic individuals; available screening tools and tests; current recommendations regarding screening promulgated by other organizations; experience with screening programs, including diving; and conclude with some issues that should be considered in designing a screening program.

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Principles and Goals of Preparticipation Screening

The World Health Organization (WHO) has developed a generally accepted set of principles for any disease screening program (Wilson 1968) (Table 1). Consideration of these may be helpful in designing a preparticipation screening program.

Several additional points are worth considering: Screening programs are generally designed to detect asymptomatic individuals. Further, most screening programs for athletes are not designed to detect disease per se but are designed to detect those individuals who need further evaluation. While this may seem like a fine distinction, it is important to recognize this goal, as it dictates that sensitivity is far more important than specificity in designing and evaluating a screening program.

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Table 1: WHO screening principles

- There should be an important problem.
- There should be an accepted treatment.
- Facilities must exist for diagnosis and treatment.
- There should be a recognizable latent or early symptom stage.
- A suitable test or examination must exist.
- The test must be acceptable to the population.
- The natural history must be understood.
- There must be an agreed policy on treatment.
- Cost must be related to other medical care expenditure.
- There must be a continuing process.

Note: Adapted from Wilson JM. The evaluation of the worth of early disease detection. *J R Coll Gen Pract.* 1968 Nov; 16 Suppl 2:48-57.

All screening programs use standardized tools, whether questionnaires, specific physical exam elements or diagnostic tests. The ideal tools for a screening program are (Grimes, Schulz 2002):

- easy, inexpensive and comfortable
- valid for diagnosis
- high sensitivity/specificity
- valid for prognosis
- reliable, with low variability of test results

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Causes of Death During Exercise

Critical to designing any screening program is a clear understanding of what disease or diseases can cause exercise-related deaths and are therefore "under suspicion" in a screening evaluation. In the case of exercise-related sudden death, this depends critically on age. Individuals under the age of 35 years are most likely to die from inherited structural heart disease, most commonly hypertrophic cardiomyopathy (Maron et al. 2009). Less important but still significant are coronary anomalies, Marfan syndrome, other cardiomyopathies and myocarditis. These diseases are generally best recognized by family history, rest echocardiogram (ECG) and rest echocardiography.

In individuals over the age of 35 years, the overwhelming cause of death is unrecognized coronary artery disease (CAD), detection of which is best approached through evaluation of risk factors and perhaps subclinical atherosclerosis and provocative stress testing.

In short, the approach and tools used for testing will vary significantly depending on the disease(s) for which the screening is being performed.

Impact of a Positive Screening Study

An important complement to any screening program is a plan for how to manage those individuals who are eventually found to have significant disease. The most authoritative source is the American College of Cardiology's (ACC) 26th Bethesda Conference recommendations regarding participation in competitive sport for individuals (American College of Cardiology 1994). The limitation of these recommendations to competitive sports is purposeful, as it was felt that, in comparison to recreational sports, competitive sports may limit the ability of an athlete to recognize and act on early symptoms — a situation that may well be analogous to the diving environment. Further, while diving was not included, the approach to classifying sports may be helpful as a framework. Sports are classified by the tertile of intensity of their dynamic (percent VO_2max: <50 percent, 50-70 percent, >70 percent) and static (percent maximal voluntary contraction: <10 percent, 10-30 percent, >30 percent) components as well as the danger of bodily injury from collision and consequences of syncope. Recommendations regarding participation are based on the likely tolerance to these stresses and dangers in specific cardiovascular diseases.

Younger Athletes

Most of the attention related to preparticipation screening in sport has focused on competitive athletes and therefore on the diseases that are most important in a younger age group. Many organizations have developed recommendations for screening programs, which can vary substantially. In the United States, the most prominent guidelines issued by the American Heart Association (AHA) recommend a targeted 12-point history and physical exam with no routine testing (Maron et al. 1996, 1998, 2007).

There is currently no national requirement for preparticipation screening in the United States, although several states do require screening for high school and collegiate athletes. Individual sports organizations (schools, teams) have implemented these programs or, for elite or professional athletes, created their own more rigorous programs. In contrast, the European Society of Cardiology (ESC) guidelines call for the addition of a screening ECG, a strategy that is required by law by many countries (Corrado et al. 2005; Douglas 2008).

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While a prospective comparison of screening programs with or without ECG would be logistically impossible, observational data are available. Most relevant is the well-documented 20-year experience in Italy showing a dramatic reduction in incidence of sudden death after implementation of a mandatory screening program administered by sports cardiologists that includes an ECG (Corrado et al. 2006). While these results have been called into question because the baseline rate of sudden death was much higher in Italy than in the United States (Pelliccia et al. 2008), visual inspection of data from the most recent years of this program suggest a lower sudden death rate associated with the more rigorous Italian screening program.

