Sport, Exercise, and the Heart

Lead Article

Expert Answers to Three Key Questions

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Exercise and the heart: the Good, the Bad, and the Ugly

Paul D. Thompson, MD

Director of Preventive Cardiology & Cardiovascular Research - Hartford Hospital, Conn - USA

This review addresses three aspects of exercise important to the clinical cardiologist, including the therapeutic use of exercise, the adaptations produced by chronic endurance exercise training, and the risks of vigorous exertion. Regular exercise is useful in reducing atherosclerotic coronary heart disease (CHD) risk, treating selected CHD risk factors, managing CHD patients after an initial cardiac event, and in improving effort tolerance in patients with angina pectoris, congestive heart failure, and claudication. Chronic endurance exercise training produces cardiovascular adaptations, including bradyarrhythmias, cardiac enlargement, and cardiac murmurs, which must be differentiated from those conditions that increase the cardiovascular risk of exercise. This risk in young subjects is due to congenital abnormalities and acquired cardiomyopathy, whereas cardiac complications in adults are largely due to atherosclerotic vascular disease. Prevention of exercise-related cardiac events is difficult because of their rarity, and depends on selective preparticipation screening and the careful evaluation of symptomatic athletes before permitting their return to competition.

Keywords: sports; athletic heart syndrome; exercise; atherosclerotic coronary heart disease; claudication; angina pectoris; congestive heart failure; congenital heart disease; risk factor; cardiovascular adaptation; screening; sudden death

Address for correspondence: Paul D. Thompson, MD, Division of Cardiology, Hartford Hospital, 82 Seymour Street, Hartford, CT 06102, USA (e-mail: pthomps@harthosp.org)

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This review will focus on three aspects of exercise important to clinical cardiologists. The first section will focus on the "Good," or the therapeutic use of exercise in modern cardiology.[1] The second section will discuss the cardiovascular adaptations to endurance exercise training characteristic of the athletic heart syndrome.[2] These normal physiologic adaptations are not "Bad," but must be differentiated from cardiovascular disease. The third section will address the "Ugly" aspects of vigorous physical activity including sudden cardiac death (SCD) and exercise-related acute myocardial infarction (MI).[3]

THE USE OF EXERCISE AND PHYSICAL ACTIVITY IN MODERN CARDIOLOGY

Regular physical exertion has documented utility in preventing atherosclerotic coronary heart disease (CHD), reducing atherosclerotic risk factors, reducing risk in CHD patients, and improving exercise capacity in patients with stable angina pectoris, congestive heart failure, and claudication.

Preventing CHD

There are no randomized, controlled studies directly testing the hypothesis that exercise reduces CHD. Furthermore, problems with exercise adherence, subject crossover, and cost will likely prohibit a direct test

SELECTED ABBREVIATIONS

CAD	coronary artery disease
CHD	coronary heart disease
HCM	hypertrophic cardiomyopathy
MI	myocardial infarction
RBBB	right bundle-branch block
SCD	sudden cardiac death
WPW	Wolff-Parkinson-White (syndrome)

of the exercise hypothesis. Nevertheless, several recent reviews have summarized the seminal studies demonstrating reduced CHD risk in physically active individuals.[4-6] This evidence satisfies accepted criteria[7] used to demonstrate that an epidemiological association is causally active.[8] These criteria include the consistency, strength, sequence, and gradient of the relationship, as well as its plausibility and coherence given other biologic data.

The mechanisms mediating the exercise effect on CHD incidence are not defined, but identifying the mechanisms is important because it may indicate how much exercise is required to reduce CHD risk. Multiple possible mechanisms have been defined, including altering known atherosclerotic risk factors, enhancing parasympathetic tone and the risk of ventricular fibrillation,[9] improving coronary artery dilating capacity and endothelial function,[10,11] and reducing the risk of coronary thrombosis and platelet deposition.[12,13] It is likely that many of these factors operate in concert.

Exercise in managing selected CHD risk factors

Exercise has beneficial effects on many cardiac risk factors, including triglycerides, high-density lipoprotein (HDL) cholesterol, blood pressure, insulin sensitivity, and body weight. Exercise and weight loss can reduce low-density lipoprotein (LDL) cholesterol and reduce the decrease in HDL cholesterol produced by low-fat diets.[14] Exercise may be curative for mild abnormalities in triglycerides, blood pressure, and insulin sensitivity, but is best used as adjunctive therapy when these risk factors are markedly abnormal.

Some of the effect on CHD risk factors ascribed to exercise training effect is not a training effect, but an acute response to recent exercise. Even a single exercise session can have beneficial effects on triglycerides, systolic blood pressure, and insulin sensitivity. The reduction in systolic blood pressure can persist for up to 12 hours. Individuals with mild hypertension could normalize their blood pressure with twice-daily exercise sessions.[15]

The magnitude of any exercise effect on CHD risk factors depends on the characteristics of the exercise intervention, individual variation, and whether exercise produces concomitant reductions in body weight. Some patients may achieve large reductions in atherosclerotic risk factors with exercise training, but the average effect in reported studies is quite small. Furthermore, even this modest effect is probably overestimated because of the fact that positive papers tend to get submitted and published—the "published positive paper bias."

A meta-analysis of 52 exercise training trials of >12 weeks duration including 4700 subjects demonstrated an average increase in HDL cholesterol levels of 4.6% and reductions in triglycerides and LDL cholesterol concentrations of 3.7% and 5%, respectively.[16] Prolonged exercise training likely produces greater changes, but the above results are probably as good, if not better, than those obtained by most patients. Furthermore, exercise is known to increase HDL, but there is evidence suggesting that exercise is less effective in altering HDL in subjects with initially low HDL levels.[17]

At least 44 randomized controlled trials including 2674 participants have studied the effect of exercise training on blood pressure. Average systolic and diastolic blood pressures decreased by 2.6 and 1.8 mm Hg in normotensive subjects and by 7.4 and 5.8 mm Hg in hypertensive subjects,[18] respectively, suggesting that exercise may serve as sole therapy in some mildly hypertensive subjects.

Physical activity also reduces insulin resistance and glucose intolerance, postprandial hyperglycemia, and possibly hepatic glucose output.[15] Nine trials of exercise training in 337 type 2 diabetics reported an average reduction of hemoglobin A_{1c} (HbA_{1c}) of 0.5% to 1%.[15] These findings may underestimate the absolute change in HbA_{1c} because of concomitant reductions in diabetic medications. The Diabetes Prevention Program reported a 58% reduction in the onset of type 2 diabetes over 2.8 years among individuals at risk for the disease who were assigned to a physical activity and weight loss intervention that produced a 4-kg decrease in body weight and an 8 MET-h/wk increase in physical activity.[19]

Physical activity is critically important for the maintenance of weight loss. The National Weight Control Registry has enrolled 3000 individuals who have maintained for 1 year a weight loss of 10% of their body weight.[20] Eighty-one percent of the registrants reported increased physical activity. Exercising women and men expended 2445 and 3298 kcal per week exercising, respectively.

At least eight studies have examined the effect of exercise on smoking cessation, but most trials were small and the results not suitable for meta-analysis.[21] One

larger trial of 281 women reported that women randomized to a 12-week exercise program or control were more likely to not be smoking at the end of the program (19.4% vs 10.2%) and at 12 months of follow-up (11.9% vs 5.4%).[22]

Treatment for patients with established CHD

Exercise training has been demonstrated to reduce mortality after MI. O'Connor et al[23] reviewed 22 randomized trials of exercise-based, cardiac rehabilitation after MI performed between 1960 and 1988 and including 4554 patients, of which 97% were men. The programs generally consisted of supervised exercise training for 2 to 6 months followed by unsupervised exercise. The mean follow-up was 3 years. Total mortality decreased by 20%, cardiovascular mortality by 22%, fatal reinfarctions by 25%, and sudden death at 1 year by 37% ($P<0.05$, for all). There was no difference in the reinfarction rate, suggesting that cardiac rehabilitation reduced deaths from recurrent infarction even though the absolute number of reinfarctions did not decrease.

These results cannot determine whether exercise training alone saves lives, nor is it clear that the results are applicable to modern cardiac care. Fifteen of the 22 studies combined exercise training with other potentially beneficial interventions such as diet instruction and smoking cessation. These studies predated the routine use of many current therapeutic agents, including β-adrenergic blocking agents, angiotensin-converting enzyme (ACE) inhibitors, thrombolytics, and acute coronary angioplasty, and may not be applicable to present day patients who often have less myocardial injury with acute events and less residual ischemia.

Exercise training as adjunctive treatment for angina pectoris

Exercise training is a useful, but underutilized, treatment for patients with mild-to-moderate stable angina. Among 18 patients limited by angina on exercise testing, only 7 continued to have exercise-induced angina after 12 weeks of exercise training.[24] Exercise training reduces angina by reducing the submaximal heart rate response to an exercise task. The lower heart rate evokes lowers myocardial oxygen demand and reduces the occurrence of angina. Exercise training also reduces exercise-induced vasospasm, which contributes to a reduction in exercise ischemia. Normal coronary arteries dilate during exercise and in response to nitric oxide agonists such as acetylcholine (ACH). In contrast, atherosclerotic coronary arteries may constrict with exercise due to endothelial dysfunction.[25] Only 4 weeks of exercise training reduces the coronary artery vasoconstrictor response to ACH in patients with baseline endothelial dysfunction.[11] Consequently, exercise training is useful treatment for patients with mild-to-moderate stable angina pectoris who are not candidates for revascularization procedures.

Exercise for patients with congestive heart failure (CHF)

Some of the decrease in exercise tolerance in CHF patients results from deconditioning. Multiple small studies have shown that exercise training can increase exercise performance in CHF patients,[26-28] but there are no studies of sufficient magnitude to provide evidence that exercise training alters survival in this group.

Exercise for patients with claudication

Patients with claudication are often severely limited and exercise training can markedly reduce this limitation. An analysis of 21 exercise training studies for patients with claudication[29] noted that exercise training increased average walking distance by 179% or 225 m to the onset of pain and 122% or 397 m to maximal pain. Improvement was greatest in those studies that trained subjects to the point of maximal tolerated pain, lasted at least 6 months, and used walking as the training mode. These results are as good as those reported for most surgical and pharmacological therapies.

CARDIAC ADAPTATIONS OR THE ATHLETE'S HEART SYNDROME

"The athlete's heart" refers to a constellation of clinical findings produced by endurance exercise training, including sinus bradycardia, atrioventricular (AV) conduction delay, systolic flow murmurs, and multiple cardiac chamber enlargement with normal or augmented function. Henschen first coined the term in 1899 when he used percussion to determine heart size in cross-country skiers.[30]

Clinical findings due to enhanced parasympathetic tone

The resting bradycardia, sinus arrhythmia, and AV conduction delay found in the athletic heart syndrome are attributed to enhanced parasympathetic and reduced sympathetic tone. Athletes may also demonstrate ST-segment–T-wave changes of early repolarization and

T-wave inversions. Some of the T-wave changes can be quite bizarre and may be similar to those in other conditions affecting the parasympathetic nervous system, such as subarachnoid hemorrhage. These extreme T-wave abnormalities in athletes must be distinguished from serious pathological conditions such as hypertrophic cardiomyopathy (HCM).[31] The sinus arrhythmia and the ST-segment changes of early repolarization observed in endurance athletes are also characteristic of young, healthy individuals, but are more marked and more frequent in athletes. All abnormalities due to enhanced parasympathetic activity should resolve with exercise and its attendant withdrawal of vagal tone. This is not always true for marked T-wave inversions,[31] however, so their failure to resolve does not necessarily imply a pathological process *(Figures 1 & 2)*.[2]

Sinus bradycardia

Maximal VO_2 and maximal cardiac output are increased in endurance athletes, but there is little change in resting oxygen consumption or cardiac output. Consequently, the larger resting stroke volume characteristic of endurance athletes permits a reduction in resting heart rate. Sinus bradycardia, generally defined as a heart rate <60 beats per minute, is typical of the athletic heart syndrome and reported in up to 91% of en-

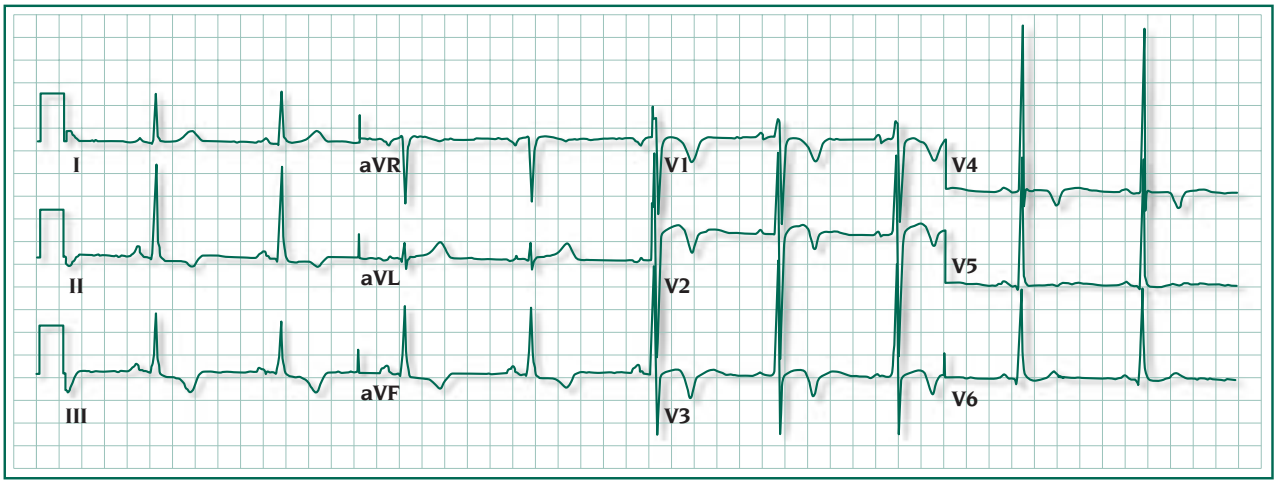

Figure 1. *ECG from a 49-year-old white male physician having run 58 to 108 km weekly and cycled 32 km weekly for 20 years. An echocardiogram showed left ventricle internal dimensions at end diastole and systole of 50 and 20 mm, respectively. The posterior and septal wall were 12 mm in thickness. Despite the diffuse T-wave inversions and borderline increased wall thickness, he was not restricted from athletic competition. (Green squares = 5×5 mm.)*

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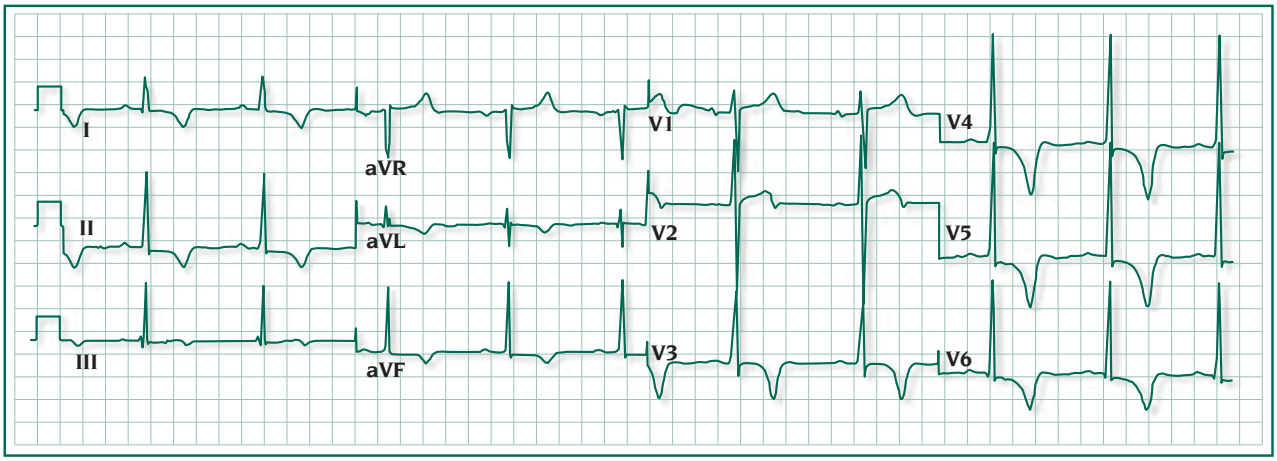

Figure 2. *ECG from a 20-year-old black American football player who weighed 119 kg and was 174 cm tall. Echocardiogram showed symmetric hypertrophy with the interventricular septum and left ventricular wall posterior wall each 17 mm. Because of probable hypertrophic cardiomyopathy, he was restricted from athletic competition. (Green squares = 5×5 mm.)*

Reproduced from reference *2 (see caption of Figure 1).*

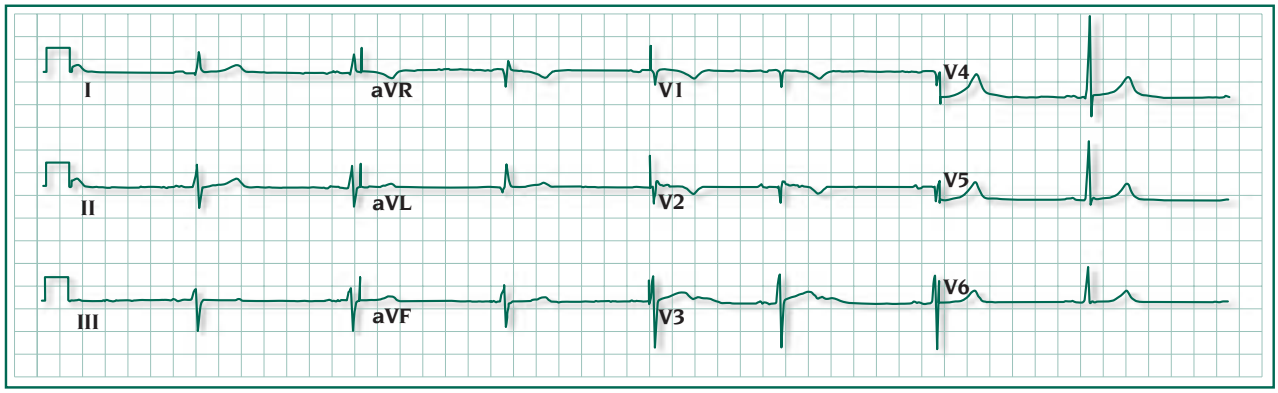

Figure 3. *ECG from a 36-year-old physician running 130 km weekly, demonstrating sinus bradycardia and increased QRS voltage. Note the 1/2 scale calibration. He was asymptomatic and allowed to continue marathon competition. (Green squares = 5×5 mm.)*

Reproduced from reference 2 *(see caption of Figure 1).*

durance athletes.[32] The bradycardia in athletes can be profound, and a rate of 25 beats per minute has been reported in one distance runner.[33] In addition to sinus bradycardia, sinus pauses or "sinus arrest" of more than 2 seconds have been documented during sleep in endurance athletes *(Figure 3).*[2]

Sinus arrhythmia

Sinus arrhythmia refers to a slight decrease in the sinus rate at the start of the expiratory phase of the respiratory cycle. Sinus arrhythmia is common in young healthy subjects, but is more marked in endurance athletes.

Atrioventricular conduction delay

First-degree AV block, or a PR-interval >0.20 seconds, is reported in 10% to 33% of endurance athletes.[34] Second-degree AV block of the Mobitz I or Wenckebach pattern (characterized by progressive prolongation of the PR interval before a nonconducted P wave) is also more common in the athletic heart syndrome.[35] Second-degree AV block with Mobitz II appearance (characterized by a nonconducted P wave without preceding PR-interval prolongation) is not typical of the athletic heart syndrome. Mobitz type II block typically occurs at the level of the His-Purkinje system, whereas Mobitz type I block is due to progressive slowing of conduction in the AV node. AV block with Mobitz II appearance may occur in endurance athletes due to enhanced vagal tone, but this is rare.[32] It presence should prompt a search for other causes and should not be attributed to the athletic training unless the athlete is asymptomatic and no other abnormalities are detected.

The prolongation of the AV interval and decrease in AV conduction velocity described above may unmask the ventricular preexcitation seen in the Wolff-Parkinson-White (WPW) syndrome. Indeed, a WPW conduction pattern is more common in endurance athletes.[34] Cardiologists should be cognizant of this fact when evaluating athletes for an asymptomatic WPW conduction pattern since the risk of sudden death in asymptomatic subjects with this abnormality is low.

Vasovagal syncope

Vasovagal syncope is more frequent in endurance-trained individuals. Compared with nonathletes and strength-trained athletes, endurance-trained individuals have a reduced ability to maintain blood pressure during orthostatic stress using lower body negative pressure.[35] These athletes have a large venous capacity from exercise training, enhanced vagal tone, and reduced sympathetic tone, all of which make them vulnerable to postural hypotension and a positive tilt-table response. Consequently, endurance-trained athletes are more vulnerable to vasovagal syncope, and positive tilt-table responses are normal in well-trained endurance athletes. Tilt-table results should not be interpreted as an adequate explanation for syncope in athletes unless the clinical situation strongly supports this explanation.

