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ARE THERE DELETERIOUS CARDIAC EFFECTS OF ACUTE AND CHRONIC ENDURANCE EXERCISE?

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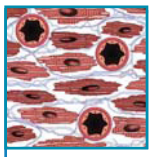

Eijsvogels TMH, Fernandez AB, Thompson PD. Are There Deleterious Cardiac Effects of Acute and Chronic Endurance Exercise? *Physiol Rev* 96: 99–125, 2016. Published November 25, 2015; doi:10.1152/physrev.00029.2014.—Multiple epidemiological studies document that habitual physical activity reduces the risk of atherosclerotic cardiovascular disease (ASCVD), and most demonstrate progressively lower rates of ASCVD with progressively more physical activity. Few studies have included individuals performing high-intensity, lifelong endurance exercise, however, and recent reports suggest that prodigious amounts of exercise may increase markers for, and even the incidence of, cardiovascular disease. This review examines the evidence that extremes of endurance exercise may increase cardiovascular disease risk by reviewing the causes and incidence of exercise-related cardiac events, and the acute effects of exercise on cardiovascular function, the effect of exercise on cardiac biomarkers, including "myocardial" creatine kinase, cardiac troponins, and cardiac natriuretic peptides. This review also examines the effect of exercise on coronary atherosclerosis and calcification, the frequency of atrial fibrillation in aging athletes, and the possibility that exercise may be deleterious in individuals genetically predisposed to such cardiac abnormalities as long QT syndrome, right ventricular cardiomyopathy, and hypertrophic cardiomyopathy. This review is to our knowledge unique because it addresses all known potentially adverse cardiovascular effects of endurance exercise. The best evidence remains that physical activity and exercise training benefit the population, but it is possible that prolonged exercise and exercise training can adversely affect cardiac function in some individuals. This hypothesis warrants further examination.

I. INTRODUCTION AND OVERVIEW

Regular physical exercise is part of a healthy lifestyle, and a plethora of cross-sectional studies demonstrate that habitual employment or leisure time physical activity is associated with reduced cardiovascular disease (CVD) risk (241). Prospective clinical trials proving that physical activity reduces CVD incidence have not been performed in healthy subjects because of multiple issues. For example, the number needed to treat and the treatment time required to document an effect is large, compliance with assignment to active or sedentary behavior would be difficult to enforce, and the cost of such a study would be enormous. There are such randomized controlled clinical trials among heart disease survivors, and meta-analyses of these studies (41, 192, 258) are consistent with the cross-sectional data in healthy individuals suggesting that exercise reduces CVD.

The amount of physical activity required to alter cardiovascular function and to reduce CVD events is not defined. It is likely that different exercise doses are required to affect autonomic tone than cardiovascular dimensions, for example. Most studies examining CVD events show a graded decrease with progressively more exertion. Even doses as low as 15 min of physical activity per day appear to reduce CVD risk and all-cause mortality (282). Higher physical activity levels further reduce mortality risks, with the most active individuals demonstrating the best overall life expectancy (143, 214, 282). Few of these studies have included individuals engaging in high-intensity, lifelong endurance activity, however, and recent evidence suggests that such intense exercise may actually increase CVD risk.

Regular, intense exercise causes structural, functional, and electrical cardiac adaptations, which are considered benign and comprise the clinical constellation of findings known as the athlete's heart. These adaptations may also have deleterious effects. Cardiac biomarkers are acutely increased by exercise, and atrial fibrillation, myocardial fibrosis, and

coronary artery calcification appear more common in older athletes compared with their inactive peers.

The popularity of endurance exercise races and the average age of its participants have increased worldwide over the last three decades. Completing a 42-km marathon or similar endurance events has become a personal goal for many individuals. This provides an impetus for both the medical and lay communities to understand the effect of endurance exercise on cardiac health. This review summarizes recent research on the effects of acute and lifelong endurance exercise on the heart and the possible risk of exercise in some individuals and patient groups. The goal is to explore the possibility that prodigious amounts or high-intensity exercise may not be beneficial and may even hurt some individuals. Exploring this possibility may ultimately help in making clinical decisions on the value of exercise in physically active individuals. This review is to our knowledge unique because it addresses all known potentially adverse cardiovascular effects of endurance exercise.