Other relevant data include a Harvard study of 510 students in whom the addition of ECG to a history and physical substantially increased the sensitivity of screening from 45 percent to 91 percent. However, the specificity fell slightly from 94 percent to 83 percent (Baggish et al. 2010). Other investigators performing cost-effectiveness modeling suggests that the addition of a rest ECG is within the generally accepted range of value for cost of life years saved (Wheeler et al. 2010). The authors found that implementation of a history and physical screening at an estimated cost of $199US per athlete would add 2.6 life years per 1,000 young athletes at a cost per year of $76,100US. Addition of an ECG to the screening program (estimated additional cost: $89US) was calculated to save an additional two life years, at a cost per year of $42,900US.

In the absence of any prospective testing of different strategies, the design of the optimal program has not been established. However, it is clear that a careful history is very important and should include family history, exertional symptoms and syncope. A physical exam is also important, as murmurs reflective of the hemodynamic abnormalities are often present at rest (Table 2). Given the accumulating data, addition of a noninvasive test such as a rest ECG may become more accepted in the United States over time, especially if financial and logistic hurdles can be overcome (Maron 2010).

Table 2: CV risk assessment: suitability/acceptabiity of tests for screening

	< 35 years	> 35 years
History	+++	+++
Physical Exam	+++	+++
Noninvasive Testing		
Resting ECG	+++	+
Exercise ECG	+	++
Stress Imaging	-	+
CIMT	-	+++
CAC	-	+++
CTA	-	+

CIMT: carotid intima medial thickening;
CAC: coronary artery calcification;
CTA: coronary computed tomographic angiography.

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Older Athletes

In comparison to younger individuals, far less attention has been paid to designing screening programs for older, usually recreational, athletes. Few detailed preparticipation guidelines exist, and there is little reported experience in this age group. Instead most authorities focus on strategies used in clinical medicine for the early detection of atherosclerotic diseases, as these are the most common cause of death in this age group.

Since most individuals are asymptomatic, the history is often more helpful in identifying risk factors rather than symptoms. Similarly, there may be few detectable abnormalities at rest or even with exercise, as events are often due to spontaneous rupture of nonobstructive plaque (Table 2).

The AHA statement issued recommendations for preparticipation screening in older athletes in 2007 (Maron, Thompson et al. 2007). This document recommends that older competitive athletes (>35 to 40 years) be "knowledgeable" regarding their personal history of CAD risk factors and family history of premature CAD. Further, stress testing should be performed selectively for individuals engaging in vigorous training and competitive sports and who meet the following criteria: men >40 years or women >55 years with diabetes mellitus, or at least two risk factors or one severe risk factor other than age. Finally, the document recommends education regarding prodromal cardiac symptoms, such as exertional chest pain.

The recommendations regarding the use of stress testing are derived from the 2002 ACC/AHA guideline, which recommends using exercise testing in the following individuals (Gibbons et al. 2002) and are similar to those of the American College of Sports Medicine (Armstrong et al. 2009). These include:

1. Evaluation of asymptomatic persons with diabetes mellitus who plan to start vigorous exercise *(Class IIa; Level of Evidence: C)*.

2. Evaluation of asymptomatic men > 45 years and women > 55 years who plan to start vigorous exercise (especially if sedentary) *(Class IIb)*.

3. Evaluation of asymptomatic men > 45 years and women > 55 years with occupations in which impairment might impact public safety *(Class IIb)*.

In contrast, the guideline recommends against routine screening of asymptomatic men or women *(Class III)* since such individuals will have a low pretest probability and be more likely to have a false positive than a true positive test. Use of a stress test as the screening strategy could result in making many normal individuals undergo unnecessary follow-up tests or procedures.

Risk Stratification

Most recommendations for preparticipation screening in older individuals begin with screening for CAD risk factors. In addition to the AHA guideline on primary prevention (Pearson et al. 2002), the ACC/AHA recently issued a set of performance measures in this area (Redberg et al. 2009). Performance measures are distilled from the strongest evidence, represent "must do" recommendations endorsed by national-quality organizations and often reinforced by public reporting and pay for performance programs. The 13 recommended performance measures for primary prevention are:

- lifestyle/risk factor screening
- dietary intake counseling
- physical activity counseling
- smoking/tobacco use assessment
- smoking/tobacco cessation
- weight/adiposity assessment
- weight management
- blood pressure measurement
- blood pressure control
- blood lipid measurement
- blood lipid therapy and control
- global risk estimation
- aspirin use

Implementation of these measures requires performance of a careful history and physical examination, laboratory testing for lipids and formal assessment of cardiovascular risk. Unfortunately, there are several risk scores available whose results may differ widely (Berger et al. 2010).