Electrocardiographic ST-segment–T-wave changes

ST-segment elevation of the "early repolarization pattern" is so common in endurance-trained athletes that it should be considered the norm rather than the exception. Persistent training into advanced age can preserve this pattern in older athletes *(Figure 4, page 148).*[2] ST-segment depression, in contrast, is rare and should prompt a search for other causes. Peaked, biphasic, and inverted T waves in the precordial leads are also frequently seen in endurance athletes. The biphasic T waves typically occur in the precordial "transition" leads where the QRS complex is changing from a primarily negative deflection in the right precordial leads to a

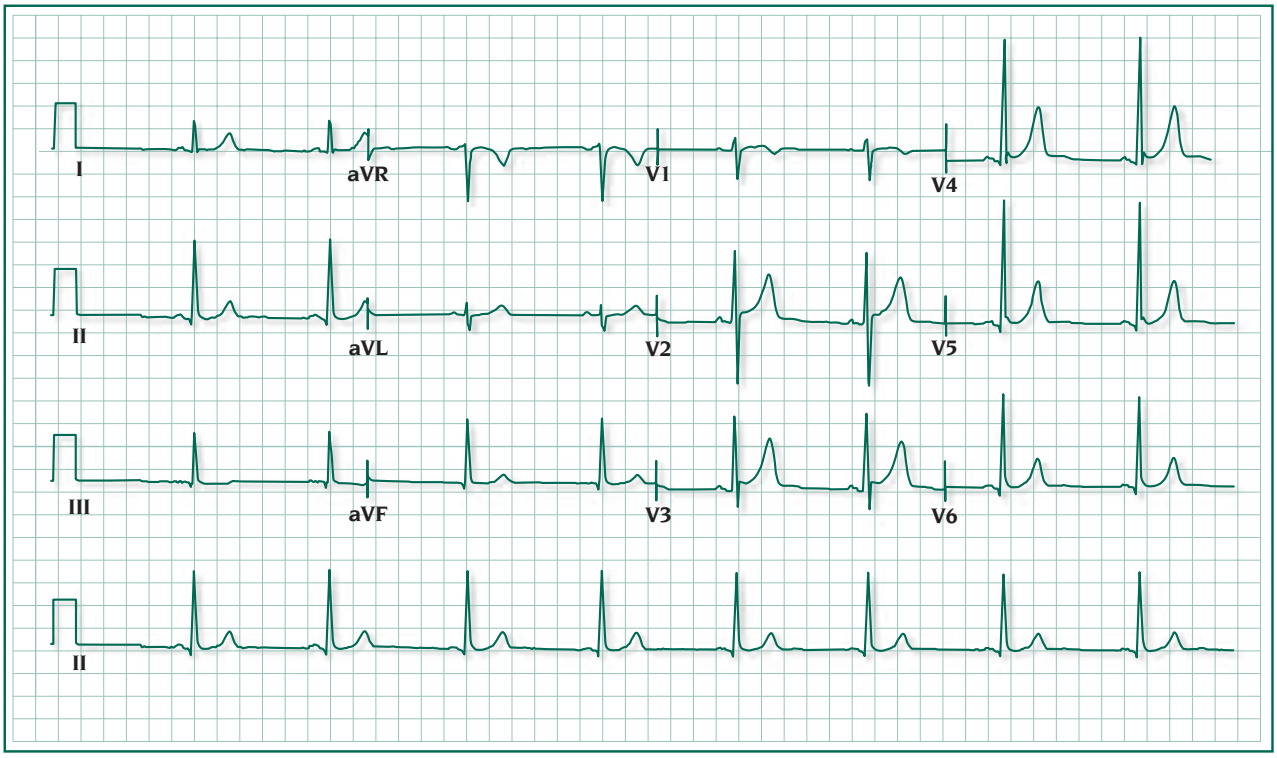

Figure 4. *ECG from a 54-year-old physician having run 60 km weekly for 40 years. The ECG shows persistence of early repolarization into middle age. (Green squares = 5×5 mm.)*

Reproduced from reference 2 *(see caption of Figure 1).*

primarily positive deflection in the left-sided leads. Deeply inverted T waves can also be normal in athletes, but are rare and require the exclusion of significant disease.[31] Among 952 healthy Italian national-caliber athletes, 375 had abnormal or mildly abnormal ECGs.[36] Only 27 athletes had marked T-wave inversions, which were suggestive of HCM in 11 and arrhythmogenic right-ventricular cardiomyopathy in 16, but only 1 of these 27 athletes had hypertrophic cardiomyopathy.[36] Such results demonstrate that mild ECG abnormalities are common in athletes, marked T wave changes are rare, and disease in asymptomatic athletes is unusual.

Evidence of cardiac enlargement

Habitual endurance exercise produces a global cardiac enlargement, which may affect both the right and left atria and ventricles. Enlargement of the left ventricle is most common, and left ventricular intracavity dimensions, and rarely wall thickness, can be large enough to suggest disease. Mild enlargement of both atria and the right ventricle can also occur, but marked enlargement of these structures is unusual in the athletic heart syndrome.

ECG evidence of chamber enlargement

The ECG in well-trained athletes may show mildly increased P-wave amplitude suggesting right atrial enlargement, P-wave notching suggesting left atrial enlargement, incomplete right bundle-branch block (RBBB), and voltage criteria for right and left ventricular hypertrophy.[32] Voltage criteria for right ventricular hypertrophy are noted in 18% to 69% of endurance athletes.[34] ECG evidence of right or left atrial and right ventricular enlargement is usually mild. Incomplete RBBB is common, but complete heart block is not generally seen as part of the athletic heart syndrome.[32] In contrast to the mild increases in atrial and right ventricular voltage, ECG evidence of increased left ventricular voltage can be marked in endurance athletes *(Figure 5).*[2]

Echocardiographic evidence of cardiac enlargement

Clinicians must know the magnitude of echocardiographically determined chamber enlargement in endurance athletes since this technique is frequently used to evaluate symptoms and abnormal ECG findings in athletes. At least 59 studies have used echocardiography to examine cardiac dimensions in athletes[37] and consistently documented increased left ventricu-

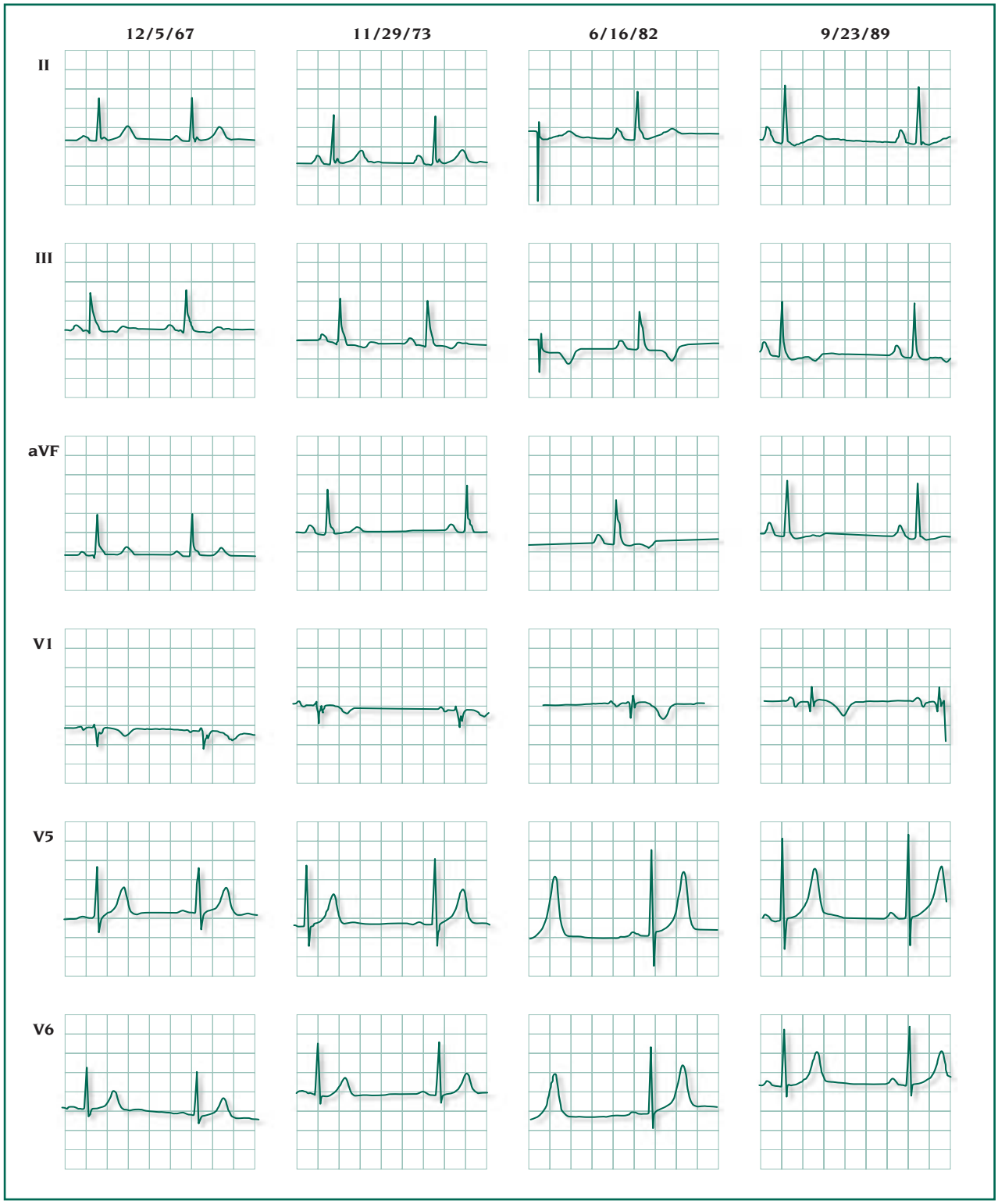

Figure 5. *ECG from a 42-year-old physician who began running 42-km footraces in his 20s. The serial tracings show classic changes of the athletic heart syndrome including increase in P-wave amplitude in lead II, increase in R- and T-wave amplitude in leads V5 and V6, deepening T-wave inversions in lead V1, and an increase in the V1 QRS duration consistent with incomplete right bundle-branch block (RBBB). He has remained healthy into his early 60s. (Green squares = 5×5 mm.)*

Reproduced from reference 2 *(see caption of Figure 1).*

lar dimensions. Thirteen studies, comparing right ventricular dimensions in athletes and controls, demonstrated an average increase in the right ventricular transverse dimension of 24% in the athletes (22 vs 17 mm).[37] Fourteen studies, comparing the left atria of athletes and controls, demonstrated a 16% larger average transverse dimension. One study has documented a larger right atrial size in athletes.[37]

Pelliccia and colleagues have explored the upper limits of echocardiographic dimensions in athletes using data obtained from Italian national athletes. These authors examined left ventricular wall thickness in 947 athletes, including 209 women.[38] Only 16 athletes or 1.7% had a left ventricular wall thickness >12 mm, the upper limit of normal. Fifteen of these athletes were rowers or canoeists (7% of all rowers and canoeists studied), sports that use a large muscle mass in both isotonic and isometric effort. The largest wall thickness in any athlete was 16 mm. All of the female athletes had wall thickness values below 11 mm.

Six of the athletes with marked left ventricular wall enlargement discontinued exercise training and were restudied after 40 to 240 (average 90) days of reduced activity.[38] Average wall thickness decreased from 12.8±0.9 to 10.5±0.4 mm, $P<0.05$. All of the athletes with increased wall thickness also had increased cavity dimensions, suggesting that the increase in wall thickness in these subjects is an adaptation to maintain normal wall stress. These results are extremely useful in differentiating the athletic heart syndrome from hypertrophic cardiomyopathy. Left ventricular wall thickness >12 mm was unusual even in elite athletes. Consequently, the presence of increased wall thickness in recreational elite athletes should prompt a search for pathological causes. No athlete had a left ventricular wall thickness >16 mm and values above this range should raise the possibility of hypertrophic cardiomyopathy. Wall hypertrophy above normal was not observed in female athletes. All athletes with wall hypertrophy also demonstrated increased cavity dimensions, which is not seen in HCM or in other diseases with pathological wall thickening. Finally, wall thickening in high-caliber athletes should regress with detraining.

These same investigators examined left ventricular cavity dimensions in 1300 elite athletes participating in 38 different sports.[39] Left ventricular end-diastolic diameter (LVEDD) was greater in male (55 mm) than in female (48 mm) athletes. LVEDD was greater than 55 mm, the upper limit of normal, in 45% of the athletes and exceeded 60 mm in 14%. The largest cardiac dimensions observed were 66 mm for a female and 70 mm for a male athlete. Regression analysis demonstrated that body surface area ($r=0.76$), heart rate ($r=-0.37$), and age ($r=0.29$) correlated with LVEDD, indicating that these three variables accounted for 60% of the variability in LVEDD. Adding gender and the type of sport to these factors accounted for 72% of the variability. Age may function in this group as a surrogate for the duration of training, although this is not certain because age did not differ between athletes whose LVEDD was or was not greater than 60 mm. The sports associated with an LVEDD ≥60 mm required a high level of endurance training or a combination of moderate endurance training and increased body size, and included cycling (49% of all cycling athletes), ice hockey (42%), basketball (40%), rugby (39%), canoeing (39%), and rowing (34%). Few athletes had evidence of left ventricular wall hypertrophy. Only 14 of the athletes, or 1.1%, had a septal thickness >12 mm, and only 4 athletes (0.3%) exceeded this posterior wall thickness. Wall thickness among all the athletes correlated with cavity dimensions. Athletes with increased cavity dimensions also tended to have larger left atrial and aortic root dimensions.

The largest changes in cardiac dimensions occur with endurance exercise training or the combination of endurance and strength training in large individuals. Increased left ventricular wall thickness can occur with strength training, but is unusual and should not readily be accepted as normal. Pluim and colleagues performed a meta-analysis on all 59 echocardiographic studies of athletes published from 1975 through 1998.[40] They divided the 1451 subjects into endurance-trained (eg, long-distance runners), strength-trained (eg, weight lifters), and combined static- and dynamic-trained (eg, rowers and cyclists) athletes. These reports included 31 studies of endurance athletes, 24 studies of strength athletes, and 23 studies of athletes trained by a combination of endurance and strength exercises. Septal thickness in endurance athletes (10.5 mm) was significantly greater than controls (8.8 mm), but less than strength-trained subjects (11.8 mm) and combination athletes (11.3 mm). Posterior wall thickness, in contrast, was actually greater in endurance athletes (10.3 mm) than controls (8.8 mm), but not different from combination- (11 mm) or strength-trained (11 mm) subjects. These results suggest that differences in wall thickness between endurance- and strength-trained athletes are small and that clinicians should not ascribe significant increases in left ventricular increased wall thickness in strength-training athletes to their athletic activity.

Functional cardiac murmurs in athletes

Both young and old endurance athletes may manifest functional cardiac murmurs. Blood flow is laminar and without turbulence until a critical Reynolds number (Re) is exceeded. Re is determined by the following formula[41]:

$$Re = \frac{\text{average velocity} \times \text{tube diameter} \times \text{fluid density}}{\text{fluid viscosity}}$$

Laminar flow is disrupted above an Re of 2000, creating turbulence and murmurs. Endurance exercise training reduces resting heart rate, increases resting stroke volume, and enhances cardiac performance. Training does not change resting cardiac output, which is delivered via a slower heart rate and a larger stroke volume. Much of the larger stroke volume is delivered more vigorously in early systole by a more dynamic ventricle. This increases blood velocity. The pulmonary and aortic valve orifices do not increase with exercise training, so the increased blood velocity produces early systolic "flow murmurs." Such flow murmurs in young athletes are due to flow across the pulmonary valve and often vary with respiration. Athletes aged ≥50 years may have mild sclerosis of the aortic valve leaflets and their flow murmurs are often due to both aortic valve sclerosis and the turbulence mentioned above. These murmurs in adults may progress to important aortic stenosis in athletes with risk factors for atherosclerosis.[42,43]

EXERCISE-RELATED CARDIAC EVENTS

Clinicians must differentiate the athletic heart syndrome from life-threatening cardiac disease and decide the level of activity advisable for individuals with diagnosed disease. This requires knowledge of the risks of exercise and of those conditions associated with exercise-related cardiac events. SCD and acute MI are the most frequent serious cardiovascular complications of exercise.[44] Exercise can also induce nonfatal cardiac arrhythmias, including ventricular tachycardia, paroxysmal atrial tachycardia, and atrial fibrillation, which will not be addressed in the present review.

Exercise-related cardiac events in children and young adults

Pathology of exercise-related cardiac events in children and young adults

Congenital cardiac abnormalities and nonatherosclerotic, acquired myocardial disease are the primary causes of exercise-related cardiac deaths in young individuals.[45-47] Atherosclerotic disease is a rare cause of exercise-related cardiac events in this group and the occurrence of an MI in this age-group should prompt a search for nonatherosclerotic causes, such as coronary anomalies, vasculitis, drug use (including cocaine and possibly anabolic steroids), or genetic abnormalities of lipid metabolism.

	Men	Women
Hypertrophic cardiomyopathy*	50	1
Probable hypertrophic cardiomyopathy	5	0
Coronary artery anomalies†	11	2
Myocarditis	7	-
Aortic stenosis	6	-
Cardiomyopathy	6	-
Atherosclerotic coronary disease	2	1
Aortic rupture	2	-
Subaortic stenosis	2	-
Coronary aneurysm	-	1
Mitral prolapse	1	-
Right ventricular cardiomyopathy	-	1
Cerebral arteriovenous malformation	-	1
Subarachnoid hemorrhage	-	1

* Three subjects also had coronary anomalies, 1 had Wolff-Parkinson-White syndrome.

† Includes: anomalous left coronary artery (LCA) from right sinus of Valsalva (n=4); intramural left anterior descending (LAD) (n=4); anomalous LCA from pulmonary artery (n=2); anomalous right coronary artery (RCA) from left sinus (n=2); hypoplastic RCA (n=2); and ostial ridge of the LCA (n=2). 3 subjects with coronary anomalies also had hypertrophic cardiomyopathy and are tabulated with that group.

Table I. *Cardiac causes of death in high-school and college athletes (N=100).*

Adapted from reference 46: *Van Camp SP, Bloor CM, Mueller FO, Cantu RC, Olson HG. Nontraumatic sports death in high school and college athletes.* Med Sci Sports Exerc. *1995;27:641-647.*

Van Camp et al reported pathological findings in 136 deaths in high-school and college athletes that occurred during or within 1 hour of sports participation.[46] Cardiac conditions were responsible for 100 deaths. Definite or probable HCM (56% of the cardiac cases), coronary artery anomalies (13%), myocarditis (7%), aortic stenosis (6%), and dilated cardiomyopathy (6%) were found most frequently *(Table I).*[46] The coronary artery anomalies included anomalous origin, intramyocardial course, and an ostial ridge at the coronary origin. Only 1 case was attributed to arrhythmogenic right ventricu-

lar cardiomyopathy, a condition in which there is fibrofatty replacement of the right and occasionally left ventricular myocardium. Two cases were caused by aortic rupture possibly associated with Marfan syndrome.

The predominance of HCM as a cause of exercise-related death and the rarity of right ventricular dysplasia in the report of Van Camp et al[46] are similar to other reports from American researchers.[45,47] In contrast, right ventricular cardiomyopathy or right ventricular dysplasia is the most frequent cause of exercise-related deaths in most Italian series,[48,49] and HCM is a rare cause of exertion-related deaths in this population *(Table II).*[46,49] Consequently, the causes of exercise-related sudden death varies not only by age, but also by nationality.

	USA N=100	**Italy** N=49*
Probable hypertrophic cardiomyopathy	56	2
Coronary artery anomalies	13	16
Myocarditis	7	6
Aortic stenosis	6	-
Cardiomyopathy	6	1
Atherosclerotic coronary disease	3	18
Aortic rupture	2	2
Subaortic stenosis	2	-
Coronary aneurysm	1	-
Mitral prolapse	1	10
Right ventricular cardiomyopathy	1	22
Cerebral arteriovenous malformation	1	-
Subarachnoid hemorrhage	1	-
Conduction abnormalities	-	8
Other	-	11

*45 of 49 deaths were associated with exertion.

Table II. *Cardiac causes of exercise-related deaths (%) in US high-school and college athletes[46] and in Italian athletes from the Veneto region.[49]*

There are several clinically important observations from these pathological studies. First, deaths among women are rare. This is not due to participation rates, since the calculated incidence rate is also lower.[46] Differences in the duration and intensity of athletic training and competition could contribute, but rates of SCD are also lower for older women in the general population,[50] suggesting that women are somehow protected against SCD. Second, no deaths were attributed to anomalous AV cardiac conduction alone, such as WPW, and an accessory pathway conduction pattern is probably more common in endurance athletes because of enhanced vagal tone.[34] The rarity of exercise-related deaths among athletes with WPW is important because many cardiologists recommend ablative therapy for such athletes even when the athletes are asymptomatic. Third, some exercise-related deaths remain unexplained and may represent electrophysiologic abnormalities such as accessory conduction pathways or QT prolongation. Such conditions would not be detectable by routine autopsy. Finally, neither these studies nor other data provide a true natural history of exercise-related cardiac events, because they do not indicate how many individuals were excluded from sports participation because of detected disease, and thereby spared an exercise-related SCD.