II. IMPACT OF EXERCISE ON CARDIAC HEALTH

The Greek physician Hippocrates (460-375 B.C.) recognized the contribution of physical activity to health: "All parts of the body, if used in moderation and exercised in labours to which each is accustomed, become thereby healthy and well developed and age slowly; but if they are unused and left idle, they become liable to disease, defective in growth and age quickly." More than 2000 years later in 1953, Morris and colleagues confirmed Hippocrates' opinion on the beneficial effects of exercise on health by demonstrating that conductors on London's double-decker buses had a lower risk of sudden cardiac death (SCD) than the physically inactive bus drivers (161). Multiple large epidemiological trials have subsequently demonstrated a strong, inverse relationship between the amount of physical activity and CVD events and overall mortality (119, 182–184, 194). These results are consistent with evidence that habitual physical activity reduces CVD risk factors including blood pressure, serum triglycerides and insulin resistance (66, 262). Powell et al. (194) used the criteria that are employed to prove causation in the absence of clinical trial data to demonstrate that the relationship between physical activity and cardiac disease was strong, consistent from study to study, preceded the CVD events, showed a gradient of reduced risk with increasing exercise, was plausible, and was coherent with the data that exercise improved CVD risk factors. They concluded that increasing physical activity was causally related to lower rates of CVD.

Given this evidence for the health benefits of regular exercise, clinicians, health care workers, and governments have developed strategies to increase physical activity in the general population (178). The American College of Sports Medicine and the American Heart Association recommend that adults perform moderate-intensity exercise for a minimum of 30 min daily at least 5 days a week, or vigorous-intensity exercise for a minimum of 20 min daily at least 3 days a week (86, 191). The majority of Americans (~66%) fail to meet these criteria (191). On the other hand, participation in endurance exercise races significantly increased over the past decades (25, 91, 112). Approximately 4.8 million United States runners finished a running event in 1990, whereas more than 15.5 million race finishers were counted in 2012 **(FIGURE 1)** (128) of whom 487,000 finished the 42-km marathon distance. It is likely that some of this participation in competitive racing is driven by the stepwise decrease in CVD risk with more exercise, or the concept that more is better.

The evidence that more exercise is better is derived from observational studies in the general population, few of whom perform the amount or intensity of endurance exercise performed by competitive athletes. The possibility that very large amounts of exercise may be detrimental or the idea that exercise may accelerate cardiac disease in susceptible populations is a relatively new concept that we will explore in this article.

III. ACUTE EXERCISE-INDUCED CARDIOVASCULAR RISKS

A. Sudden Cardiac Death

There is general consensus that vigorous exercise acutely, albeit transiently, increases the risk of SCD, but only in individuals with underlying cardiac disease, either occult or manifest (263). The largest studies demonstrating the risk of exercise are the Physicians' Health Study (PHS) (4) and the Nurses' Health Study (NHS) (283).

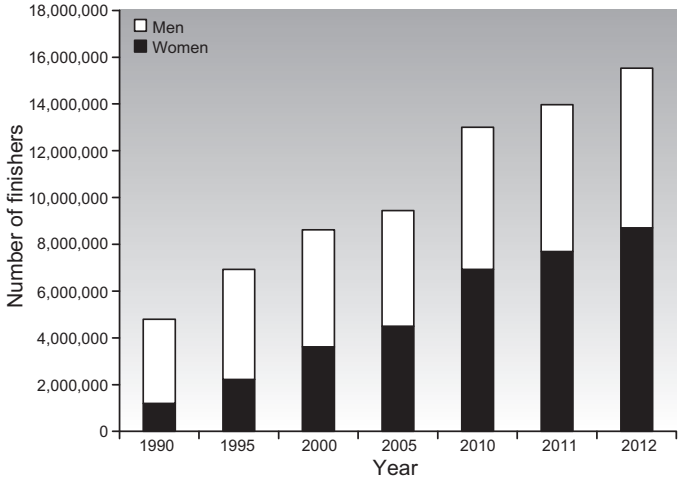

FIGURE 1. Trends in United States race finishers 1990–2012. (Data from Running USA.)