A recent review presented a case vignette of a 56-year-old woman with several risk factors; estimates of risk varied from 2 percent for 10-year Framingham Risk Score (heart attack and death) to an overall lifetime risk as high as 50 percent. Nevertheless, risk assessment is most often accomplished using the Framingham Risk Score (FRS) (National Cholesterol Education Program 2001). This score

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classifies individuals into high, medium and low 10-year risk for cardiovascular events and stroke. Individuals with known CAD and those with diabetes and peripheral vascular disease (considered to be "CAD-equivalents") are placed in the highest risk category. In other individuals, risk is calculated using a weighted combination of age, sex, total cholesterol, HDL cholesterol, smoking history and blood pressure. Calculators are available online at *http://hp2010.nhlbihin.net/atpIII/calculator.asp*.

Preventive interventions are recommended based on these estimates of 10-year risk. Individuals classified as having low 10-year risk, defined as an event rate of <10 percent, should be treated with reassurance, and further risk assessments should not be performed for five years. Individuals estimated to be at high risk, defined as a 10-year risk >20 percent, should be treated with aggressive risk-factor modification to secondary prevention goals. It is less clear how individuals classified as having an intermediate 10-year risk (event rate of 10-20 percent) should be treated. ACC/AHA recommendations suggest considering referral for further tests, such as atherosclerosis imaging (see below) for reclassification into either low- or high-risk groups (Greenland et al. 2007).

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Although carefully validated, there is widespread concern that the Framingham Risk Score is flawed. In addition to the ambiguity in intermediate-risk individuals, it fails to capture important risk factors such as family history, the severity of risk factors and emerging risk factors such as inflammation as manifested in hs-CRP (Kannel et al. 1961). Risk in some demographic categories, such as younger women, is underestimated. More important, it is clear that events do occur in individuals estimated to be at low risk (Akosah et al. 2003). For example, National Health and Nutrition Examination Survey data classify 85 percent of healthy adults between ages 20 and 79 years as low risk by Framingham Risk Score, with only 2 percent as high risk, although epidemiological data suggests that more than one-third will die from cardiovascular disease (American Heart Association 2010; Ajani, Ford 2006).

Atherosclerosis Imaging and Stress Testing

As a result, some have suggested the use of additional testing to detect atherosclerosis, often termed subclinical disease. While there are several techniques available (Crouse 2006), the most prominent tests are ultrasound evaluation of the carotid intima media thickness (CIMT) and CT-based coronary artery calcium scoring (CAC). Both tests have been studied extensively in large community-based studies and accurately predict both prevalent and incident cardiac events (Kaul, Douglas 2009). However, no prospective studies have been performed comparing the clinical impact of strategies incorporating the use of either test as a guide to a risk reduction treatment to that of the use of a Framingham Risk Score alone.

CIMT: Measurement of carotid intima media thickness was developed in the 1980s and is typically carried out using high-frequency ultrasound transducers. The rationale for using CIMT to refine CAD risk assessment is based on multiple large (>1000 patients) prospective studies that have been reviewed in detail in a recent meta-analysis (Lorenz et al. 2007). Each study demonstrated a statistically significant association between CIMT and the risk for myocardial infarction, CAD death and stroke. The age- and sex-adjusted overall estimate of the risk of myocardial infarction was 1.15 (95 percent CI, 1.12 to 1.17) per 0.10 mm CIMT difference. Further, CIMT progression is well documented to slow with risk-factor-targeted interventions, and this slowing is associated with a reduced risk of future CHD events (Hodis et al. 1998; Espeland et al. 2005). The major limitations of CIMT are cost, as it is generally not reimbursed, its operator dependence and lack of widespread availability. Nevertheless, CIMT is a well-established surrogate marker for atherosclerosis and coronary artery disease.

CAC: A newer test, CAC appears to also be of independent and additive value in predicting CAD events, although data are limited in women and nonwhites. The best data come from the NHLBI MultiEthnic Study of Atherosclerosis (MESA) observational trial, which uses multiple imaging modalities to describe the characteristics and progression of subclinical atherosclerosis in a population-based sample of 3,601 women and 3,213 men aged 45-84 years and without known CVD (Bild et al. 2002). Detrano et al. (2008) found that MESA subjects with a CAC score >300 had a hazard ratio of 9.67 (95 percent CI, 5.20 to 17.98, P<0.001) for cardiovascular events compared with those with a CAC of 0. The addition of CAC significantly increased the discriminant accuracy for predicting all CAD events from a c-index of 0.77 for risk factors alone to 0.82 for risk factors plus CAC.