The risk of sudden death during exercise in young subjects

The incidence of major cardiovascular complications during exercise is low in young individuals because the prevalence of cardiac abnormalities is low. Furthermore, even when cardiac abnormalities are present, they do not always result in a cardiac event. For example, the prevalence of echocardiographic evidence of left ventricular hypertrophy consistent with HCM is approximately 1/500, or 0.2%, among American adolescents,[51] but the incidence of exercise-related SCD is much lower. This could be due to self-selection of affected individuals away from athletic participation, effective screening programs, or genetic variants in the disease. The absolute incidence of death during or within 1 hour of sports participation among US high-school and college athletes is 1 death per year for every 133 000 men and 769 000 women, respectively,[46] confirming the higher sudden death rate among men. These numbers overestimate the incidence of cardiac events, because of the 136 deaths, only 100 were caused by cardiac disease.

Reducing the cardiovascular risk of exercise in young subjects

Since cardiac conditions are the predominant cause of nontraumatic exercise-related cardiac events, cardiovascular screening before athletic participation is prudent, but there is debate over what constitutes adequate screening.

The American Heart Association recommends a personal and family history as well as a physical examination before high school participation, with the examination

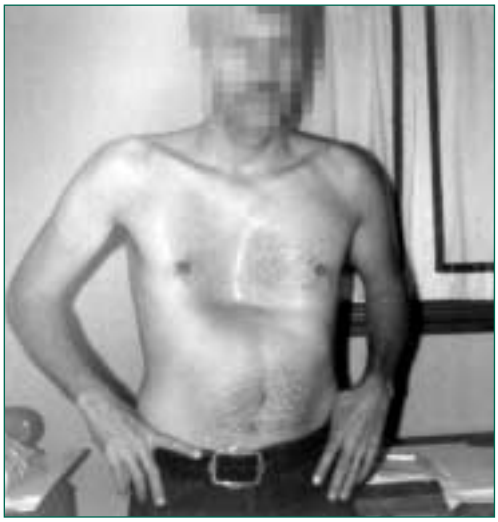

Figure 6. *Photograph of a 38-year-old recreational basketball player showing an asymmetric pectus excavatum. An off-center or asymmetric pectus is characteristic of Marfan syndrome. The subject demonstrated other skeletal abnormalities not readily visible in this picture, including increased carrying angle of the arms and increased wing span. His ascending aorta was 70 cm and he underwent aortic root replacement.*

repeated at least every 4 years.[52] The examination should include a visual inspection for the stigmata of Marfan syndrome *(Figure 6),* blood pressure determination, and cardiac auscultation standing, sitting, and during the Valsalva maneuver. Routine ECG or echocardiography is not recommended, although more extensive testing is warranted in certain instances and when cardiac symptoms are present. This document also emphasizes the importance of requiring basic resuscitation skills for coaches and other personnel who attend athletic training and competition. If cardiac disease is detected, eligibility is based on the *26th Bethesda Conference Recommendations for Determining Eligibility for Competition in Athletes with Cardiovascular Abnormalities (1994).*[53]

Other authors have argued for more extensive preparticipation screening including the routine use of electrocardiography and echocardiography.

In a population of 5615 high-school athletes, Fuller et al elicited a medical history, performed cardiac auscultation, and obtained a resting ECG.[54] Cardiovascular abnormalities requiring further evaluation were detected in 10% of the athletes, including: a suggestive cardiac history (2%), abnormal auscultatory findings (3%), hypertension (0.3%), or an abnormal ECG (2.6%). Only 22 athletes were denied participation for severe aortic insufficiency (AI) (n=1), severe hypertension (n=5), WPW ECG pattern (n=6), premature ventricular contractions (PVCs) (n=5), RBBB (n=4), and supraventricular tachycardia (SVT) (n=1). The patient with severe AI underwent valve replacement, the hypertensive patients were treated, and the patient with SVT underwent therapeutic ablation, but 15 of the 22 excluded subjects were lost to follow-up. Over the 3 years of the study, there was one cardiac arrest in an athlete with an anomalous right coronary artery who had passed screening. The authors concluded that a screening ECG increases the detection of cardiac abnormalities, but most of the clinically significant abnormalities could have been detected by the physical examination alone.

Italian experts advocate routine echocardiographic screening.[49] A national law in Italy since 1971 requires that athletes undergo an examination before being allowed to compete. The physician in charge of athlete clearance is legally responsible and can be prosecuted in both civil and criminal actions for preventable medical events.[55] The basic exam includes a history, physical examination, ECG, and step test. Athletes with abnormalities can be referred for a 24-hour ECG recording, an echocardiogram, and a formal exercise test.

This program has screened 33 735 athletes, referred 3016 for echocardiography, and disqualified 621 athletes from competition.[49] Of those disqualified, 58.7% were because of cardiac issues, including 22 athletes with HCM. Four disqualified athletes died over a mean 8.2 years of follow-up. No athlete with HCM died, although 49 other athletes who were cleared for competition died, yielding an annual death rate of 1 per 62 500 athletes. The authors compared the frequency of HCM as a cause of exercise deaths in the United States and in Italy, and concluded that the low prevalence of HCM among their athletes who died was most likely a result of the screening program.

There are problems with this conclusion. First, the prevalence of HCM in this population is surprisingly low. Only 0.06% of the athletes had this diagnosis, whereas the expected prevalence, at least in a population of healthy young Americans studied by echocardiography, is 0.2%.[51] Either the frequency of HCM is lower in Italy or potential athletes with HCM self-select themselves out of competitive endeavors. Second, few excluded athletes died. Only four of the 365 athletes denied participation died because of a cardiac condition. We do not know how these excluded athletes were medically managed, but the death rate is extremely low, raising the possibility that screening detects and prohibits low-risk individuals. Third, the annual death

rate of one per 62 500 athletes is similar to, if not higher than, the death rate of one per 133 000 male athletes reported in the United States where screening is not as organized.[46] Consequently, these results actually raise questions about the effectiveness of extensive cardiovascular screening in preventing cardiac events.

Recommendations

There are no measures of proven effectiveness for reducing exercise-related cardiac events in children. We support the American Heart Association's Recommendations for screening athletes which essentially involves a history and physical examination.[52] Simple inspection and cardiac auscultation can often detect many of the conditions associated with sudden death during exercise. The American Heart Association's Recommendations do not advocate routine electrocardiography or echocardiography because of their cost and the high rate of falsely abnormal results demonstrated in studies to date using these techniques.

Perhaps the most efficient way to reduce cardiac events in the young is to carefully exclude cardiac disease in athletes who have developed symptoms related to exertion. Many athletes who ultimately die during sports participation were symptomatic, but were not fully evaluated. We also advocate that coaches and officials be required to have updated cardiopulmonary resuscitation skills. Such individuals are often present when an athlete collapses and may be able to sustain the athlete until additional professional help is available.

Exercise-related deaths in adults

The pathology of exercise-related events in adults

Exercise-related cardiac events in adults are predominantly due to atherosclerotic coronary artery disease.[44] SCD and acute MI among *previously healthy adults* in the general population are usually produced by atherosclerotic plaque rupture with acute coronary thrombosis.[56] Black et al, in 1975, reported 13 individuals who suffered a cardiac event during vigorous exertion, and suggested that physical activity could induce acute plaque rupture, which he called "Black's Crack in the Plaque."[57] Black attributed the cardiac events to coronary spasm with subsequent infarction (A. Black, personal communication).

More recent angiographic[58-60] and necropsy[61] evidence confirms plaque rupture with subsequent thrombosis as the proximate cause of exercise-related coronary events in both adult athletes[58] and the general population.[59,60]

The mechanism of exercise-related plaque disruption

The risk of SCD[62-64] and acute MI[59,65,66] is increased during vigorous exertion compared with rest, especially in physically inactive individuals. The mechanism for this increased risk is not defined. Vigorous exertion could induce arterial injury, worsen an existing injury, or increase the risk of thrombosis in a damaged arterial segment.

Black et al suggested that the increased "twisting and bending" of coronary arteries during exertion increased the frequency of plaque rupture.[57] These authors noted that the coronary arteries were subjected to a ballooning action from the pulsation of blood, an accordion motion associated with lengthening and contracting during the cardiac cycle, a twisting motion, acute bending during contraction, and flow currents.[57] These motions are exacerbated by the increases in heart rate and contractility produced by exercise. Exercise increases the excursion of the epicardial coronary arteries because of increased end-diastolic and reduced end-systolic cardiac dimensions during exertion. Also, exercise dilates normal coronary arteries, but can produce vasoconstriction in atherosclerotic segments.[25] Such spasm over a thickened, noncompliant atherosclerotic plaque could itself contribute to plaque rupture. Interestingly, exercise-related cardiac events are more frequent in habitually sedentary subjects. Since exercise training can improve coronary artery vasomotion, this may be one mechanism mediating a reduction in exercise-related events among more active individuals. Exercise might also induce acute events by deepening existing coronary fissures. Physical exertion increases systolic blood pressure, thereby increasing shear forces in the coronaries and possibly increasing coronary fissuring.

Exercise could also facilitate plaque disruption by chemical mechanisms. Healthy subjects exercised for 25 minutes to exhaustion demonstrated increases in platelet-to-leukocyte aggregation, and plasma elastase levels.[13] Increased platelet-to-leukocyte aggregation could increase leukocyte adherence to the arterial wall, facilitating leukocyte migration into the wall where the leukocytes could contribute to disruption of the fibrous cap.[13] Elastase is produced by activated neutrophils and degrades elastic fibers in the extracellular matrix, thereby facilitating plaque disruption.

Exercise also has multiple prothrombotic effects that could increase the risk of thrombosis over an injured arterial segment. Maximal exertion increases platelet P-selectin expression and platelet-to-platelet aggregation.[13] Both changes contribute to the development

of platelet thrombi. Exercise-induced platelet aggregation is greater in sedentary subjects,[12] possibly because exercise training reduces the catecholamine response to any absolute workload. Lower catecholamine levels reduce the chance of catecholamine-induced platelet aggregation. This discussion of plaque rupture and thrombosis as a cause of exercise-related cardiac death applies primarily to previously *asymptomatic* subjects. Patients with known coronary heart disease who die during exertion often have necropsy evidence of previous infarction, but no evidence of an acute coronary lesion or recent myocardial injury.[67] The absence of any acute coronary lesion suggests that such subjects die of ventricular fibrillation originating from areas of myocardial scarring.

The risk of sudden death during exercise in adults

The risk of exercise is considerably greater in adults because of the increased prevalence of atherosclerotic disease. Nevertheless, exercise complications are relatively rare even in adults, and the rarity of exercise-related events limits the number of cases available for estimating incidence. Two of the most frequently cited studies on the incidence of exercise-related events collected deaths in the US State of Rhode Island[62] and cardiac arrests in Seattle.[63] There were only 10[62] and 9[63] events in these studies, so that small changes in the numerator could greatly affect the estimated incidence. There are few other studies based on well-defined unselected populations, and selected populations, such as military recruits, may have undergone cardiovascular screening or be otherwise selected so that their results may not be applicable to the general population.

We collected all deaths, in men, during jogging, from 1975 through 1981 in Rhode Island and calculated the incidence of death using a random-digit dial telephone survey and state population estimates.[62] There was 1 death per year for every 7620 joggers aged 30 through 65. Half of the victims had known coronary artery disease (CAD) by history or ECG criteria. If these men were eliminated and we assumed that no other joggers had known CAD, the annual incidence of sudden death was 1 death per every 15 240 previously healthy joggers. This agrees with the annual incidence of 1 exercise-related cardiac arrest per 18 000 previously healthy, physically active men in Seattle,[63] suggesting that these studies approximate the true event rate.

There are methodological problems with these studies. SCD is the initial presenting complaint in approximately 25% of patients with CAD. Consequently, these studies do not provide a true measure of the incidence of exercise-related cardiac events in adults because neither collected exercise-related MI or both deaths and SCD survivors. The prevalence of joggers in the Rhode Island study was based on self-report from the random-digit telephone survey.[62] Self-report may overestimate the number of joggers and underestimate the rate of jogging deaths. The telephone calls were placed between 5 and 8 PM. The first person over age 15 years to answer the phone was interviewed. If joggers were running during this time period, the prevalence of joggers would have been underestimated and their death rate overestimated. A major problem in estimating the risk for previously asymptomatic men is the assumption that other men with known heart disease did not jog. Both the Rhode Island and Seattle estimates also have wide confidence limits because of the small number of events. The 95% confidence limits for the Rhode Island study suggest that 1 death during jogging will occur per year for every 4000 to 26 000 asymptomatic men.[62] These studies were published almost 20 years ago, but to our knowledge have not been supplanted by more recent data.

Incidence figures are also lacking for exercise-related SCD in adult women both from these studies and the literature in general. This reflects the delayed development of CAD in women, lower rates of vigorous physical activity among older women, and the lower incidence of SCD in women in general.

Although the absolute death rate for ostensibly healthy individuals is low, the death rate per hour of exercise is increased.[62-64] The relative risk of sudden death was 7-fold higher during jogging than during more sedentary activities in Rhode Island.[62] The Seattle study calculated the incidence of cardiac arrest based on the habitual activity level. In men who spent <20 minutes per week in activities requiring ≥6 kcal min of energy expenditure, the relative risk of an exercise related cardiac arrest was 56 times greater than at rest, whereas the relative risk was increased only 5-fold in men who spent ≥140 minutes per week in such activities.[63] This demonstrates that regular exercise reduces the risk of sudden death during exercise, but that exercise transiently increases the risk even among habitually active individuals.

If exercise does indeed reduce the absolute annual incidence of exercise-related sudden death, the annualized death rate should be considerably lower in middle-aged athletes. Unfortunately, few studies have estimated the incidence of sudden death among such

subjects. Maron et al calculated the frequency of cardiac arrest among 215 413 participants in the Marine Corps and Twin Cities Marathons from 1976 to 1994.[68] There were 4 and 1 deaths, respectively, per 50 000 participants over this time span. If a marathon time of 4 hours was used, the death rate was 1 per every 215 000 hours of competition. This number exceeds the incidence of sudden death among joggers in the Rhode Island population (1 per 396 000 exercise hours)[62] as well as the incidence of cardiac arrest among the most active group in the Seattle study (1 arrest per 4 800 000 exercise hours).[63] The number of marathoners who died[68] prohibits firm conclusions, but the higher hourly rate in the marathoners suggests that prolonged, competitive tasks augment the exercise risk.

The risk of MI during exercise

Two large studies have determined that 4.4%[63] to 5.8%[66] of MIs occur during or within 1 hour of vigorous exertion. These reports included recurrent MI in the database, and therefore cannot provide the percentage of exercise MIs in previously asymptomatic subjects. Both studies confirmed the exercise sudden death literature by demonstrating an increased incidence of MI during vigorous exertion and a higher incidence of exertion-related events in physically inactive subjects. Unfortunately, neither study determined the absolute incidence of exercise-related MI.

We have estimated the incidence of exercise-related MI during vigorous exercise in previously healthy individuals[69] using data from the Lipid Research Clinics (LRC) Primary Prevention Trial of previously healthy hypercholesterolemic men and available SCD incidence figures. In LRC, the incidence of exercise-related MI was seven times higher than the incidence of exercise SCDs.[70] Assuming a 7-fold higher MI rate and an absolute risk of SCD during exercise of 1 per 15 000[62] to 18 000[63] healthy men, the annual rate of exercise MI would be 1 per 2142 to 2571 exercising men. Using 95% confidence limits from the Rhode Island study, the annual rate could range from 1 per 571 to 3714 men per year. This represents a significant risk, but no study to our knowledge has determined the absolute incidence directly.

Reducing the cardiovascular risks of exercise in adults

Reducing exercise-related events in adults ultimately requires preventing atherosclerotic cardiovascular disease. Interestingly, exercise-related MIs are more frequent in patients who are hyperlipidemic,[59] smokers,[59] obese,[59] diabetic,[59] and physically least active.[59,65] Such data suggest that one of the most important interventions before initiating a vigorous exercise program in middle-aged, sedentary adults is treatment of their other atherosclerotic risk factors. In contrast to exercise-related events in the general population, among athletes who developed an exercise-related atherosclerotic cardiac event, hypertension (19% vs 33%), hypercholesterolemia (14% vs 56%), and cigarette smoking (58% vs 94%) are less frequent.[58] These results are based on only 36 athletes and controls, but do suggest that the established risk factors may not be as useful in identifying well-conditioned athletes at risk for exercise-related cardiac events. This does not obviate the need to treat risk factors in both athletes and nonathletes, because such treatment may stabilize coronary atherosclerotic lesions and thereby reduce the incidence of cardiac events.

The role of exercise stress testing to detect cardiac ischemia in athletes and in sedentary individuals starting vigorous exercise training is controversial. The American College of Sports Medicine (ACSM) recommends exercise stress testing prior to vigorous exercise for "high-risk individuals," including men over 45 and women over 55 years of age, individuals with more than one CAD risk factor, and those with known CAD.[71] Most authorities agree with these recommendations for those with established CAD. In contrast, the *American College of Cardiology [ACC]* and the *American Heart Association [AHA] Guidelines for Exercise Testing* listed routine exercise testing prior to vigorous exercise in asymptomatic persons as a class IIB or a situation where use was not well established by evidence or opinion.[72]

The ACC and AHA Committee's reluctance to endorse routine exercise testing in asymptomatic adults prior to exercise is based on several considerations. The incidence of cardiac events among asymptomatic adults is extremely low, which reduces the utility of any routine screening procedure. The utility of any routine screening procedure depends on the prevalence of the disease in the population, and since the frequency of asymptomatic hemodynamically significant disease is low among asymptomatic individuals, false positive results are common. It is not clear, even among advocates of exercise screening, how often such tests should be repeated. A truly positive exercise test requires a hemodynamically significant coronary obstruction, whereas acute coronary events often involve plaque rupture and thrombosis at the site of previously nonobstructive atherosclerotic plaque.[73] Consequently, positive exercise tests are a stronger predictor of angina pectoris than of sudden death or acute MI, the major

risks of vigorous exercise.[74] Similar considerations affect the use of other screening exercise procedures such as radionuclide or echocardiographic imaging, although such techniques would reduce the incidence of false positive results.

Recommendations

There are no techniques documented to reduce exercise-related cardiac events in adults. We do not recommend routine exercise for the considerations presented above, but strongly advocate the use of exercise testing among active adults who develop symptoms possibly related to cardiac disease. Indeed, many adults, including athletes, who suffered exercise-related cardiac events had ignored prodromal symptoms.[75] Noakes reported prodromal symptoms in 71% of 28 marathoners who suffered cardiac events.[76] Most continued to train and race despite their symptoms. Consequently, it seems prudent that exercising adults should know the nature of possible cardiac symptoms and the importance of having these symptoms evaluated before proceeding with exercise. Exercise stress testing is extremely useful in evaluating nonspecific discomforts and possible prodromal symptoms in active people. Just as athletes should heed possible prodromal symptoms, physicians should not dismiss possible cardiac symptoms in even the fittest adult athletes, since no athletes are immune to cardiac disease. Excluding important cardiac disease in *symptomatic* athletes may be one of the most efficient ways to prevent exercise-related complications. It is also prudent to require cardiopulmonary resuscitation skills in officials supervising exercise-related events for adult athletes. Automated external defibrillators may also prove useful in preventing exercise-related deaths if available at athletic events involving large numbers of middle-aged athletes, but the cost effectiveness of this suggestion, given the rarity of exercise-related events, requires careful evaluation.

Cardiac event rates in patients with known coronary artery disease

Four studies since 1980 have reported exercise complication rates among patients participating in exercise-based cardiac rehabilitation programs.[77-80] These reports estimate an average of 1 cardiac arrest and 1 MI per 120 000 and 222 000 patient-hours of participation *(Table III).*[77-80]

FUTURE DIRECTIONS

Despite the knowledge available regarding the benefits, physiologic adaptations, and risks of physical activity, there are many areas requiring further study. It remains unclear what quality and quantity of physical activity is required to reduce the incidence of CAD. Since risk almost certainly rises with intensity, it is important to define the beneficial threshold of activity so that individuals can achieve benefit with minimal risk. In the absence of better-defined thresholds, the recommendation that adults engage in a minimum of 30 minutes of moderately intense exercise on most, preferably all, days of the week is reasonable.[81] There is also little information on how to better quantify the risks of exercise for the general population and for those individuals with diagnosed cardiac disease. At present, all patients with the same pathological condition are treated similarly, but it is not certain that disease phenotype alone determines risk.