Similar results have been obtained by others. A meta-analysis of six studies showed strong incremental relationships between increasing CAC scores and higher event rates (Greenland et al. 2007). In particular, patients with intermediate FRS but a CAC score >400 had an elevated annual CAD death or myocardial infraction rate of 2.4 percent. These data support the proposed strategy of using CAC to reclassify intermediate risk individuals into either high- or low-risk categories. Those recategorized as high-risk (>20 percent 10-year risk of estimated coronary events, i.e., CAD equivalent risk status) would then receive more intensive preventive treatment. In contrast, while individuals with a CAC of 0 may have obstructive disease (Gottlieb et al. 2010), they have generally been found to have a low event rate (Hecht 2010) and low conversion rate to a positive CAC score, with a "warranty period" of at least four years (Min et al. 2010). The major limitations to CAC are cost, as it is generally not reimbursed, and radiation, which is generally 1-2 milliSieverts (mSv).

The MESA study provides the best head-to-head comparison of CIMT and CAC in predicting CAD risk (Folsom et al. 2008). In almost 6,700 subjects followed over a maximum of 5.3 years, both tests were associated with risk of incident events (CAD, stroke, fatal CAD). However, CAC was associated more strongly than CIMT with a hazard ratio for an incident event of 2.1 (95 percent CI, 1.8 to 2.5) per standard deviation (SD) increment of CAC score as compared to 1.3 (95 percent CI, 1.1 to 1.4) per SD increment of CIMT. Receiver operating characteristic curve analysis also suggested that CAC scoring was a better predictor of events than CIMT, with an area under the curve of 0.81 versus 0.78. However, a separate cost-effectiveness analysis of CAC scoring as a CAD risk prediction tool suggests that its use in an asymptomatic population is expensive and not cost-effective, with a cost per identification of a new "at risk" case of $9,789US and a cost per QALY of $86,700US (O'Malley et al. 2004).

CCTA: The newest test to identify atherosclerosis is coronary computed tomographic angiography (CCTA). This test uses modified CT technology to produce high temporal and spatial resolution, noninvasive images of the coronary artery lumen and walls, enabling detection and characterization of critical stenoses and nonobstructive plaque with high sensitivity and specificity (Budoff et al. 2008). Recent longitudinal data suggest that both stenosis and plaque burden provide independent, incremental prognostic value to conventional risk assessment (Chow et al. 2010). Limitations to use of CCTA are cost, as it is generally not reimbursed, and radiation, which is generally 10-20 mSv.

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Exercise testing: Although the ACC/AHA guidelines recommend preparticipation stress testing in selected circumstances, there are few data supporting its ability to risk-stratify in an asymptomatic population. This is not surprising, as a positive test requires the presence of coronary lesions severe enough to cause ischemia when workload is increased, and the target population for screening generally does not have such advanced disease. However, a study of 25,927 healthy men (aged 20-82 years) who underwent stress echocardiography and were subsequently followed for an average of 8.4 years suggests there is some value. While stress testing did not significantly enhance the prediction of prognosis in individuals without cardiac risk factors, in those with risk factors a positive stress echo added incremental information. Nevertheless, less than 6 percent of tests were positive, and the sensitivity of a positive stress ECG was only 61 percent (Gibbons et al. 2000). There is no indication that the addition of imaging to exercise stress adds actionable, additional information in asymptomatic low- or intermediate-risk individuals or even in otherwise low-risk diabetics (Young et al. 2009).

In considering the use of any of these tests, it is critically important to remember that all available data are observational and descriptive. No risk-assessment strategy, whether formal calculation of FRS, atherosclerosis testing or exercise testing, has been studied prospectively as a strategy to improve outcomes (Douglas et al. 2009). Since the addition of tests adds to costs and in some cases increases risk through radiation, their widespread, routine use is not generally recommended. For example in 2004, the United States Preventive Services Task Force (USPSTF) released its recommendations regarding use of rest ECG, stress test, CIMT and CAC as screening tests for CAD (USPSTF 2004). In formulating their recommendations, the USPSTF defined possible benefits as a reduction in CAD events through the detection of high-risk individuals who would benefit from more-aggressive risk-factor modification or detection of individuals with severe CAD whose life would be prolonged by CABG.