The greatest gains in our understanding of the Good, Bad, and Ugly of exercise will likely be based on studies of individual and genetic variations. The study of the genetic determinants of the individual response to pharmacologic agents has been labeled pharmacogenomics. Several investigative groups have initiated studies of genetic variants contributing to the individual response to exercise training or "exercise genomics." These studies may answer many of our present ques-

Source	Cardiac arrest	MI	Fatalities	MI + arrest
Van Camp and Peterson,[77] 1986	111 996	292 990	783 972	81 101
Digenio et al,[78] 1991	120 000	-	160 000	120 000
Vongvanich et al,[79] 1996	89 501	268 503	268 503	67 126
Franklin et al,[80] 1998	146 127	97 418	292 254	58 451
Average	116 906	219 970	752 364	81 669

Table III. *Incidence of cardiac events in cardiac rehabilitation participants.*

tions about exercise. It may be possible to tailor therapy for individual patients based on which patients are most likely to improve their CAD risk factors with exercise therapy. Genetic testing may also prove useful in differentiating the extreme cardiac hypertrophy occasionally seen with the athlete's heart syndrome from disease.

Genetic testing may also in the distant future supplant present screening techniques. We at present do not know if all patients with an inherited disease are at identical exercise risk. Genetic variants in HCM appear to affect the natural history of the disease[82] and could affect the risk of exercise. Genetic variants of the long QT (LQT) syndrome appear to produce different susceptibilities to catecholamine stimulation and to exercise.[83] Individuals with LQT1 are more likely to experience ventricular tachycardia or SCD during exercise than at rest (62% vs 3%), whereas patients with LQT2 and LQT3 are more likely to suffer events during rest than exertion (34% vs 13%).[83] These are examples of genetic variants affecting exercise risk, but genotypic information in the future may allow some athletes with cardiac disease to participate in sport despite a phenotype presently considered exclusionary.

It may also be important to determine the interaction of genetic variants with the environmental stimulus of exercise training. Does exercise training affect the expression of genes associated with hypertrophic cardiomyopathy? Does the increased vagal tone and resting sinus bradycardia produced by exercise training increase the overall SCD risk for patients with LQT2 and LQT3 despite their possible protection from exercise-induced events? Increased knowledge of the interaction of genetics with the environmental stimulus of exercise may in future permit maximizing the Good of physical activity while minimizing the Bad and, especially, the Ugly.

THREE KEY QUESTIONS

Heart-conscious readers of this article will not have failed to note that: *"Even a single exercise session can have beneficial effects on triglycerides, systolic blood pressure, and insulin sensitivity. The reduction in systolic blood pressure can persist for up to 12 hours. Individuals with mild hypertension could normalize their blood pressure with twice-daily exercise sessions."* They would doubtless agree with the concluding recommendation: *"that adults engage in a minimum of 30 minutes of moderately intense exercise on most, preferably all, days of the week is reasonable."* However, any resolve to adopt a new athletic life may have been tempered by reading about the risks associated with a hasty decision to commence serious exercising, in particular the small, but far from negligible, risk of sudden cardiac death. This applies not only to the fledgling or amateur sportsperson, but also to the confirmed athlete; not only to seniors, but also to college-age youngsters and young adults; not only to subjects with documented cardiac conditions, but also to those hitherto in apparently perfect health. Three experts now look into what is needed to avoid undue risk and optimize the benefits of sport for the heart. Antonio Pelliccia asks: **"What constitutes adequate and cost-effective cardiac screening prior to vigorous activity for collegiate athletes and older adults?"** Reed E. Pyeritz focuses on one aspect of screening that is assuming growing importance: **"What is the current and future role of genetic testing in the screening and evaluation of athletes?"** But what about those with a known cardiac problem: does this rule out competitive sports altogether? This question is posed by Sam Firoozi, Sanjay Sharma, and William J. McKenna: **"How does the cardiologist evaluate and advise young individuals with potentially dangerous cardiac conditions who want to engage in competitive sports?"** There is no concealing the fact that the prerequisites for engaging in one's chosen sport have changed from a perfunctory visit to the family GP for a quick checkup to an increasingly sophisticated screening strategy. But isn't this a small price to pay in order to fully—and as safely as possible—derive the expected benefit from sport in terms of protecting the heart and even improving a certain number of cardiovascular disorders?

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What constitutes adequate and cost-effective cardiac screening prior to vigorous activity for collegiate athletes and older adults?

Antonio Pelliccia, MD

Institute of Sports Science - Italian National Olympic Committee - Rome - ITALY

Preparticipation screening in competitive athletes is vital in view of the risk of sudden death during sports events. There is still uncertainty over the most appropriate screening strategy. Physical examination and medical history lack sufficient diagnostic power. Routine ECG improves the detection of unsuspected structural cardiac disease, eg, hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, and dilated cardiomyopathy. However, routine ECG also yields a large proportion of abnormal patterns, that occur in most cases in the absence of cardiac disease and are thus false positives. In adult and senior athletes, screening aims to identify and/or assess coronary artery disease. The American Heart Association consensus panel guidelines restrict exercise testing to masters athletes at risk for coronary artery disease or those aged >65 years.

Keywords: sudden cardiac death; athletic heart syndrome; electrocardiogram; echocardiogram
Address for correspondence: Antonio Pelliccia, MD, Institute of Sports Science, Via dei Campi Sportivi 46, 00197 Rome, Italy
(e-mail: ant.pelliccia@libero.it)

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Sudden and unexpected cardiac deaths of competitive athletes are tragic events, which raise alarm in the lay public and medical community—with deaths of professional and elite athletes often heightening this concern even more—because of the intuitive perception that athletes represent the healthiest segment of our society. Inevitably, a number of clinical and ethical issues also arise, including the feasibility and efficacy of preparticipation cardiovascular screening to prevent these tragedies. This paper discusses the methods and results of the medical programs that have been implemented in various countries to screen competitive athletes for cardiovascular disease.

CAUSES OF SUDDEN CARDIAC DEATH IN ATHLETES

A variety of cardiovascular abnormalities have been found to be responsible for sudden death in competitive athletes,[1-8] with substantial differences related to age.

Young athletes

In young athletes (ie, ≤35 years) a spectrum of congenital or acquired cardiac lesions have been reported as causes of sudden death, with hypertrophic cardiomyopathy (HCM) being the predominant abnormality, accounting for more than one third of all cases[1,2]; the second cause is congenital coronary artery anomalies (CCAA), with anomalous origin of the left main coronary artery from the right (anterior) sinus of Valsalva being most frequent.[3,4] Arrhythmogenic right ventricular cardiomyopathy (ARVC) is responsible for an increasing number of sudden deaths in young athletes and represents the most common cause of sudden death in Italian competitive athletes (approximately, 25%).[5,6] Taken together, HCM and CCAA (ARVC and CCAA, respectively, in Italy) account for about two thirds of all causes of sudden death in young athletes.

SELECTED ABBREVIATIONS AND ACRONYMS

ARVC	arrhythmogenic right ventricular cardiomyopathy
CCAAs	congenital coronary artery anomalies
DCM	dilated cardiomyopathy
HCM	hypertrophic cardiomyopathy
LQTS	long QT syndrome
MRFIT	Multiple Risk Factor Intervention Trial
WPW	Wolff-Parkinson-White (syndrome)

Other, less frequent diseases, include ruptured aortic aneurysm (usually in the context of Marfan syndrome), idiopathic dilated cardiomyopathy (DCM), aortic valve stenosis, mitral valve prolapse, myocarditis, Wolff-Parkinson-White (WPW) syndrome, and long QT syndrome (LQTS).

Adult and senior athletes

In adult and senior athletes (ie, >35 years) the most common cause of sudden death is ischemic heart disease, which is generally associated with atherosclerosis.[7,8]

Time of sudden death

Various considerations suggest that exercise training and competition represent a triggering factor in relation to sudden death: the majority of athletes (up to 90%) collapse during or immediately after a training session, or in the context of an official athletic event[2,9]; time of death is usually between 3 PM and 9 PM, corresponding to the period commonly spent in training and competition. Sudden deaths are more frequent from August through January, corresponding to the competitive seasons for most sports (including basketball and football) in the US.[9] These considerations have prompted the consensus recommendation that athletes at risk for sudden death should be ineligible for competitions, so as to minimize, and possibly prevent, the occurrence of such tragedies.[10]

SCREENING YOUNG ATHLETES FOR CARDIOVASCULAR DISEASE

At present, uncertainty exists regarding the most appropriate strategy for screening young athletes, and a number of issues are still debated, including the feasibility of implementing a nationwide medical program targeting millions of athletes (about 25 million subjects in the USA, and 6 million in Italy), the broad spectrum of diseases that make up the target of the screening, and, consequently, the cost-effectiveness of the diagnostic testing implemented in the screening. Another concern is the likelihood that routinely performed 12-lead ECG or echocardiography may introduce false positive and false negative results, raising legal issues related to the exclusion of athletes from the various (including economic) benefits derived from sport *(Figure 1)*. In order to clarify this controversial issue, the American Heart Association (AHA) provided a consensus panel statement for health professionals, with guidelines for preparticipation cardiovascular screening of young competitive athletes.[11] The Sudden Death and Congenital Defects Committee of the AHA has recommended a uniform cardiovascular screening program including history and physical examination as the most cost-effective protocol.

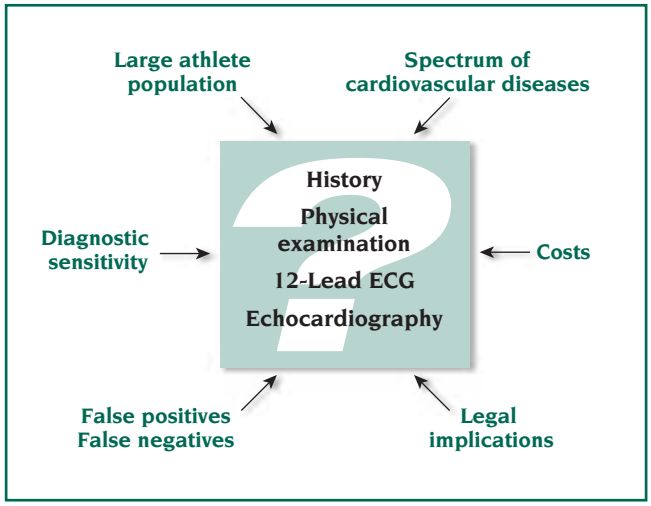

Figure 1.
Flow chart showing the different factors that impact the strategy of preparticipation cardiovascular screening in competitive athletes.

Medical history and physical examination

This simple protocol is relatively easy to implement in a large athlete population, and, in the opinion of the AHA, would improve the safety of collegiate athletic activities without exacerbating costs.[11] However, medical history has low specificity for most of the cardiac diseases that lead to sudden death, and only a minority of individuals with HCM, ARVC, and congenital coronary artery anomalies (less than 30%)[2,4,6] reported symptoms (such as impaired consciousness, palpitations, or chest pain) prior to death. Furthermore, physical examination is usually unremarkable in HCM, because most patients have the nonobstructive form of the disease, without heart murmurs, and physical examination is also negative in most CCAA and ARVC patients. Cardiac abnormalities that are likely to be detected with the standard screening protocol include Marfan syndrome, systemic hypertension, and valvular diseases (eg, aortic valve stenosis).

Therefore, it is not surprising that screening athletes on the basis of history and physical examination (and without noninvasive testing) fails to identify the majority of critical cardiovascular abnormalities. This is confirmed by the analysis conducted by Maron in 134 young athletes who suffered sudden death

in spite of the fact that they had undergone preparticipation medical evaluation.[2] Of the 115 athletes evaluated by history or physical examination, cardiac disease was suspected in only 4 (3%) and only in one case (a patient with Marfan syndrome) was a correct diagnosis made.

12-Lead ECG

The standard 12-lead ECG has been proposed as a simple and cost-effective means of enhancing the diagnostic efficacy of screening, based on the fact that ECG patterns are abnormal in more than 90% of patients with HCM,[12] in the majority of those with ARVC,[13] as well as in most patients with WPW syndrome, long QT interval, and Brugada syndrome.[14]

However, trained athletes have long been known to present a wide spectrum of ECG changes, believed to result from physiologic adaptation of the heart to training. The most common among them include marked increase in R- and/or S-wave voltages in precordial leads, ST-segment elevation, T-wave changes (either markedly tall, flattened, or frankly inverted), and deep Q waves *(Table I).*[15-17] These alterations, however, may closely resemble those observed in patients with structural cardiac disease, such as HCM or ARVC, and, therefore, raise the issue of differential diagnosis between the athletic heart syndrome and pathologic cardiac conditions.

Determinants and clinical significance of abnormal ECG patterns in trained athletes

Despite several observational studies that have exhaustively described the spectrum of ECG abnormalities in athletes in the last 3 decades,[15-17] the clinical significance and long-term consequences of these abnormalities is still largely unknown (ie, do they merely represent an innocent expression of the "athlete's heart," or do they reflect the presence of cardiac diseases with a potential of adverse clinical consequences?).

We have addressed this question by comparing the ECG patterns and echocardiographic findings related to cardiac morphology and function of 1005 trained athletes, engaged in a variety of sporting disciplines.[18] Our study showed that a large proportion (40%) of these athletes had abnormal ECGs evocative of structural cardiac disease, including 15% with distinctly abnormal and sometimes bizarre patterns. In contrast, structural cardiovascular abnormalities were identified clinically and/or by echocardiography in only 5% of athletes.[18]

Early repolarization pattern	22%-100%
↑ QRS voltages (suggestive of LVH)	14%-85%
Prolonged PR interval	10%-35%
Negative T waves	3%-30%
Deep Q waves	10%
Prolonged QTc	≤10%
Left/right atrial enlargement	≤7%
Abnormal precordial R-wave progression	≤5%
Left or right bundle-branch block	≤2%

Table I. *Commonest 12-lead ECG abnormalities reported in athletes. LVH, left ventricular hypertrophy.*

Using stepwise logistic regression analysis, we identified those factors that were most frequently associated with ECG abnormalities. Cardiac remodeling was the most frequent such factor: athletes with the most marked ECG abnormalities also showed the greatest dimensional increase in left ventricular cavity, wall thickness and mass, as well as left atrial size. In addition, participation in endurance sports (such as cycling, rowing, canoeing, and cross-country skiing) and male gender were also frequently associated with the presence of abnormal ECG patterns.

Of particular clinical interest was a small, but important, subset of athletes showing striking ECG abnormalities suggesting the presence of HCM, with diffuse, symmetric, and marked T-wave inversion, increased R- or S-wave voltages in the precordial leads, or deep Q waves, as shown in *Figures 2 and 3 (page 168);* other athletes showed patterns suggestive of ARVC, with T-wave inversion in precordial leads V1 to V3 (or V4), but in the absence of corroborating echocardiographic and familial evidence of these diseases.

In a more recent study, we carried out a long-term longitudinal evaluation of the cardiac morphology and clinical profile of 50 athletes presenting initially with distinctly abnormal ECG patterns strongly suggestive of structural cardiac disease.[19] Our preliminary findings showed that most (98%) of these athletes, studied over an 8-year period, did not develop any clinical and/or echocar-diographic findings consistent with heart disease, such as HCM, DCM, or ARVC. Indeed, we observed that a large proportion of the abnormal ECGs (48%) largely returned to normal, or became less

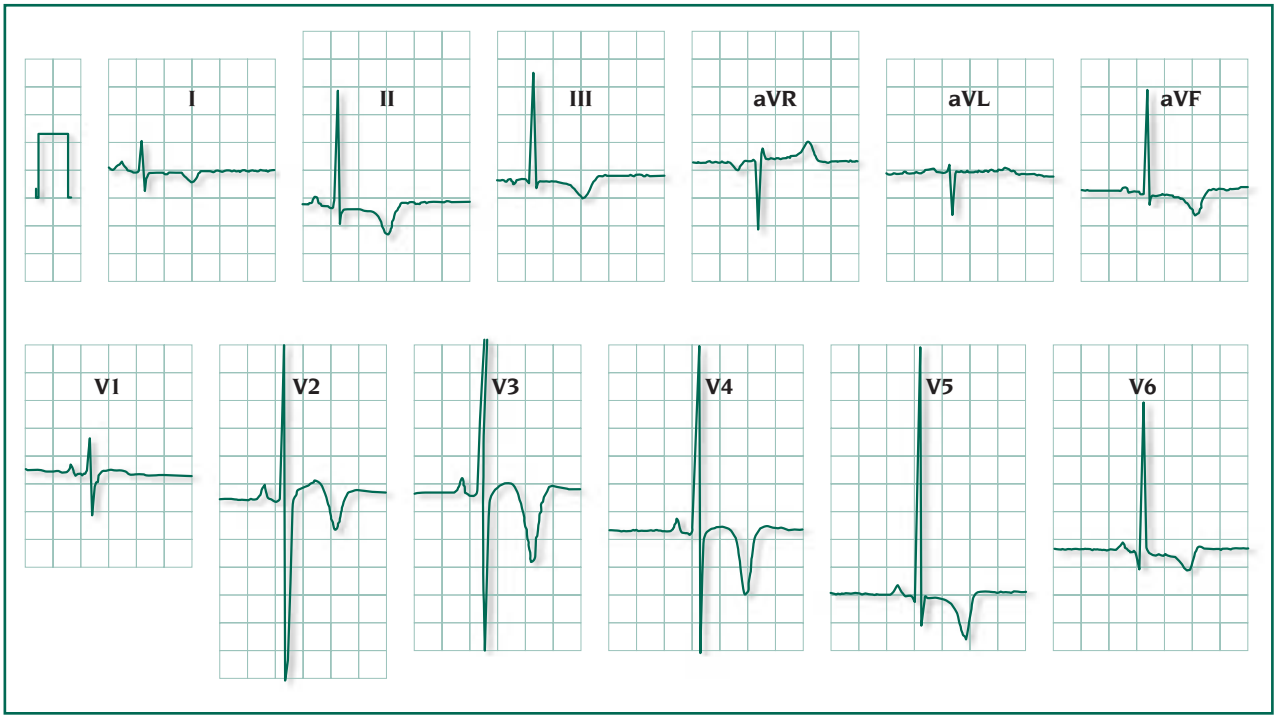

Figure 2. *Markedly abnormal ECG pattern from a young athlete, strongly suggestive of structural cardiac disease, such as HCM. Diffuse and deeply inverted T waves are present in the anterior and lateral precordial leads (V2 to V6), lateral (I) and inferior standard leads (II, III, and AVF), associated with increased precordial R- and S-wave voltages.*

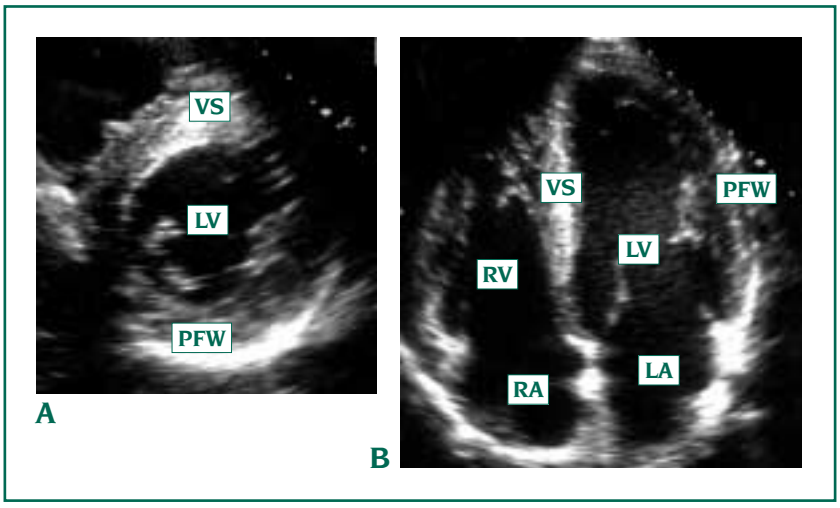

Figure 3. *Parasternal short axis* ***(A)*** *and apical 4-chamber* ***(B)*** *echocardiographic views of the heart in the same athlete as in* Figure 2, *showing normal cardiac dimensions and absence of structural abnormalities (left ventricular end-diastolic cavity dimension = 52 mm, maximum ventricular thickness = 11 mm). Calibration dots are 1 cm apart.*

Abbreviations: *LA, left atrium; LV, left ventricle; PFW, posterior free wall; RA, right atrium; RV, right ventricle; VS, ventricular septum.*

abnormal, over this period. Although the mechanisms responsible for normalization were not clarified, detraining was shown to exert a major influence, since 75% of athletes examined after complete deconditioning showed a less abnormal (or completely normal) ECG pattern. In conclusion, although the causes of abnormal ECG patterns in trained athletes remain elusive, it cannot be excluded that long-standing athletic conditioning may itself preferentially and markedly alter the ECG, and, therefore, it is likely that, in certain individuals, abnormal ECGs are not the expression of a pathologic cardiac condition, but a conspicuous component of the "athletic heart syndrome."

Efficacy and limitations of the 12-lead ECG in preparticipation screening

The diagnostic efficacy of routine ECG in preparticipation screening has received confirmation from findings extending over nearly 3 decades from an Italian national-based program, in which 12-lead ECG was routinely used.[20] This Italian experience showed that the ECG (in addition to history and physical examination) was able to identify or suggest the presence of a certain number of cardiovascular diseases

responsible for the occurrence of sudden cardiac deaths during athletic events. Among a population of over 33 000 young athletes (of ≤35 years) enrolled in the screening program in the Veneto region between 1979 and 1996, the presence of cardiovascular disease was suspected in 9%, in most cases on the basis of ECG abnormalities,[21] and confirmed in 2%, including in 22 athletes with unsuspected HCM. The Italian experience demonstrates that even though routine electrocardiography is able to identify athletes with HCM, athletes at risk of cardiac diseases represent only a minority of those with electrocardiographic abnormalities. Similar screening programs using routine electrocardiography in US high-school athletes have also yielded a large proportion (about 10%) of abnormal findings, most of them attributable to minor cardiovascular abnormalities that did not preclude training and competition.[22] Thus, the low diagnostic accuracy of the 12-lead ECG in trained athletes is a serious impediment to the efficacy of screening.