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An additional potential benefit would be for those engaged in occupations endangering the health of others, in whom considerations other than health benefits to the individual may influence the decision to screen for CAD. Possible harms identified were a lack of evidence of improved health outcomes and possible false positive tests, which may lead to unnecessary invasive procedures, overtreatment and labeling. False negative tests were also of concern, as the majority of events in low-risk individuals will occur in those with negative tests.

As a result of this formulation, the USPSTF advised against the use of testing in adults at low risk as a Class D recommendation (at least fair evidence that the service is ineffective or that harms outweigh the benefits). Their use in adults at increased risk was deemed to have insufficient evidence, or Class I (evidence that the service is effective is lacking, of poor quality or conflicting and the balance of benefits and harms cannot be determined). In part as a consequence of the USPSTF recommendations, Medicare coverage for risk stratification in asymptomatic individuals is provided only for determination of total cholesterol, HDL and triglycerides once every five years. All other testing (rest ECG, stress test, CIMT, CAC, CCTA) are not covered (Medicare.com 2010).

Issues to Consider in Designing a Preparticipation Screening Program for Divers

Screening Program Experience in Diving

In contrast to younger individuals, there are few published experiences with preparticipation screening programs in older individuals. However, there is a small published literature on screening programs in diving outlining their "yield." The first used the records of three British organizations with identical requirements for divers to complete an annual questionnaire (which was held to be a legal declaration) and to undergo regular examinations by their primary care physician according to the following schedule:

- every five years for those <40 years
- every three years for those aged 40-50 years
- annually for those over 50 years (Glen et al. 2000)

Data on 2,962 exams on 2,094 divers were analyzed and showed cardiovascular symptoms in 1.2 percent, a murmur in 1 percent and cardiovascular medication use in 4 percent. A mere 2 percent were felt to have "failed" the exam, and 1 percent received a referral to a cardiologist. Overall, no significant unknown abnormalities were detected. A second study relied on New Zealand Department of Labour records requiring in-depth interview, testing and medical examination every five years for registered divers. Of 336 divers undergoing at least two exams, only 10 were cited, with five receiving a conditional certificate of fitness, four were considered temporarily unfit for diving, and only one was declared permanently unfit — for a spinal injury detected by questionnaire (Sames et al. 2009).

Design Considerations

There are many considerations in designing a screening program. These include addressing the following questions: Whom to screen? When to screen? How often? What disease to screen for? What screening questions and tests to use? Who will perform screening? Who will perform any needed additional evaluation? What will additional evaluation consist of? How will results be translated into clearance for diving? What happens if someone "fails"? Finally, who will pay for all this? The answers to these questions can be complex and must be addressed individually by each program to ensure alignment with goals and resources.

The screening experience and the literature suggest that individuals of all ages be asked about their fitness level assessment, cardiovascular history, symptoms and signs, and undergo a brief physical exam. For those under 35 years of age the AHA Preparticipation checklist can serve as a template (Maron 1996, 1998, 2007). For those over 35 years, assessment of CAD risk factors, symptoms and signs can follow the recommendations in the ACC/AHA primary prevention guidelines and performance measures (Pearson et al. 2002; Redberg et al. 2009). In those over 35 years with at least intermediate risk, it is reasonable to recommend selective testing of some kind. However, it is unclear if this should be stress testing or CAC score. To date, the evidence does not favor the use of CIMT or CCTA over these other options.

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It is important to note that, regardless of age, all symptomatic individuals should be required to have a full medical evaluation before diving. Indeed 10 percent of those experiencing a fatal event had prior symptoms (Denoble, Caruso et al. 2008). Any screening recommendations are critically predicated on the willingness to implement a program to exclude individuals with positive screens or even identified disease from participation in diving.

Other aspects of a screening program include the education of divers, diving staff and physicians about possible prodromal cardiac symptoms and the importance of their recognition in preventing events (Maron et al. 2007). This is especially true in the unforgiving undersea environment, in which the ability to respond in an emergency is severely limited. Similarly, divers and diving staff should be trained to handle cardiovascular emergencies.

The design of any sport-specific screening program should consider the unique stresses associated with its pursuit. In the case of diving, paramount among the concerns is the limited ability to recognize and respond to an emergency. In addition, the hyperbaric environment can alter intracardiac hemodynamics, changing flow across a patent foramen ovale or causing pulmonary hypertension. It can also alter drug metabolism in unpredictable ways. Professional diving carries additional risk but even different types of recreational diving can have very different risks. In instituting any new program, there should be a reasonable expectation that it would both change behavior and improve outcomes.

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