In view of these considerations, we recently carried out a prospective study comparing ECG patterns and cardiac morphology and function assessed by echocardiography in a large population of elite and professional athletes. Thus, we examined 1230 athletes screened "positive" for suspected cardiac disease, mostly on the basis of their ECG abnormalities. Among these 1230 individuals, structural cardiac disease could only be confirmed in a small subset of 67 (5%) at echocardiography, including virtually all athletes with HCM, ARVC, and DCM. However, echocardiographic assessment showed that an overwhelming majority of athletes (95%) were free of pathologic conditions and thus represented false positives. This high proportion of false positives in our athlete population is likely explained by the low prevalence of pathologic cardiac conditions (5%) in these young asymptomatic subjects having undergone medical evaluation only because of the mandatory screening program implemented in Italy.

We also sought to assess the incidence of false negatives (ie, the specificity) of routine electrocardiography in athletes. For this we examined 4450 athletes who had been cleared at screening and considered free of cardiovascular disease. The absence of pathologic cardiac conditions was confirmed in virtually all of these subjects (over 99%) by echocardiography. Only a small subset of 13 athletes (0.3%) had conclusive evidence of structural cardiac abnormalities (ie, were false negatives).

Based on this experience, it is safe to assume that no additional diagnostic testing is routinely required for those athletes cleared by routine electrocardiography at preparticipation screening. In conclusion, routine echocardiography appears to have a negligible additional diagnostic impact in preparticipation screening, as it identifies only an small subset (ie, less than 1%) of athletes with undetected (or unsuspected) cardiovascular diseases.

SCREENING ADULT AND SENIOR ATHLETES FOR CARDIOVASCULAR DISEASE

This category of athletes comprises many individuals aged above 60, and a substantial proportion of subjects who resume training and competition after long periods of complete physical inactivity or with only sporadic training experience. Overall, a substantial number of adult and senior athletes with documented cardiovascular disease wish to compete in masters events.

The AHA has recently published an expert consensus document with guidelines for preparticipation screening and assessment of cardiovascular disease in masters athletes (ie, ≥40 years).[23] The AHA statement suggests that, for the sake of prudence, preparticipation evaluation be highly recommended to all adult/senior athletes before entering sport training programs and competitions. The preparticipation evaluation should emphasize the detection of unknown coronary artery disease and, for this purpose, specific recommendations were issued concerning what to look out for when taking the personal and family history; indeed, exercise testing is recommended for all athletes having a cardiovascular risk profile for coronary artery disease *(Table II, page 170).*[23] In this regard, the AHA expert panel acknowledges that a number of studies are controversial with respect to identification by exercise ECG of subjects at risk in a large cohort of asymptomatic individuals, and, therefore, does not recommend the routine use of exercise ECG in healthy asymptomatic individuals without any risk factor. Nevertheless, some clinical trials, notably the Multiple Risk Factor Intervention Trial (MRFIT),[24] suggest that, in an adult population with coronary risk factors, exercise ECG findings of myocardial ischemia are associated with greater incidence of future coronary events. In addition, the Seattle Heart Watch Study showed that asymptomatic men over 40 years of age, with >1 coronary risk factors and >2 abnormal findings at exercise ECG, demonstrated a substantial increment in 5-year cardiac risk.[25] Indeed, as the incidence of coronary artery disease increases with advancing age, the likelihood that

Dyslipidemia	Total cholesterol >200 mg/dL, LDL >130 mg/dL, HDL <35 (<45 in women) mg/dL
Systemic hypertension	Systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg
Diabetes mellitus	Fasting plasma glucose >125 mg/dL or Treatment with insulin or oral hypoglycemics
Positive family history	Myocardial infarction or sudden death in a first-degree relative <60 years old
Age	If >65 years, even in the absence of symptoms or risk factors
Smoking habit	

Table II. *American Heart Association (AHA) recommendations for exercise testing in master athletes.*[23]

positive exercise ECGs represent a true expression of ischemic heart disease rises in mature individuals. The AHA expert panel also acknowledges that maximal exercise testing is only a preliminary investigation when estimating the likelihood of the presence of coronary artery disease, and a positive exercise ECG deserves further diagnostic evaluation to confirm the presence and severity of ischemic heart disease.[23]

CONCLUSIVE REMARKS

In conclusion, screening athletes for cardiovascular disease is an ambitious project, which presents intrinsic difficulties and limitations related to costs and feasibility. A program to screen several million athletes raises innumerable challenges in terms of organization, implementation, and efficacy, and requires huge financial support, and is fraught with uncertainty since the likelihood of preventing sudden death in competitive athletes through preparticipation screening continues to be a widely debated clinical issue. The long-standing Italian experience, with a preparticipation medical program specifically designed for large populations of competitive athletes, has been implemented for almost 30 years and is worthy of note for its objectives and results. The cardiovascular screening program implemented in Italy, which routinely includes standard electrocardiography, appears to be able to alert to, or identify, most cardiac diseases responsible for sudden death in young athletes, including HCM, ARVC, and DCM. However, the Italian experience also shows that screening trained athletes by means of electrocardiography yields a large proportion of abnormal ECGs, most of which turn out to be false positives. Consequently, routine ECG in trained athletes usually requires additional diagnostic investigations to exclude the presence of cardiac disease, and is likely to raise clinical and legal controversies regarding cardiovascular diagnosis, eligibility to professional sports, and insurance issues.

In contrast to young athletes, where governing authorities or school organizations are expected to provide preparticipation medical evaluation, it is unrealistic that such organizations also provide screening programs for adult and senior athletes. Therefore, it is the primary responsibility of adult and senior athletes themselves to contact a specialized physician for the purpose of periodical cardiovascular evaluation and counseling prior to engaging in vigorous physical exercise or resuming competition.

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What is the current and future role of genetic testing in the screening and evaluation of athletes?

Reed E. Pyeritz, MD, PhD

Professor of Medicine and Genetics - University of Pennsylvania School of Medicine - Chief, Division of Medical Genetics - Hospital of the University of Pennsylvania - Pa - USA

A host of medical problems attend athletics, from acute events (eg, sudden death) to chronic conditions (eg, degenerative arthritis). There is increasing interest in genetically identifying athletes at heightened risk for morbidity or mortality. The focus has been on uncommon disorders caused by mutations in single genes. Eventually the focus will expand to include multifactorial conditions, such as coronary artery disease. Genetic testing, even for Mendelian disorders such as Marfan syndrome, familial hypertrophic cardiomyopathy, and the long QT syndromes, is more complicated than other forms of testing in medical practice, and involves issues of analytic and clinical validity, clinical utility, cost, discrimination and stigmatization. Moreover, genetic testing requires pretest and posttest counseling that either is ignored by practitioners or is beyond their current level of understanding.

Keywords: genetic predisposition; genetic testing; sudden death; family history; Marfan syndrome

Address for correspondence:
Dr Reed E. Pyeritz, Maloney 538, 3400 Spruce Street, Philadelphia, PA 19104, USA
(e-mail: reed.pyeritz@uphs.upenn.edu)

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Participating in regular exercise provides unquestioned advantages to the vast majority of humans. In the future, the genetic predispositions to these multifarious benefits will be disentangled, and health care professionals will be able to predict who will gain the most from certain types of exercise. In turn, this will enable the prescription of highly individualized programs of exercise—be they for fitness, competition, or rehabilitation—for people of all ages and constitutions. Undoubtedly, the same genetic screening will be used to identify people at the highest potential to succeed as competitive athletes, and a host of ethical issues will emerge.

In this article, I do not address these somewhat futuristic concepts that deal with the benefits of exercise. Rather, the focus is on identifying those individuals who are at risk for suffering harm from exercise. The main question relates to the use of tests to identify a risk based in the genotype, now and in the near future.

The first issue that might come to the mind of a busy clinician is how pervasive a consideration of genetic risk needs to be in everyday practice. My answer began to crystallize two decades ago and is summarized by a statement in a weekly news magazine. "There's no disease that doesn't have a genetic component, unless you count crossing the street and getting hit by a truck."[1] With the completion in 2001 of the draft of the Human Genome Project, my naiveté of 1984 is obvious; many genetic defects of hearing or sight can increase the likelihood of being hit by a truck. While this perspective risks trivializing the issues, it does avoid the knotty problem of producing a list of 50, or 500, "genetic" conditions associated with risks of exercise, and have clinicians infer that genetic factors are unimportant in all other cases. Even with a compendium of all 3.2 billion nucleotides in the haploid set of human chromosomes, no one should consider the application of this information simple.

As with most clinical issues involving genetics in medicine, the answer to the question posed by the title of this article will evolve, perhaps more quickly than we expect. Certainly, new knowledge about genetic variation and genetic interactions, technologic developments that facilitate analyses, and societal perspectives on the legal, ethical, and eco-

SELECTED ABBREVIATIONS

FHC	familial hypertrophic cardiomyopathy
LQTS	long QT syndrome
MFS	Marfan syndrome

nomic aspects of genetic testing will influence how health care professionals can, and should, respond. The discussion must be framed, in part, by time; there is much concern about sudden death associated with exercise, but far more morbidity and costs are attributed to the long-term effects of exercise, at least in some individuals. Finally, while this series of articles in *Dialogues in Cardiovascular Medicine* addresses, predictably enough, cardiovascular concerns, the effects of exercise on all tissues and organs bear clinical attention. These various issues can be illustrated with a few examples. In the acute situation, we are interested in preventing events that cause death or a prolonged inability to compete, such as ventricular fibrillation, myocardial infarction, and rupture of the anterior cruciate ligament. In the perspective of a person's life, we might like to predict who is most at risk of degenerative arthritis of the knees or neurodegeneration from isolated or repeated head trauma. In between these extremes of chronicity, one day we should be able to predict how well an individual will recover from strenuous training or competition, how long it will take, and what specifically can be done to hasten recovery. Given my research interests over the years, I must emphasize the thread of the extracellular matrix that connects most of these issues, both physically and temporally.[2,3]

The extraordinary attention surrounding the Human Genome Project, insight that the total number of human genes is measured in the tens of thousands (ie, a manageable number), weekly announcements of the identification of genes that cause (or are, at a minimum, associated with) various diseases, and direct-to-physician (and now, direct-to-consumer) marketing of genetic testing have established numerous false hopes. The first is that genetic testing is an exact science. Another is that any disease that "runs in families" has, or will soon have, a detectable genotype. But the most pervasive, and to my mind insidious, assumption is that genetic testing is equivalent to all other medical testing. Each of these points deserves some comment, before discussing identifying people at risk for exercise-related problems.

CRITICAL PROPERTIES OF A GENETIC TEST

The actual scope of "genetic testing" will be discussed subsequently, but for now we will focus on what comes to the mind of most people—examining the genotype at the level of DNA. As with any biomedical test, scrutinizing DNA involves issues of analytic validity, clinical validity, and clinical utility. Few existing DNA-based tests have had all three of these issues rigorously addressed.[4,5] *Analytic validity* refers to the ability of a given technique to detect accurately and reliably either a normal or a mutant DNA sequence. More than a dozen distinct methods are used commercially to detect mutations, and several different techniques could be applied for a given mutation or gene. *Analytic validity* is far too technical for most practitioners to want to consider, but it is important to realize that no single approach is foolproof. *Clinical validity* refers to the likelihood that detecting a given mutation means that a disease is, or will be, present. This aspect of a test requires considerable research, preferably before the test is introduced into practice. Issues of sensitivity, specificity, predictive value, disease prevalence, penetrance of the genotype, and variability of the phenotype all come into consideration. *Clinical utility* refers to the clinical risks and benefits of utilizing a given genetic test in routine practice. For example, can identifying a person bearing a particular mutation lead to interventions that produce benefit, such as avoidance of morbidity or prenatal diagnosis for couples that are interested? Assessment of clinical utility usually requires formal outcomes research, which should include consideration of economic issues.

THE SCOPE OF GENETIC TESTING

Tests that assess the genotype of an individual do not necessarily require analysis of DNA. For example, examining a protein or a substrate can strongly suggest a defect at the level of the genome with sufficient specificity for confirmation by finding a mutation to be unnecessary. This approach can be particularly powerful when coupled with the family history, which might show others similarly affected in an unambiguous inheritance pattern. An example is testing for type III collagen deficiency in a patient with a history (or a family history) of vascular rupture. Finding a deficiency of the protein in cultured skin fibroblasts confirms the diagnosis of the vascular form of Ehlers-Danlos syndrome without having to search for a mutation in the *COL1A1* gene.[6] Genetic tests are useful for a number of purposes, as outlined in *Table I (page 174).*

Current interest in testing for cardiovascular diseases, from the perspectives of health professionals and test developers, focuses on genes of large effect that represent causes of adverse short-term consequences, especially mortality. For example, I am called frequently for advice on where to send a blood sample for analysis of mutations in genes that cause Marfan syndrome (MFS), familial hypertrophic cardiomyopa-

Purpose	Example	Gene(s)
Diagnosis	Hemochromatosis	*HFE*
Predictive testing		
Presymptomatic diagnosis	Myotonic dystrophy	*DMPK*
Susceptibility determination	Breast cancer	*BRCA1, BRCA2*
Reproductive testing		
Carrier screening	Cystic fibrosis	*CFTR*
Prenatal diagnosis	Tay-Sachs disease	*HEXA*
Preimplantation diagnosis	Marfan syndrome	*FBN1*
Newborn screening	Phenylketonuria	Based on elevated metabolite

Table I. *The purposes of genetic testing.*

thy (FHC), and long QT syndrome (LQTS) *(Table II).*[7] The genes that, when mutated, cause most forms of these three autosomal dominant conditions are well known, and hundreds of mutations have been described.[8,9] However, analytic validity, clinical validity, and clinical utility have not been rigorously studied for any of these conditions. The extensive intragenic heterogeneity for all of the genes involved, and for FHC and LQTS, considerable intergenic heterogeneity, make knowing where to start in a de novo genetic analysis difficult to predict. Few genotype-phenotype correlations exist for any of the conditions to stimulate searching for a mutation in a given family. Moreover, because detecting mutations is so time-consuming and expensive,[10] few clinical laboratories in the world offer testing. The conclusions of an American Heart Association Expert Panel convened in 1998 are still valid today, to wit, in the absence of technologic advances in mutation detection and outcome studies of clinical utility, there are few indications for genetic testing for these conditions.[11]

Condition	Type	Gene	Locus	Clinical molecular tests available[7]
Familial hypertrophic cardiomyopathies	1	*MYH7*	14q12	no
	2	*TNNT2*	1q32	no
	3	*TPM1*	15q22.1	no
	4	*MYBPC3*	11p11.2	no
	5	?	?	no
	6	?	7q31-ter	no
	7	*TNNI3*	19q13.4	no
		MYL3	3p	no
		TTN	2q24.3	no
		MYH6	14q12	no
		ACTC	15q14	no
		MYLK2	20q13.3	no
Long QT syndromes	1	*KCNQ1*	11p15.5	M, L
	2	*KCNH2*	7q35-q36	M, L
	3	*SCN5A*	3p21	M. L
	4	?	4q25-q27	L
	5	*KCNE1*	21q22.1-q22.2	M, L
	6	*KCNE2*	21q22.1	M, L
Brugada syndrome		*SCN5A*	3p221	M, L
Marfan syndrome		*FBN1*	15q21	M, L

Table II. *Some Mendelian conditions associated with sudden death during exercise.*

Abbreviations: *L, testing by linkage analysis; M, testing by mutation detection.*

MARFAN SYNDROME AS AN EXAMPLE

The situation with MFS is instructive and somewhat simpler than with FHC and LQTS, if only because just a single locus is involved.[12] The principal risk in MFS is dissection of the aorta, especially in the dilated root *(Figure 1).* Questions that are typically posed include: I'm not sure if this young athlete has MFS, would you do a blood test to make sure? My athletic department does not want to pay for echocardiograms for every basketball player; can't you screen them all with the gene test? This young woman had a father who died of an aneurysm; can you test her DNA to make sure that she does not have MFS, assuming he did? Given what can be achieved in some areas of medicine, these are not unreasonable queries. Each raises issues that are largely generic to all hereditary conditions. MFS is due to mutations in the *FBN1* gene, which encodes the extracellular matrix protein fibrillin-1. For the tall, lanky athlete who might show a few signs of a systemic connective tissue disorder (eg, scoliosis, pectus excavatum, joint hypermobility, myopia), the appropriate workup involves a detailed ophthalmologic

examination, an echocardiogram, a pedigree analysis, and an examination by a physician who knows the diagnostic criteria for MFS.[13] Most of the conditions that have overlapping signs with MFS, such as familial ectopia lentis, familial aortic aneurysm, and the MASS phenotype (mitral valve prolapse, an aortic root that may be a top-normal diameter, myopia, stretch marks, and mild skeletal changes)[14] can also be

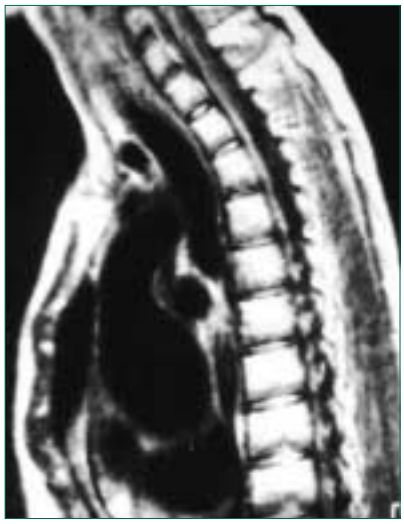

Figure 1. *Aortic root dilatation in the Marfan syndrome. In this parasagittal magnetic resonance image of an adolescent male, the aortic root is dilated to about twice normal caliber.*

caused by mutations in *FBN1,* so even if DNA from the young athlete were analyzed and a change found, it would not necessarily mean MFS. Furthermore, the *FBN1* gene is quite large, spanning over 200 000 nucleotide base-pairs of chromosome 15; about 10 000 of the base-pairs actually encode the fibrillin-1 protein. As with virtually all human genes, considerable variation occurs among the base pairs of *FBN1* among people with no features of a disorder of connective tissue. Such polymorphic variation is often difficult to separate from pathologic changes; the latter become evident when placed in the context of a family in which MFS can be linked to the specific change in nucleotide sequence. If one were to screen a team of individuals, chances are that one or a few would have a sequence variation that would be difficult to interpret, and would cause consternation until the importance of the change was understood. This process would be time-consuming and costly, as would have been the original mutation screening. Ultimately, performing echocardiograms on the entire team (which I am not necessarily advocating) would have been much simpler and cheaper. Finally, the young woman illustrates the power—and the costs—of the simplest test that any health care professional can perform: the family history.[15] This young athlete said that her father died of an aneurysm. The follow-on questions need to be: How old was he? When did he first have symptoms? Where was the aneurysm? Who can we call to verify his history? Could he have had a myocardial infarction instead? What risk factors did he have? What has been the health history of your other close relatives? Perhaps it was a cerebral aneurysm or an abdominal aneurysm, and MFS should not be much of a consideration, but if he were young, then other genetic considerations come into play. Perhaps it really was a myocardial infarction (when you hear hoof beats, think of horses, not zebras). His daughter could benefit from screening for risk factors for atherosclerosis. The cost of the initial family history is minimal in dollars and time. As in this example, making sense of the family history can be time-consuming and labor-intensive, but the results help direct the decisions about whether to recommend genetic testing, and which tests to select.

THE SPECIAL NATURE OF GENETIC TESTING

A number of considerations set genetic tests apart from the usual kind of assessments that are ordered by health care professionals, often with only cursory informed consent. Genetic tests often are not completely informative: a positive result does not necessarily mean a person will develop the condition, while a negative result may mean that the test had less than 100% sensitivity, or that a mutation was not present in that gene, but in another gene that was not assayed. Genetic tests are often costly for a variety of reasons, and insurance company reimbursement is inconsistent. Additionally, patients should be wary of insurance companies interested in excluding or otherwise penalizing individuals with, or at risk for, a potentially costly disorder. Most importantly, a test performed on the DNA of an individual conveys information not only about that person, but about relatives. Not infrequently, relatives do not want others in the family to know something about their health. Issues of confidentiality and privacy pervade genetic testing. For all of these reasons, and others that continue to emerge, genetic tests do not exist in isolation. They demand pretest counseling, informed consent, and posttest counseling. Any health care professional interested in asking for a genetic test should be comfortable with providing these three necessities, or should refer the patient to a medical geneticist or genetic counselor before ordering the test.[4,5]

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How does the cardiologist evaluate and advise young individuals with potentially dangerous cardiac conditions who want to engage in competitive sports?

Sami Firoozi, MD, MRCP; Sanjay Sharma, MD, MRCP; William J. McKenna, MD, FRCP, DSc

Department of Cardiological Sciences - St George's Hospital Medical School - London - UK

There is growing interest and awareness regarding the risk of sudden cardiac death in the young athlete taking part in competitive sports. Most sudden deaths in these subjects occur in the context of underlying inherited/genetic cardiac disorders. Cardiac evaluation of every athlete is impractical and needs to be targeted at individuals at higher risk. In practice, efforts should be channeled into athletes with cardiac symptoms or those with a family history of inherited cardiac disease or premature sudden death. There are potential pitfalls in the evaluation of noninvasive tests when distinguishing between physiological adaptations to exercise and cardiac pathology. Physicians evaluating young athletes need to be aware of the spectrum of physiological adaptations and familiar with conditions responsible for sudden death in this population.

Keywords: young athlete; sudden death; cardiovascular evaluation; competitive sport; cardiomyopathy

Address for correspondence:
Prof William J. McKenna, Department of Cardiological Sciences, St George's Hospital Medical School, Cranmer Terrace, London SW17 0RE (e-mail: wmckenna@sghms.ac.uk)

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In 490 BC, Pheidippides, the renowned Athenian Marathon runner, suffered a sudden cardiac death (SCD) after running from the battlefield of Marathon to Athens to announce the great victory of the Greeks over the invaders. The sudden death of athletes remains a topic of interest among physicians and has led to the recognition of a number of cardiovascular disorders in this population. Approximately 80% of nontraumatic sudden deaths in young athletes are due to inherited or congenital structural and functional cardiovascular abnormalities, which provide a substrate for arrhythmias predisposing to SCD.[1-3] Hypertrophic cardiomyopathy (HCM) accounts for 40% to 50% of SCD in young athletes; the other causes are summarized in *Table I.*

- Hypertrophic cardiomyopathy (responsible for up to 50% of cases)
- Arrhythmogenic right ventricular cardiomyopathy
- Congenital coronary artery anomalies
- Premature coronary artery disease
- Wolff-Parkinson-White syndrome
- Long QT and Brugada syndromes
- Idiopathic dilated cardiomyopathy
- Myocarditis
- Marfan syndrome
- Congenital aortic stenosis

Table I. *Causes of sudden cardiac death in young athletes.*

The precise incidence of cardiovascular-related SCD in young athletes is unknown as comprehensive data are lacking, but it is thought to be uncommon, with estimates from the USA suggesting 1 in 200 000 competitors.[4] The true incidence is likely to be higher for a number of reasons. Firstly, the pathologist carrying out the postmortem in young athletes rarely has experience of the conditions involved, and so subtle cases are missed. Furthermore, some conditions such as the ion channelopathies, which predispose to fatal arrhythmias, are not associated with structural heart disease, and so the cause of death may remain unclear. Secondly, the lack of a national registry for SCD in athletes leads to an underestimate of SCD in athletes. There is reliance on media coverage, which focuses on higher profile athletes and on voluntary hospital reporting. In addition, retrospective data from referral centers regarding the etiology of sudden death in young athletes are subject to bias depending on the particular expertise or area of interest of the institution. Thirdly, on the event of SCD in athletes, the

SELECTED ABBREVIATIONS AND ACRONYMS	
ARVC	arrhythmogenic right ventricular cardiomyopathy
DCM	dilated cardiomyopathy
HCM	hypertrophic cardiomyopathy
LBBB	left bundle-branch block
RBBB	right bundle-branch block
SCD	sudden cardiac death
WPW	Wolff-Parkinson-White syndrome

coroner's priority is to exclude foul play rather than establish the precise cardiovascular diagnosis.

The majority (>80%) of SCD in young athletes occur either during or immediately after strenuous physical activity.[5] This suggests that exercise may be a trigger for cardiac arrhythmias in individuals with certain cardiac disorders.

ARGUMENTS FOR AND AGAINST CARDIOVASCULAR EVALUATION OF ATHLETES

Physical exercise benefits cardiovascular health.[6] In prospective epidemiological studies, exercise is consistently associated with a reduced risk of coronary artery disease and SCD.[7-9] On the other hand, it is also recognized that a small, but significant, proportion of athletes die suddenly, possibly related to physical exercise as a trigger in the context of underlying cardiac disease, which provides the substrate for lethal arrhythmia.[10,11] Throughout history, society has made a special place for those few individuals who are faster, stronger, and physically gifted. Sudden death in an athlete is tragic and highly publicized, especially when high profile individuals are involved, and raises concern in the community who regards athletes as the healthiest cohort of society.

Ideally, all athletes would be evaluated for cardiovascular disease prior to athletic participation. However, the routine evaluation of all athletes is impractical due to the large numbers of individuals who need to be evaluated relative to the small potential positive yield. As well as not being cost-effective, this approach would put a substantial burden on health care resources. On the other hand, athletes deserve to be evaluated to ensure that athletic participation does not represent a risk. Therefore, a common sense middle ground is sought by targeting high-risk situations.

ATHLETES WITH A DEFINITE DIAGNOSIS OF CARDIOVASCULAR DISEASE

The 26th Bethesda conference was organized in January of 1994 to formulate guidelines for participation in competitive sports for athletes with an identified cardiovascular abnormality.[12] Experts in cardiovascular medicine and sports cardiology generated recommendations by means of consensus, and these provide the basis for physician advice to patients. The guidelines depend on the nature and severity of the cardiovascular abnormality and the classification of sport involved.

Athletes with unequivocal HCM should not participate in most competitive sports, with the possible exception of sports with the lowest degree of intensity (eg, bowling, golf, or curling).[13] This is regardless of the presence of symptoms, the magnitude of left ventricular hypertrophy (LVH), or left ventricular outflow tract obstruction. In view of the lower risk of sudden death in older HCM patients, individual judgment can be used where there is an absence of established risk markers for sudden death. These include: (i) nonsustained ventricular tachycardia on Holter monitoring; (ii) a family history of premature (age <40 years) SD due to HCM; (iii) a history of unexplained syncope; (iv) abnormal blood pressure response during upright exercise; (v) severe LVH (maximal wall thickness >30 mm); and (vi) >100 mm Hg severe outflow tract obstruction. With the advent of preclinical genetic diagnosis of HCM, a small number of young athletes may be identified to be gene-positive, but phenotypically normal. The clinical significance of these findings will depend on the gene in question and will become clearer with better understanding of the genotype-phenotype relationship. At present, there is little evidence to preclude these individuals from competitive sports in the absence of symptoms or a family history of SCD.[13]

There are fewer data with regard to the relative risks of athletic training in athletes with the other cardiomyopathies such as arrhythmogenic right ventricular cardiomyopathy (ARVC) and idiopathic dilated cardiomyopathy (DCM). As a result, athletes with these conditions are advised not to participate in any competitive sports.[13]

The current recommendations for participation in competitive sports for athletes with other cardiovascular abnormalities are summarized in *Table II.*

ATHLETES WITH FEATURES SUGGESTIVE OF CARDIAC DISEASE

Cardiovascular evaluation in the young athlete should be directed at identifying those conditions that

Diagnosis	*Recommendation*
HCM	• Should not participate in most competitive sports, with the possible exception of those of low intensity • Older athletes may participate depending on RFS
ARVC	• Should not participate in competitive sports
Coronary artery anomalies	• Should be excluded from competitive sports • Participation in sports >6 months after surgical treatment would be allowed for an athlete without ischemia on EST
WPW	• Athletes without structural heart disease, palpitations, or tachycardia can participate in all competitive sports • Athletes with reentrant tachycardia should be treated with RFA. • Athletes with atrial flutter/fibrillation with slow accessory pathway conduction and no syncope can participate freely. Those with syncope and/or fast accessory pathway conduction should be treated with RFA • Athletes with successful ablation of accessory pathway who are asymptomatic, have normal AV conduction on EPS, and have no recurrence of tachycardia for 3-6 months can participate in all sports
Ion channelopathies*	• Should not participate in competitive sports
Idiopathic DCM	• Should not participate in competitive sports
Premature coronary artery disease	• If considered low risk†, can participate in low- and moderate-intensity sports. Should be reevaluated annually • If considered to be high risk†, only permitted to participate in low-intensity sports. Should be reevaluated every 6 months T
Marfan syndrome	• Athletes without a family history of premature SCD and without aortic root dilatation can participate in low- and moderate-intensity competitive sports. Serial 6-monthly monitoring of aortic root should be repeated • Athletes with aortic root dilatation can participate in low-intensity sports only
Myocarditis	• Should be withdrawn from competitive sports for ≈6 months after onset of symptoms for convalescence • Return to competitive sports is permitted after normalization of ventricular function and absence of clinically relevant arrhythmias on ambulatory ECG monitoring
Aortic stenosis	• Athletes with mild AS (<20 mm Hg) can participate in all competitive sports • Athletes with mild-to-moderate AS (21 to 40 mm Hg) can participate in all low-intensity sports. Some, depending on EST, can participate in low- and moderate-intensity sports • Athletes with severe AS (>40 mm Hg) or symptoms should not engage in any competitive sports.

*Long QT and Brugada syndromes.
†Low risk defined by: (i) normal systolic function; (ii) normal exercise tolerance for age; (iii) no ischemia on EST; (iv) no exercise-induced complex ventricular arrhythmia; and (v) no hemodynamically significant coronary artery stenosis.

Table II. *Current recommendations regarding athletic participation for athletes with cardiac conditions causing sudden death in young athletes.*

Abbreviations: *ARVC, arrhythmogenic right ventricular cardiomyopathy; AS, aortic stenosis; AV, atrioventricular; DCM, dilated cardiomyopathy; EPS, electrophysiological study; EST, exercise stress testing; HCM, hypertrophic cardiomyopathy; RFA, radio frequency ablation; RFS, risk factor stratification; SCD, sudden cardiac death; WPW, Wolff-Parkinson-White syndrome.*

may place the athlete at risk from sudden death. The basic components of evaluation include the clinical history and cardiac examination along with the resting ECG and the 2-D transthoracic echocardiogram to look for structural and functional abnormalities. In the case of HCM, the resting 12-lead ECG and 2-D echocardiogram in particular are the gold standard tests for diagnostic purposes. The diagnosis of HCM would depend on the demonstration of LVH in the absence of other etiology. The majority of other conditions in question (eg, DCM, Wolff-Parkinson-White (WPW) syndrome, long QT syndrome, aortic stenosis)

would also be diagnosed with this evaluation protocol. In some conditions however, such as ARVC, extra investigations such as ambulatory Holter monitoring, signal average ECG, and exercise testing are often required for diagnosis. Likewise, in the case of premature coronary disease or congenital coronary anomalies, exercise testing and myocardial perfusion imaging may often be necessary for diagnosis.Given the time, expense, and potential psychosocial disruption from performing cardiovascular evaluation, it is reasonable to prioritize those athletes who can be defined as being at higher risk of having cardiac abnormalities. This would permit the channeling of finite financial and manpower resources into relevant target areas and would be the most efficient strategy. This can be achieved by evaluating specific groups of athletes.

Diagnosis	*ECG changes*
HCM	• Pathological Q waves • ST-segment flattening and/or depression • Marked (>0.2 mV) T-wave inversion • Left axis deviation
ARVC	• T-wave inversion in anterior precordial leads • Ventricular ectopic beats with LBBB morphology • QS complexes in leads V1-V3 • QRS prolongation (<110 milliseconds) in V1-V3 • Epsilon waves
WPW	• Short PR interval • Delta wave
Long QT syndrome	• Prolonged QT and QTc intervals • U waves • Repolarization abnormalities
Brugada syndrome	• RBBB and ST-segment elevation in anterior precordial leads

Table III. *Electrocardiographic changes seen in conditions causing sudden death in young athletes.*

Abbreviations: *ARVC, arrhythmogenic right ventricular cardiomyopathy; HCM, hypertrophic cardiomyopathy; LBBB, left bundle-branch block; RBBB, right bundle-branch block; WPW, Wolff-Parkinson-White syndrome.*

	Athlete's heart	**HCM**
Maximal left ventricular wall thickness	<16 mm	≥16 mm
LVH pattern	Concentric	ASH/variable
Left ventricular cavity size	Large	Small
Diastolic function	Normal	Impaired
Left atrial size	Normal	Dilated

Table IV. *Echocardiographic features of athlete's heart and HCM.*

Abbreviations: *ASH, asymmetrical septal hypertrophy; HCM, hypertrophic cardiomyopathy; LVH, left ventricular hypertrophy.*

Athletes with symptoms

Syncope and palpitation. Syncope is important and should not be dismissed as benign without further investigation. The exact circumstances need to be defined to see whether it is recurrent and whether it is exertion-related or situational in nature. Its association with palpitations or warning signs should be sought to try and elucidate an underlying mechanism. Unexplained syncope in a young athlete in the context of exercise should be considered as an aborted sudden death until proven otherwise. The objective in evaluating an athlete complaining of palpitation is to define the likelihood of clinically significant arrhythmia. Evaluation should be aimed at looking for structural heart disease and conduction abnormalities and should include 12-lead ECG, echocardiography, ambulatory ECG (Holter) monitoring, and tilt testing. If syncope is recurrent and preceded by palpitation or presyncope, a cardio-memo device could be used to monitor the cardiac rhythm. If syncope occurs infrequently, it may be necessary to implant a Reveal device to exclude arrhythmia as the cause. The significance of syncope and/or palpitations is influenced by the presence or absence of underlying cardiac disease.

Dyspnea on exertion. Breathlessness on exertion is a difficult problem to subjectively quantify, particularly in athletes who have different expectations regarding levels of exercise tolerance compared with the sedentary population. In addition to the ECG and echocardiogram (assessing left ventricular and valvular function), a chest x-ray and peak flow recording are useful. Such athletes should ideally be assessed using objective measurements of exercise capacity such as cardiopulmonary exercise testing with assessment of peak oxygen consumption rate (peak VO_2) as well as submaximal indices of exercise capacity, which may also

offer further insight into potential mechanisms of symptomatic limitation.

Chest pain. It is important to ascertain whether the pain is atypical in nature or whether it represents angina. Angina needs to be investigated further by echocardiography (to look for HCM, anomalous coronary arteries, and aortic stenosis), resting ECG, exercise testing and assessment of coronary artery disease risk factors. If doubt persists regarding an athlete with angina, myocardial perfusion imaging and/or coronary angiography may be indicated.

Athletes with a family history of inherited cardiac disease

Many of the conditions causing SCD in the young athlete are genetic, with an autosomal dominant inheritance pattern.[1,2] In general, when there is a known family history of an inherited cardiac disorder, the risk for individuals developing the disease is 1 in 2 unless the penetrance of the disease causing mutation is low. If an athlete is known to have a family history of inherited cardiac disease, a thorough evaluation is warranted. The evaluation of these athletes would include a clinical history and examination, resting 12-lead ECG and 2-D echocardiography.

During evaluation of the athlete, symptoms such as exertional or postprandial chest pain, sustained palpitation, presyncope, or syncope should be sought, as in the context of a family history they are suggestive of an underlying cardiovascular abnormality. A detailed family history and pedigree to confirm the exact nature and pattern of inheritance of cardiac disease is important. The presence of premature (age <40 years) sudden death(s) in the family would be relevant, as it would indicate a malignant phenotype and have implications should the athlete under evaluation be affected. Clinical examination would be directed, depending on the family history, at outflow tract obstruction (in the case of HCM), aortic stenosis, sensorineural deafness (in the case of long QT syndrome), or the typical features of Marfan syndrome. On analyzing the resting ECG, typical features of the conditions in question are looked for, which are summarized in *Table III.* The echocardiogram is carried out to look for structural heart disease including the cardiomyopathies and valvular abnormalities.

Athletes with a family history of unexplained premature sudden death

The presence of unexplained premature (age <40 years) sudden death in the family, particularly in parents or grandparents, means that the risk to the athlete in question potentially approaches 1 in 2. Under these circumstances, it is important to try to obtain as much information regarding the premature sudden death as possible. It would be important to try to get details of any autopsy reports or old medical notes. The particular points needing attention include:

- Heart weight, postmortem expert review of histology;
- Previous symptoms suggestive of cardiovascular disease or hemodynamic/electrical instability;
- Coronary artery disease risk factors.

The aim would be to attempt to determine the probability of whether the premature sudden death is relevant to the athlete under evaluation and to try to establish the cause. The evaluation of the athlete would involve similar steps as for an athlete with a known family history of cardiac disease.

POTENTIAL DIFFICULTIES IN EVALUATION OF THE YOUNG ATHLETE AND THE DIFFERENTIATION OF ATHLETE'S HEART FROM PATHOLOGY

Regular physical training leads to cardiovascular adaptations with both structural and functional changes, which are referred to as the "athlete's heart." These include an increase in left ventricular cavity size and wall thickness of 10% to 20% and an increase in left ventricular mass of up to 45%.[14-17]

LVH vs HCM

In the majority of athletes, LVH is mild and does not lead to absolute measurements exceeding normal limits. In a minority however, LVH is quite marked and raises the differential diagnosis of HCM. This is confirmed by a large echocardiographic study of over 900 elite athletes, which showed that 2% had a maximal left ventricular wall thickness >13 mm.[18] The distinction in this minority has important implications, as the diagnosis of HCM in an athlete is grounds for disqualification from competition in order to minimize the risk of sudden death. An incorrect diagnosis of HCM in an elite athlete may result in unnecessary withdrawal from competitive sport, with adverse physical, financial and psychological consequences.

Differentiation between physiological LVH and HCM is helped by characteristic echocardiographic features, which are derived from a number of studies *(Table IV).* In general, HCM patients have localized hypertrophy with reduced cavity dimensions and evidence of impaired diastolic function, while athletes do not show segmental hypertrophy, have normal or slightly

increased left ventricular cavity dimensions, and normal diastolic function. Furthermore, an athlete with significant LVH as a result of training alone would be expected to have supranormal metabolic exercise indices such as the pVO_2. Studies have shown that pVO_2 and other indices of metabolic exercise are abnormal in most HCM patients regardless of the magnitude of LVH.[19] This provides a further tool for the differentiation of physiological LVH and HCM.

Some HCM gene carriers may have incomplete disease expression or an atypical phenotype with an abnormal ECG and a normal 2-D echocardiogram.[20,21] Such individuals may be at increased risk of sudden death and present a difficulty in management, as correct diagnosis is important both in terms of prognosis and implications for familial evaluation.[22] The concept that ECG abnormalities in the highly trained athlete are part of the spectrum of the "athletic heart syndrome" is misleading and abnormal q waves, left axis deviation, T-wave inversion and ST-segment depression should lead to serious consideration of underlying cardiac abnormality.

Left ventricular cavity dilatation vs DCM

Regular intensive physical exercise can lead to an increase in cardiac dimensions including left and right ventricular cavity enlargement.[15] In a significant proportion (30%) of athletes, the left ventricular cavity size exceeds the upper limits of normal and in a minority the magnitude of left ventricular cavity enlargement is comparable to that encountered in some patients with DCM.[17] The systolic function in the majority of cases of physiological left ventricular dilatation is normal and therefore assists in the differentiation from DCM. In some athletes, however, the ejection fraction at rest may be subnormal due to a large end diastolic cavity size, yet exercise capacity is excellent due to augmentation of the ejection fraction upon exercise. Furthermore, unlike in HCM, the ECG has a very low sensitivity and specificity for the diagnosis of DCM. As a result, the evaluation of the athlete using ECG and echocardiography may not differentiate between physiological and pathological left ventricular dilatation.

Under these circumstances, the presence of symptoms associated with fluid congestion, palpitations or syncope, a positive family history of DCM, or a subnormal cardiopulmonary exercise test result, would help in the distinction between athlete's heart and DCM.

Repolarization changes vs ion channelopathies

Minor repolarization abnormalities including mild elevation of the J point associated with mild ST-segment elevation in the anterior chest leads and mild T-wave inversion (<0.2 mV) in V1-V2 and the inferior leads are a frequent finding in young athletes. A significant proportion of young athletes also possess minor intraventricular conduction abnormalities such as incomplete right bundle branch block (RBBB).

With better understanding of the long QT and Brugada syndrome, it is becoming clearer that in some cases of these conditions, similar repolarization changes to those commonly seen in young athletes are present. For example, it is recognized that in some subtypes of the long QT syndrome, abnormalities of T-wave morphology, T-wave microalternans, and small U waves in the proximity of the terminal portion of the T-wave are present.[23] Similarly, in the Brugada syndrome, the characteristic electrocardiographic abnormality is the presence of ST-segment elevation along with RBBB in the anterior leads.[24] These features raise the possibility of misdiagnosing a young athlete as being normal and allowing competitive participation in the face of a potentially lethal cardiac disorder. Furthermore, both the long QT and Brugada syndromes do express incomplete penetrance[24] with latent ECG changes, and, therefore, relying on the ECG for their diagnosis would lead to false negatives. In some other cases, the ECG changes may be subtle and there may be a need for provocation tests to confirm the diagnosis. These difficulties are highlighted by the relative lack of exposure and consequent unfamiliarity with these conditions in most cardiologists' daily practice.

In cases of uncertainty, the presence of a history of syncope or a family history of premature sudden death should raise the level of suspicion and lead to expert help being sought.

SUMMARY

Resources are not available to evaluate all young athletes prior to participation in competitive sports. As a result, the cardiovascular evaluation of young athletes needs to be targeted at high-risk areas and focus on those individuals who are at greatest risk, those with symptoms, and those with a family history of premature cardiac disease or sudden death. The involvement of amateur and professional sporting bodies and organizations with the above approach would hopefully improve the safety of athletic participation. The 12-lead ECG is the most sensitive practical tool for identification of underlying cardiac abnormalities.

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Surfing the Heart

Alphagalileo – Medow Braun Home – ESC Newscast 2002 – Cardiology Online

Claudio Ceconi, MD

e-mail: cceconi@libero.it - *Cardiovascular Research Center - S. Maugeri Foundation - Gussago - ITALY*

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Well worth a bookmark.

ESC Newscast 2002

http://www.escardio.org/newscasts/newsindx.htm

Berlin 2002, at a glance!
As was the case for the previous European cardiology meeting, the most renowned European cardiologists summarize, in a personal way, a session or a study presented during the *XXIVth Congress of the European Society of Cardiology,* Berlin, 31 August - 4 September, 2002.
About 50 reports have been broadcast live from the congress and are still available on the web site or downloadable as a digest, providing the cardiologist's view alongside that of the journalists covering the event.

Cardiology Online
International Academy of Cardiology

http://www.cardiologyonline.com/institutes.htm

The International Academy of Cardiology is a private initiative in the field of cardiovascular medicine supporting scientific meetings and publications.
In the web site of the Academy is provided an interesting and useful tool consisting of a powerful database of Universities and Medical Institutes. The queries can be launched choosing USA or Global (non-USA) as search fields pointing to thousands of individual links. An ever-growing directory of cardiology and medical centers.

All sites accessed October 1st, 2002

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Icons of Cardiology

Karl F. W. Ludwig: a founder of cardiovascular physiology

Arnold M. Katz, MD

Professor of Medicine Emeritus, University of Connecticut School of Medicine
Visiting Professor of Medicine and Physiology, Dartmouth Medical School
From the Cardiology Division - Department of Medicine - University of Connecticut School of Medicine - Farmington, Conn - USA

There are at least three ways by which a scientist becomes an icon. Most often this is by a major discovery that explains past observations and provides a basis for future advances; Harvey's description of the circulation is a clear example. A second way is to devise a method that, by making it possible to understand previously unknowable details about a natural process, stimulates the development of an immature science. In Cardiology, this is exemplified by the recipients of two Nobel Prizes: Einthoven, whose invention of the string galvanometer made possible the development of electrocardiography, and Forssmann, Cournand, and Richards who, by introducing the clinical use of cardiac catheterization, provided the scientific basis for modern cardiology and cardiac surgery. The third way to become an icon, which is both the least common and most difficult to document, is to create a new "school of thought," often by training the following generation of leaders in a new scientific paradigm. An example of the latter achievement is provided by Karl Friedrich Wilhelm Ludwig *(Figure 1)* who, in addition to both physiological discoveries and inventions, laid the foundation for modern cardiovascular physiology.

Figure 1. *Karl Friedrich Wilhelm Ludwig.*

Reproduced from reference 2: *Hamilton WF, Richards DW. The Output of the Heart. Chap II. In Fishman AP, Richards DW, eds.* Circulation of the Blood: Men and Ideas. *New York, NY: Oxford University Press; 1964. Copyright © 1964, Oxford University Press.*

BIOGRAPHY

Ludwig was born in the electorate of Hesse in 1816 and studied at the Universities of Marburg, Erlangen, and Bamberg. As a student he is described as having been ardent, spirited, and argumentative[1-4]; at one point—possibly because of his political activities—he was asked to leave Marburg, but returned to receive his MD in 1840 and, in 1846, an appointment as "Extraordinary Professor" for Comparative Anatomy. In 1849, he moved to Switzerland to become Professor and Chairman of Anatomy and Physiology at the University of Zurich, then went to Austria in 1855 as Professor and Chairman of Physiology and Zoology at a medical surgical military academy in Vienna. In 1865, he accepted the Chair of the Physiology Department in Leipzig where he was to spend the rest of his life. There he designed the new Leipzig Institute of Physiology, described by Welch as a "palace of science" (cited by 4).

Ludwig was among those responsible for a paradigm shift in physiology, from the superficial and speculative vitalism of the 18th century that viewed animal function as the manifestation of energy that was neither physical nor chemical (the "vital force"), to an experimental science that explained natural functions according to the laws of physics and chemistry. This paradigm shift was aided by Ludwig's two-volume *Lehrbuch der Physiologie des Menschen (Textbook of Human Physiology),* published in 1852 and 1856,[5] which includes what is probably the first description of the dependence of cardiac work on diastolic volume ("Starling's Law of the Heart).[6] Ludwig's text is stated to have "appeared like a meteor on the scientific horizon."[3]

DISCOVERIES

In 1842, when he was 26 years old, Ludwig described the role of glomerular filtration in urine formation; following the new paradigm of explaining physiological processes according to

Keywords: history of medicine; Karl Ludwig; physiology; cardiology; nephrology; kymograph; teaching

Address for correspondence:
Dr Arnold M. Katz, 1592 New Boston Road, PO Box 1048, Norwich VT, 05055-1048
(e-mail: arnold.m.katz@dartmouth.edu)

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physical laws, he provided evidence that the glomerulus filtered plasma from the circulation into the renal tubule.[7] Other discoveries include the all-or-none law and staircase phenomenon (treppe), the role of hydrostatic pressure and filtration across the capillary wall in generating lymph, and the ability of depressor nerve stimulation to lower blood pressure. As noted below, it is often difficult to identify Ludwig's contributions because he generally published his work under the sole authorship of his students.

INVENTIONS

In 1846, Ludwig invented the kymograph *(Figure 2),* which made it possible to obtain accurate, permanent records of physiological data. In my medical physiology course in 1952, I used smoked-drum kymographs that differed little from the one developed by Ludwig more than a century earlier. The device was simple, but messy. Sooty smoke from burning kerosene was spread over a sheet of paper that was attached to a slowly turning drum and scratched by a pointed stylus that floated on a column of mercury that was connected to an artery. At the end of the experiment, the paper was removed and dipped in shellac to make the permanent record. In the middle of the 19th century, Sir Michael Foster compared this instrument with what was then available in Britain:

> I remember very well when Sharpey [Foster's professor] was lecturing on blood pressure, and was describing to us the new results of Ludwig, endeavoring to explain to us the blood pressure curve, all he had to help him was his cylinder hat, which he put upon the lecture table before him and with his finger, traced upon the hat the course of the curve. (cited by 8).

Ludwig's other inventions include a flow meter and a technique for making a cast of the blood vessels. His most important contribution, however, was training a generation in the new paradigm of experimental physiology.

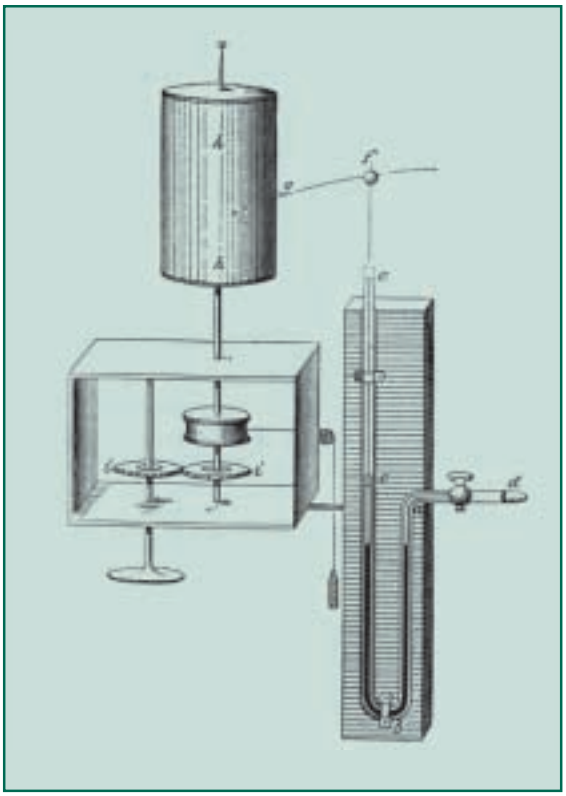

Figure 2. *Sketch of Ludwig's kymograph. A stylus connected to a float on a column of mercury (right), which can be connected to an artery so as to record blood pressure, scratches a sooty drum (top left) that is rotated by a clockwork mechanism (lower left).*

Reproduced from reference 2: *Hamilton WF, Richards DW. The Output of the Heart. Chap II. In Fishman AP, Richards DW, eds.* Circulation of the Blood: Men and Ideas. *New York, NY: Oxford University Press; 1964. Copyright © 1964, Oxford University Press.*

STUDENTS

Ludwig trained more than 200 scientists of all nationalities[1,9]; according to Osler, Ludwig "had the honor of having trained a larger number of physiologists than any other living teacher; his pupils are scattered the world over, and there is scarcely a worker of note in Europe… who has not spent some time in his laboratory."[10]

These include three of the four founding basic science professors at Johns Hopkins Medical School: William H. Welch, Professor of Pathology, John J. Abel, Professor of Pharmacology, and Franklin P. Mall, Professor of Anatomy. Other pupils were Henry P. Bowditch, the first Professor of Physiology at Harvard; Sir John Burdon-Sanderson, who became professor of Physiology at Oxford; Warren P. Lombard, who became Professor of Physiology at the University of Michigan; and Otto Frank who was discussed earlier in the present series.[11]

Ludwig, a radical activist as a student, changed remarkably in his later life. Burdon-Sanderson described him as:

> …a man who was utterly free from selfish aims and vain ambitions, who was scrupulously conscientious in all that he said and did, and was what he seemed to be and seemed what he was, and had no other aim than the advancement of his science (cited by 9).

Lombard described his interactions with those who worked in his laboratory:

> Every morning he visited the tables of the different men and discussed with them the next step to be taken…or he would take them into his private room and critically discuss the methods employed, making suggestions as to the direction in which new and more effective methods could be sought, carefully go over the curves and other data already obtained and the inferences to be drawn from them. This was not done offhand, for each night when he left the labo-

> ratory he carried to his rooms above, records and protocols of investigations in progress, for careful study (cited by 8).

As noted by Garrison[9]: "Most of his important discoveries were published under the names of his pupils, some of whom…merely sat on the window-sill, while Ludwig and his faithful assistant, Salvenmoser, did all the work." Cannon[12] quoted Lombard's description of his arrival in Ludwig's laboratory:

> [Lombard] told the professor that he was interested in fatigue but knew nothing about how to study it. Ludwig then defined a concrete problem for him, assembled the apparatus, and put him to work. When he encountered difficulties the old teacher helped him. At the end, Dr Lombard wrote an account of the methods he had used and the results he had obtained and submitted it to the professor preliminary to publication. In a short time the paper was returned almost entirely rewritten, with only Lombard's name at the top of it. He took the paper to Ludwig and protested. "You have set the problem for me," he said; "you have shown me how to use the apparatus and solve my troubles; you have rewritten the paper, and your name should appear here with mine." "No," Professor Ludwig replied. "You have done the work and you should get the credit, but," he added, "if you never do anything more, people will think that I did it."[12]

When questioned about making his students the sole authors of the papers to which they contributed, Ludwig pointed to the name "The Leipzig Institute of Physiology" at the top of each paper and said: "That is enough" (cited by 7).

Ludwig's view of teaching was expressed in a letter to Lombard:

> Destiny has conferred on us professors the favor of helping the responsive heart of youth to find the right path. In the seemingly insignificant vocation of the school master there is enclosed a high, blessed calling. I know no higher (cited by 1).

CONCLUSION

In the interest of full disclosure, I acknowledge that Ludwig can be viewed as my scientific great-great-grandfather. His pupil, Otto Frank, trained Carl Wiggers, who trained my father, Louis N. Katz, who helped shape my life and career. One wonders how many others who are active today can also trace their scientific ancestry to this 19th-century Icon of Cardiology.

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Sudden death in young athletes

B. J. Maron, W. C. Roberts, H. A. McAllister, D. R. Rosing, S. E. Epstein

Circulation. 1980;62:218-229

Athletes are regarded as the healthiest segment of the population by the medical and lay community and, as a result, the sudden and unexpected death of these individuals, although uncommon, raises profound attention and publicity. The lack of data on large series of sudden deaths in young athletes meant that the main causes of such events remained poorly defined. This is of particular relevance as sudden death among athletes is most prevalent in this age-group. Such data help in the identification of young athletes at risk of sudden death and would provide the rationale for pre-participation cardiovascular evaluation.

This study by Maron et al was one of the first to report on the causes of death in young competitive athletes. The series included 29 elite athletes between the ages of 13 and 30 years who engaged in a variety of sports and suffered sudden death and underwent postmortem examination. Sudden death occurred during of shortly after severe exertion on the athletic field in 22 of the 29 athletes. The athletes who constituted the study group were identified both prospectively from news media reports and retrospectively from review of two autopsy registries.

Structural heart disease was identified in 28 of the 29 (97%) athletes, and was almost certainly the cause of sudden death in 22 cases. Although the cause of sudden death in one patient without structural heart disease was unclear, a primary rhythm disturbance remained possible. A range of cardiac disorders was observed, but the most frequently encountered disorder was hypertrophic cardiomyopathy (HCM), accounting for almost half (14/29) of deaths in the series. The remaining disorders identified include anomalous origin of the left coronary artery (3 cases), atherosclerotic coronary disease (3 cases), ruptured aorta (2 cases), idiopathic concentric left ventricular hypertrophy (LVH) (5 cases), and hypoplastic coronary arteries (1 case). Cardiac disease was unrecognized during life in most of the athletes, with only two athletes being given the correct diagnosis antemortem.

The application of these data to the general athletic population is potentially problematic. The sample size is relatively small and unlikely to be a representative sampling of sudden death in athletes. Furthermore, due to the study design, unavoidable bias would influence the selection of athletes, as those with cardiac disease would be referred to the centers whose autopsy registry was reviewed.

The findings of this study raised important points regarding the evaluation of young athletes prior to participation in competitive sports. Evaluation using clinical history and examination would be insensitive for detecting the leading causes of sudden death and, even with addition of the ECG, could miss cases of HCM. The definitive diagnosis of HCM and most of the other conditions causing sudden death in athletes could only be made by echocardiography. This study provided insight into the conditions leading to sudden death in young athletes and laid the groundwork for subsequent larger studies.

1980

Jack Nicklaus wins his 5th Professional Golfers' Association (PGA) Championship; Tatyana Kazankina of the USSR sets a new 1.5-km women's record in 3:52:47 min; and Reinhold Messner of Italy becomes the first solo climber to scale mount Everest

An overview of randomized trials of rehabilitation with exercise after myocardial infarction

G. T. O'Connor, J. E. Buring, S. Yusuf, S. Z. Goldhaber, E. M. Olmstead, R. S. Paffenbarger Jr, C. H. Hennekens

Circulation. 1989;80:234-244

Over one million individuals in the USA suffer myocardial infarction and over 60% survive the initial event. The beneficial effects of exercise in such individuals has been recognized for many decades and ambulation early after myocardial infarction and the implementation of exercise-based rehabilitation are widely practiced. Exercise training improves functional capacity and work efficiency, thereby decreasing the metabolic and circulatory demands of daily activities. Exercise also lowers heart rate and blood pressure, which are two major determinants of myocardial oxygen demand. These adaptations are accompanied by favorable neurohormonal and metabolic changes, such as reduction of norepinephrine and body weight, increased lean body mass, lower serum triglycerides, platelet adhesiveness, and increased high-density lipoproteins and fibrinolysis.

Prior to this overview, over 20 studies tried to define the benefits of exercise after myocardial infarction. Owing to their small size, however, they were unable to demonstrate a significant reduction in morbidity and mortality.

This overview analyzed results from over 4500 patients and included data from 22 studies with at least 1 year follow-up between 1960 and 1988. The majority of the subjects included were male and the analysis was heavily weighed towards men in the 5th and 6th decades of life. The subjects were randomized to exercise rehabilitation or the comparison groups. In 6 of the studies, the exercise rehabilitation group received only exercise programs, whereas, in the remaining studies, these individuals underwent risk factor modification in addition to exercise. The end points studied were total mortality, cardiovascular mortality, sudden death, and fatal and nonfatal myocardial infarction.

This overview demonstrated that cardiac rehabilitation programs including exercise lead to a statistically significant 20% reduction in total (odds ratio [OR] = 0.80 [0.66, 0.96]) and cardiovascular mortality (OR = 0.78 [0.63, 0.96]), which was apparent at 1 year following randomization and persisted throughout the follow-up period. It was interesting to note that neither the 6 "exercise only," nor the remaining "exercise plus other interventions" studies attained traditional levels of significance. The OR for sudden death (0.63 [0.47, 0.97]) showed a large reduction, but did not reach statistically significant levels. The lack of availability of data regarding sudden death and the differing definitions of what constitutes a "sudden death" limit the interpretation of findings for this end point and more than likely shift the outcome towards null. There was a small nonsignificant increase in the risk of nonfatal myocardial reinfarctions (10.2% vs 9.5%, OR 1.09 [0.76, 1.57]). This may be due to chance or may represent either a true increase in nonfatal myocardial infarction or increased survival from myocardial infarction.

The relatively small number of "exercise only" studies, combined with the fact that they may have included formal or informal non-exercise measures, made definitive conclusions regarding the independent effects of exercise post–myocardial infarction difficult. As a result of this overview, however, other randomized large studies were carried out, which confirmed the benefits of exercise rehabilitation programs following myocardial infarction and the potential mechanisms of benefit involved.

1989

Roger Kingdom of the USA sets the 110-m hurdle record (12:92) in Zurich; Arturo Barrios of Mexico sets the 10-km record (27:08:23) in Berlin; and tests results reveal that 50 athletes tested positive for steroids during the 1988 Olympics

The athletic heart syndrome

T. P. Huston, J. C. Puffer, W. M. Rodney

N Engl J Med. 1985;313:24-32

Athletic heart syndrome encompasses a constellation of cardiac findings seen in the highly trained athlete. These findings can be broadly divided into structural and electrocardiographic changes.

Chronic physical demand on the heart leading to adaptive responses can be either in the form of volume overload or pressure overload. Volume overload is encountered in isotonic activities such as endurance running, where sustained increases in cardiac output are required. In contrast, pressure overload is encountered in isometric activities such as weightlifting, where brief increases in cardiac output against huge aortic pressures are required. In practice, most athletes do not fit into a purely isotonic or isometric category, and represent a combination of the two, producing a combination of morphological adaptations.

These morphological changes may be evident soon after the commencement of training and regress with detraining. The increased left ventricular (LV) dimensions seen in isotonic athletes also lead to an increase in LV mass. The magnitude of these increases is, in most cases, modest and does not approach the extent seen in myocardial diseases. In some cases, however, the increases are of sufficient magnitude to raise the differential diagnosis of hypertrophic (HCM) or dilated (DCM) cardiomyopathy. However, certain echocardiographic features (eg, ratio of wall thickness–to-cavity size for HCM and the ejection fraction for DCM) can aid the distinction between athlete's heart and cardiomyopathy.

Most ECG abnormalities observed among athletes are a reflection of the vagotonic state and are commoner in athletes taking part in dynamic rather than static exercise. These include resting sinus bradycardia often associated with sinus arrhythmia, sinus pause, wandering atrial pacemakers, and low degrees of atrioventricular (AV) block (first-degree and Mobitz type I second-degree AV block). More advanced degrees of AV block, atrial tachyarrhythmias at rest, and atrial fibrillation (AF) are rare and cannot be assumed to be part of the physiological spectrum of athlete's heart.

Elevation of the J point associated with ST-segment elevation is common among athletes and is typically seen in the anterior precordial leads. It is associated with physical conditioning, normalizes with detraining, is considered benign and not representative of myocardial disease, and is often associated with tall T waves or T-wave inversion. The mechanism responsible for ST-segment elevation is thought to be a result of a decrease in resting sympathetic tone uncovering an inherent asymmetry of repolarization. Depression of the ST segment is very uncommon and when present is mild (-0.1 mV), with normalization on exertion. T waves are either tall and peaked or inverted with abnormalities most often in the lateral precordial leads. Tall peaked T waves are associated with ST-segment elevation, while T-wave inversion is mild and normalizes with exercise.

ECG voltage criteria for LVH are a common finding in athletes. Right ventricular hypertrophy is also evident on the ECG of athletes, but is less prevalent. Increases in voltage occur with conditioning and regress with cessation of training.

Knowledge of the athlete's heart enables the physician to reassure the athlete and avoid unnecessary further evaluation and possible inappropriate disqualification from competition.

1985

Germany's Boris Becker, aged only 17 years, beats Kevin Curren for Wimbeldon tennis title; French cyclist Bernard Hinault wins his fifth Tour de France; and Britain's Steve Cram breaks both the 1.5-km (3:29:67 min) and 1-mile (3:46:31 min) world records

The incidence of primary cardiac arrest during vigorous exercise

D. S. Siscovick, N. S. Weiss, R. H. Fletcher, T. Lasky

N Engl J Med. 1984;311:874-877

Several epidemiological studies have suggested that regular habitual exercise is associated with decreased cardiovascular morbidity and mortality and a reduction in the risk of sudden cardiac death. Conversely, the relationship between vigorous exercise and sudden death has long been recognized and been a subject of debate. Overall, however, the net effect of habitual vigorous exercise is believed to be favorable.

Previous studies have not looked at the risks of sudden death with vigorous exercise along with the benefits of habitual exercise training in the same population, making explicit conclusions regarding habitual activity difficult.

This community-based study was carried out to determine whether the risk of sudden death is increased during vigorous exercise and the extent to which it detracts from the potential benefit of habitual vigorous exercise. By assessing the two components of the effect of vigorous exercise in the same population it was possible to put the risks and benefits into perspective.

One hundred and thirty-three sudden cardiac deaths in males between the ages of 25 and 75 years with no history of cardiac disease formed the study cohort. The subjects' wives were interviewed to ascertain the pattern of leisure-time activity over the previous year, the circumstances surrounding the sudden deaths, and the presence of potential risk factors for sudden death.

These findings suggest that the risk of sudden cardiac death is transiently increased during vigorous exercise. The increase in risk was particularly large for men with low levels of habitual activity. Among men who engaged in low levels of habitual activity, the risk during exercise was particularly large as compared with the risk at other times (relative risk [RR] 56). In contrast, among men with the highest level of habitual activity, the risk during exercise was increased to a much lesser extent (RR 5).

The study supports the clinical impression that unusual exercise may be associated with greater risk and, even among men who are habitually active, the risk of sudden death increases with exercise. Furthermore, the data also support the view that habitual participation in exercise is associated with an overall reduction in the risk of sudden cardiac death.

1984

French new wave film director François Truffaut dies of cancer, aged 52 years;
Steffi Graf plays her first professional tennis match;
and Steve Jones of Britain runs the Chicago Marathon in a world record time of 2:08:05 h

Triggering of acute myocardial infarction by heavy physical exertion. Protection against triggering by regular exertion. Determinants of Myocardial Infarction Onset Study Investigators

M. A. Mittleman, M. Maclure, G. H. Tofler, J. B. Sherwood, R. J. Goldberg, J. E. Muller

N Engl J Med. 1993;329:1677-1683

The American Heart Association (AHA) recommends increasing physical activity as an important means of reducing the risk of myocardial infarction (MI). A sedentary lifestyle has consistently been shown to increase the risk of coronary artery disease. However, it is well recognized that heavy physical exertion sometimes leads to MI. Studies have showed that in about 5% of patients with a heart attack such physical activity preceded symptoms. Heavy physical exertion, therefore, appears to be a double-edged sword, both triggering and preventing MI.

This multicenter, interview-based study used a case-crossover design to quantify the relative risk of MI after heavy exertion as compared with periods of lighter exertion or no exertion, and its potential modification by habitual physical activity in 1228 patients with confirmed acute MI. In the interview, data were obtained on the timing of the MI, the estimated usual frequency of physical exertion during the previous year, and the intensity and timing of heavy exercise and other potential triggering factors in the 26 hours prior to the onset of the MI (hazard period). The degree of physical exertion was quantified on a scale from 1 to 8 metabolic equivalents (METS). Patients were considered to have engaged in heavy exertion if they reported a peak exertion level estimated to be 6 METS or more during the period of interest.

Heavy physical exertion was associated with a transient risk of MI in the subsequent hour that was 5.9 times higher than the risk during periods of lighter or no exertion. The relative risk varied greatly depending on the usual frequency of heavy exercise carried out by the patient. It was only 2.4 among those reporting regular physical exertion, but 107 among those who were habitually sedentary. Recall bias is unlikely to confound these results, as the patients were unaware of the 1-hour hazard period and because the case-crossover design eliminated potential confounding factors that differed among patients.

The findings of this study generally agreed with other studies, which quoted the relative risk of sudden death from cardiac causes to be between 5 and 100 during periods of heavy exertion. Furthermore, other studies have also shown that the risk of sudden cardiac death during heavy exertion is decreased with habitual exercise.

This study demonstrates protection against the triggering of MI with regular exertion and provides further evidence encouraging regular physical activity, as recommended by the AHA. Such a program most likely lowers the overall risk of MI, since it may lower the baseline risk, and also decrease the relative risk that an episode of heavy physical exertion will trigger an MI.

The mechanism involved in the triggering of MI is thought to be the disruption of a vulnerable coronary plaque in response to hemodynamic stresses associated with strenuous exercise. Thereafter, hemostatic and vasoconstrictive forces determine whether the resultant thrombus becomes occlusive. The protective effect of regular exercise, as suggested in this study, was postulated to be due to a reduction in number and the stabilization of the coronary plaque and this has been supported by more recent studies. Further studies in this area may lead to further clarification of some of the uncertainties regarding the beneficial effects of physical exertion and lead to new forms of prevention.

1993

Danny Blanchflower, the North Ireland soccer legend, dies at 67;
Germany beats Australia in Düsseldorf (4-1) to win the 82nd Davis Cup;
and Eduardo Frei is elected President of Chile

The upper limit of physiologic cardiac hypertrophy in highly trained elite athletes

A. Pelliccia, B. J. Maron, A. Spataro, M. A. Proschan, P. Spirito

N Engl J Med. 1991;324:295-301

Long-term regular physical training leads to structural adaptations, eg, increased left ventricular (LV) wall thickness, LV end-diastolic cavity diameter, and LV mass, characterizing the "athlete's heart." The increase in LV wall thickness is generally modest, but, in rare cases, the increase is significant and raises the differential diagnosis of hypertrophic cardiomyopathy (HCM). This is crucial as HCM is the commonest cause of sudden death in young athletes. The distinction between physiological athlete's heart and HCM is dependent largely on the assessment of whether the magnitude of LV hypertrophy (LVH) is in excess of that expected in response to athletic training alone. Furthermore, although this distinction can usually be made on the basis of either the ECG or echocardiogram, the ECG changes in some cases of HCM can be equivocal or nondiagnostic and therefore require echocardiographic differentiation. Prior to this study, however, the upper limits of physiological hypertrophy remained unknown due to the fact that previous echocardiographic studies had focused on small groups of athletes.

This landmark study defined the upper limits of LVH as a result of athletic training by assessing 947 elite athletes free of cardiovascular disease during intensive training. The athletes had a mean age of 22 years (range 13-49 years) and represented a wide range of disciplines including both predominantly isotonic and isometric activities.

The cardiac dimensions of the athletes were characteristic of highly trained individuals. The LV cavity size ranged from 40 to 66 mm and exceeded the upper limit of normal (54 mm) in 38% of the study population, with a small, but significant, proportion (4%) exceeding 60 mm. The interventricular septum thickness ranged from 6 to 16 mm and the posterior wall thickness ranged from 6 to 13 mm.

Only 16 athletes (1.7%) had an LV wall thickness compatible with HCM (≥13 mm). All were male and either rowers, canoeists, or cyclists. No female athlete had an LV wall thickness >11 mm. All 16 male athletes had an enlarged LV cavity (diameter >54 mm), and normal systolic function and left atrial size.

There was an independent significant association between wall thickness and age, gender, body size, and type of sport (rowing, canoeing, and cycling). Diastolic function was normal in all athletes with LVH, in contrast to HCM, where there is generally a degree of diastolic abnormality. The ECG was normal in 9 of 16 athletes with LV wall thickness of ≥13 mm. The other 7 had minor abnormalities, such as voltage criteria for LVH, mild T-wave inversion, and first-degree heart block. No athlete had ECG changes typically seen in HCM such as deep T-wave inversion, pathological q waves, ST-segment depression, and marked left axis deviation.

This study provided important insight into the differentiation of athlete's heart from HCM. As no athlete had an LV wall thickness >16 mm, it can be deduced that LVH >16 mm very likely represents pathological LVH such as HCM. Furthermore, an LV wall thickness ≥13 mm was very uncommon and was seen in the context an enlarged LV and only in certain sports. This finding itself may be enough to distinguish athlete's heart from HCM, since most HCM patients have a normal or small LV cavity. No female athlete had an LV wall thickness >11 mm, and this suggests that athletic training virtually never leads to LVH compatible with a diagnosis of HCM. Finally, as the athletes in this study were almost entirely white, caution should be exercised in the evaluation of athletes of different ethnicity based on these findings.

1991

Fu Mingxia of China, aged only 12, wins a World Swimming Championships gold medal; the New York Giants win SuperBowl XXV, defeating the Buffalo Bills 20-19; and Monica Seles beats Jana Novotna (5:7 6:3 6:1) to win the Australian Women's Tennis championship

Screening for hypertrophic cardiomyopathy in young athletes

D. Corrado, C. Basso, M. Schiavon, G. Thiene

N Engl J Med. 1998;339:364-369

Most sudden deaths (SD) in athletes are due to cardiovascular disease, with nearly half of SDs in young athletes being due to hypertrophic cardiomyopathy (HCM). This paper reports on the findings of a pre-participation program, which prospectively evaluated over 33 000 athletes in the Veneto region of Italy between 1979 and 1996, on the basis of clinical and family history, 12-lead ECG, limited exercise testing, and additional tests in case of positive findings at initial evaluation.

A total of 269 SDs were reported in people below the age of 35 years: 49 were athletes (1.6 per 100 000/year) and 220 were nonathletes (0.75 per 100 000/year), giving a relative risk of SD in athletes vs nonathletes of 2.1 (P>0.001).

In 40 of the 49 athletes, SD occurred either during (35 cases) or immediately after (5 cases) sporting activity, 14 athletes had previously reported palpitations, syncope, or both; 16 had had ECG or rhythm/conduction abnormalities. The most common cause of SD in the athletes was arrhythmogenic right ventricular cardiomyopathy (ARVC) (11 cases; 22.4%), atherosclerotic coronary artery disease (CAD) (9 cases; 18.4%), and anomalous origin of a coronary artery (6 cases; 12.2%). ARVC (P=0.008) and anomalous origin of a coronary artery (P<0.001) were associated with SD significantly more often among athletes than nonathletes. HCM caused only 1 SD (2%) among athletes, vs 16 SDs in nonathletes (7.3%). None of the nonathletes who died suddenly from HCM had been screened prior to death.

During pre-participation screening, the most frequent cardiovascular conditions leading to disqualification were rhythm and conduction abnormalities (38.3%), hypertension (27.1%), and valve disease (21.4%). Of the 33 735 athletes screened, 3016 (9%) were referred for echocardiography, and HCM was identified in 22 young athletes (0.07%). During a mean follow-up of 8.2±5 years, none of the 22 athletes disqualified due to HCM died.

In this study, SD in young athletes was related to the expected underlying cardiac disorders, but the prevalence of each disorder differed substantially from previous studies. Prior studies, mainly from the USA, have consistently found HCM to be the leading cause of SD in young athletes (40% to 50% of cases). In this Italian study, HCM caused only 1 SD among the athletes, but caused SD in young nonathletes with a similar frequency to reports from the USA. Furthermore, a high prevalence of ARVC and premature CAD was noted in both groups. The low prevalence of HCM among young athletes suffering SD was most likely the result of the long-standing pre-participation screening in practice in Italy. This is supported by the similar prevalence of HCM among the nonathletes in this study and studies from USA.

Of the young athletes screened, altogether 22 (0.07%) were identified with HCM and disqualified. Other studies suggest a prevalence of 0.2% for HCM in the general population. The prevalence of 0.07% is reasonably similar, seeing that the screening was based mainly on ECG, while US studies are based on echocardiography. Furthermore, using clinical evaluation and ECG made it possible to target echocardiography to only 10% of the screened population, resulting in considerable cost saving. This adds strength to the argument that a screening program based largely on ECG is effective at picking up HCM among young athletes.

1998

An IRA bomb explodes in the town of Omagh, killing 27 people; South Africa defeats the Australian Wallabies (16-12) to win the rugby tri-nations championship; and Finnish F1 racing driver Mika Häkkinen wins the German Grand Prix at Hockenheim on his way to securing the 1998 drivers' championship

Investigation of the physiological basis for increased exercise threshold for angina pectoris after physical conditioning

D. N. Sim, W. A. Neill

J Clin Invest. 1974;54:763-770

In patients with coronary artery disease, physical conditioning can increase the exercise threshold for angina. Physical conditioning results in alterations of exercise hemodynamics reflected in a lower heart rate and systolic blood pressure at any given workload. The decrease in these determinants of myocardial oxygen consumption after conditioning suggests that the increased tolerance for exertion in patients with a limited myocardial oxygen supply might be due to a lower myocardial oxygen requirement at a given level of exertion. The other possibility is that of increased myocardial oxygen supply. This study investigated the physiological basis for the increased exercise threshold for angina and looked to define the effect of conditioning on myocardial oxygen supply.

Eight patients (all men) with angiographically confirmed coronary artery disease, normal left ventricular function, and exertional angina completed 11 to 15 weeks of endurance exercise conditioning. Angina threshold was determined using upright bicycle exercise and atrial pacing. Supine resting measurements of brachial artery and left ventricular pressure, paired arterial and coronary venous blood sampling for oxygen, pH and lactate analyses, and coronary blood flow were made and the measurements were repeated at subangina and angina threshold following pacing.

Resting heart rate and the heart rate × systolic blood pressure product (RPP) at the same level of work were lower after conditioning ($P<0.02$). The exercise angina threshold, as determined by bicycle exercise testing, was higher after conditioning in all the patients as reflected by the work level reached ($P<0.05$) and the duration of exercise ($P<0.005$). Similarly, the systolic blood pressure and RPP at the onset of angina were higher after conditioning. The angina threshold determined by atrial pacing, however, was not increased by exercise conditioning, with the heart rate, systolic brachial and left ventricular blood pressure, and RPP virtually the same before and after conditioning. Various indirect indices of myocardial oxygen consumption demonstrated a rise with bicycle exercise after conditioning, but remained unchanged with pacing after conditioning.

The effects of exercise conditioning on measures of myocardial oxygen supply were not significant. Atrial pacing did not significantly increase coronary blood flow or myocardial oxygen consumption. There was no change in coronary arteriovenous oxygen gradient after conditioning, in contrast to other previous studies.

The increase in exertional threshold angina, and the decrease in resting heart rate and in heart rate at the same levels of workload indicate that the patients did experience a conditioning effect. The data suggest that exercise conditioning did not change myocardial oxygen supply, at least during angina induced by atrial pacing. However, the data also point to a difference between exercise and pacing-induced tachycardia. Indirect indices of myocardial oxygen consumption at the angina threshold after conditioning were higher for exercise, but not for pacing. This suggests that exercise conditioning exerts some effect pertaining specifically to exercise and does not carry over to a different stress such as pacing-induced tachycardia. The study did indicate that the increase in exercise capacity of angina patients after exercise conditioning appeared to be due to a functional adaptation in either delivery or utilization of oxygen by the myocardium, rather than an alteration of the coronary arteries, as confirmed by coronary angiography. This study was unable to ascertain the mechanisms involved, as critical measurements during exercise would need to be obtained directly for valid comparisons.

1974

Jimmy Connors and Billie Jean King win the US Open single tennis crowns; US President Gerald Ford pardons former President Richard Nixon of all federal crimes; and a military coup in Ethiopia overthrows Emperor Haile Selassie

Physical activity and the incidence of coronary heart disease

K. E. Powell, P. D. Thompson, C. J. Caspersen, J. S. Kendrick

Annu Rev Public Health. 1987;8:253-287

Nowadays, the beneficial effects of regular exercise on cardiovascular health are well established, with physicians prescribing regular exercise, as well as statins, aspirin, and angiotensin-converting enzyme (ACE) inhibitors, to individuals deemed to be at risk of coronary heart disease (CHD). Exercise rehabilitation programs form a routine part of secondary prevention for CHD. The primary preventative role of exercise in CHD had been the subject of many studies in the second half of the twentieth century. The general message from most was a lower a risk of CHD in physically active individuals. This review formed a systematic analysis of all these studies and provided an assessment of the quality of each one.

Forty-three studies met the selection criteria where the incidence of cases could be separated from prevalent cases and where it was possible to estimate incidence rates, relative risk, odds ratios, mortality ratios, or where a regression analysis had been done. The particular area of interest was data comparing the risk of CHD between inactive and active persons. In terms of design, 36 were prospective cohort studies, 3 were retrospective mortality studies, and 4 were observational case-control studies. The majority of the studies provided information primarily about North American and European working-age men.

The existing literature reviewed supports the notion that there is an inverse association between physical activity and CHD. No study reported a significant direct association between physical activity and the incidence of CHD. Approximately two thirds of the studies reported either a significant association or a graded response or both. The repeated observation in different settings and populations is evidence that physical inactivity is a fundamental cause of CHD. Interestingly, methodologically superior studies were more likely to report an inverse association, suggesting that less carefully conducted studies have obscured the association. The relative risk of CHD associated with inactivity was about 2.0, with better studies tending to report higher relative risks. Furthermore, even well-accepted risk factors such as hypertension, hypercholesterolemia, and smoking had relative risks only marginally greater than inactivity. Most studies adequately demonstrated that the activity level predated the onset of CHD, therefore implying a cause-and-effect relationship.

Potential confounding factors such as age, sex, smoking status, serum cholesterol, and blood pressure were considered by many of the studies, and the inverse association between inactivity and CHD was just as likely to be present in these studies as those that made no adjustments. This suggests that physical activity exerts a protective effect on CHD that is independent of these other risk factors.

The inverse association between physical activity and CHD incidence is consistently observed, appropriately sequenced, biologically graded, and plausible. The risk of inactivity seems to be similar in magnitude to that of conventional CHD risk factors. Given the increasing sedentary lifestyle of the Western world, these findings have important public health implications and should encourage regular physical activity in the population at risk.

1987

Kapil Dev takes his 300th Test wicket. At the age of 28, he is the youngest bowler to achieve this milestone; Edwin Moses, the US 400-m hurdler, is defeated by Danny Harris, bringing to an end his 122–race winning streak stretching back over ten years; and Ajax wins the 27th European Football Cup

Exertion and acute coronary artery injury

A. Black, M. M. Black, G. Gensini

Angiology. 1975;26:759-783

Our understanding of the pathogenesis of the acute coronary syndromes has progressed significantly over the last three decades. The respective roles played by the atherosclerotic plaque, the inflammatory cascade, and the coagulation systems are better defined. It is also widely accepted that regular exercise is beneficial to cardiovascular health. However, it is also well known that unusual or strenuous physical exertion of emotional stress is associated with acute myocardial infarction and sudden death.

The authors of this study, more than 25 years ago, supported the hypothesis that exertion can be a very definite precipitating factor of acute coronary occlusion and that the relationship of exertion to acute coronary insult, myocardial infarction, and sudden death is very much significant. They went on to present 12 clinical cases and three angiographic cases where acute coronary artery injury occurred during or immediately after strenuous exertion and/or severe emotional stress. In all the cases, the clinical picture, including symptoms and ECG findings, correlated with pathological findings consisting of coronary artery occlusion on a background of a "vulnerable" plaque.

The mechanism suggested involves the initial "cracking" of the plaque, which can put the coronary artery into spasm. If spasm is severe and prolonged enough, it can lead to myocardial infarction and even ventricular fibrillation and cardiac arrest, and if short-lived results in angina. The initial injury is of such nature that at some later interval further injury in the nature of extension of the crack or fissure occurs and produces an acute occlusion. This interval is labeled as the preocclusion latent period and can be as short as a few seconds or as long as weeks or months, supporting the idea that the preocclusion state is not related to gradual vessel occlusion by thrombosis, but rather that of a cracked plaque that finally elevates or ruptures.

Coronary arteries are unique in that they are subjected to regular vigorous movements even at resting heart rates. Over 80% of coronary artery occlusions are found within the epicardial course of the vessel and not in branches within the myocardium. The movements of the coronary arteries include pulsation, shortening and lengthening, twisting, snapping (acute bending), and flow currents. These movements are substantially increased with physical exercise or any adrenergic drive requiring an increased cardiac output and can lead to the fracturing of a vulnerable plaque. The pathological changes within the plaque will vary depending on whether the plaque simply heals and becomes stable, is complicated by acute inflammatory processes including edema and hemorrhage, or becomes vulnerable or fragments and ruptures with discharge of its contents downstream.

The authors conclude that the above concept of the "crack in the plaque" accounts for the sudden appearance of clinical coronary artery disease during or shortly after physical or emotional exertion. It could also account for the exacerbation of symptoms or sudden death occurring in individuals with asymptomatic coronary artery disease. Our current improved understanding of the pathogenesis of acute coronary syndromes supports the authors' conclusions.

1975

US golfer Tiger Woods is born on 30th December 1975 in Cypress, California; Raul Ramirez wins the Davis Cup for Mexico by defeating Jimmy Connors in the final match; and the Indonesian army occupies East Timor

Sport, Exercise, and the Heart

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selected by **Paul D. Thompson, MD**

Director of Preventive Cardiology & Cardiovascular Research - Hartford Hospital, Conn - USA

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