The PHS examined SCD during and for 30 min after vigorous exercise in 21,481 male physicians (4). Vigorous exercise was identified at baseline by asking, "How often do you exercise vigorously enough to work up a sweat?" The study compared SCDs among the participants who did or did not respond affirmatively to this question. PHS also used a "nested case-control design" to compare SCD events within an individual during the SCD hour of exertion (an estimated 30 min of exercise plus the subsequent 30 min) and during the hour before and after the exercise hour. There were 122 SCDs in the total cohort over the 12 yr of follow-up of which 23 were exercise-related: 17 during exercise and 6 in the 30 min postexercise. The risk of an exercise-related SCD using the individual case-control study was 16.9% higher during vigorous exercise ($P < 0.001$), with 95% confidence limits of 10.5 to 27.0%. The absolute risk of an exercise-related SCD was extremely low, however, at only 1 death per 1.42 million hours of vigorous exercise, but the absolute risk of a nonexertion SCD was even lower at 1 per 19 million hours. The risk of an exercise-related versus sedentary SCD decreased from 74 to 19 to 11 with increasing baseline physical activity of <1, 1–4, and >5 vigorous exercise session per week. The increase in risk during exercise and the decrease in this risk with exercise sessions per week suggest that exercise acutely increases, but ultimately decreases, the risk of SCD.

The NHS reported 288 SCDs among 84,888 woman over a 24-yr period and only 9 deaths occurred during moderate or vigorous exertion (283). Moderate or vigorous exertion was defined as any task requiring ≥5 metabolic equivalents of task or METs (1 MET = 3.5 ml of O_2 per min). The absolute risk of an exercise-related SCD was extremely low at 1 per 36.5 million hours of exercise compared with 1 per 59.4 million hours of low or no exertion. Nevertheless, in a nested case-control study similar to that performed in PHS, the risk relative (RR) of SCD was 2.38-fold higher (95% CI=1.23–4.60, $P = 0.01$) during moderate or vigorous exercise than during low or no exercise. This increased RR of an exercise-related event disappeared among women exercising 2 or more hours weekly, again suggesting a decrease in risk with habitual exercise. Increased moderate to vigorous exercise was also associated with a decreased long-term overall risk of SCD when most biological variables were not included ($P = 0.006$), but this was close to, but not statistically significant, when multiple anthropometric and historical parameters were included in the statistical adjustment ($P = 0.06$). The observations that the risk of SCD increases during moderate or vigorous exercise, but that habitual exercise also decreases the SCD risk again suggests, as in PHS, that exercise acutely increases, but ultimately decreases, the risk of SCD.

Most studies have defined "vigorous exercise" as requiring ≥6 METs (263), but the risk is probably not related to the absolute exercise workrate but to the workrate relative to that individual's maximal capacity. Higher relative workrates produce greater cardiac stress because they require a higher percentage of the individual's maximal heart rate and generate more catecholamine spill over into the circulation. Increased catecholamine concentrations are arrhythmogenic. It is assumed that most exercise-related SCDs are due to ventricular fibrillation, but the pathological substrate for SCD varies with the age of the victim.

Young individuals defined as those <30 or 40 yr of age die during exercise primarily from inherited or congenital cardiac conditions such as hypertrophic cardiomyopathy, coronary artery anomalies, and right ventricular cardiomyopathy (RVCM), although acquired conditions such as viral myocarditis can also cause deaths in this age group **(FIGURE 2)** (145). There are also occasional instances of exercise-related aortic rupture in individuals with congenial connective tissue diseases such as Marfan syndrome. Much of the data on exercise-related SCD in the young come from studies of young athletes. One large United States case series found that 44% of the deaths among young athletes were attributable to definite hypertrophic cardiomyopathy (HCM) or possible HCM (144). In contrast, ARVC is the predominant cause of exercise-related in Italy (33). The reasons for these differences are not clear. Italy has a mandated athlete screening program requiring a preparticipation ECG so it is possible that athletes with HCM are detected, prohibited from competition, and therefore not at risk for an exercise-related SCD. Alternatively, Italians were among the first to recognize RVCM as a cause of exercise-related death (261), so physicians may be more aware of the disease and diagnose it more readily at autopsy in that country.

Older individuals die during exercise primarily from coronary artery disease (CAD) (263). Acute atherosclerotic plaque erosion or rupture leading to acute coronary thrombosis is detected in most (263), but not all (109), previously asymptomatic individuals who die or suffer a myocardial infarction during exercise. Some apparently asymptomatic individuals are found to have only advanced CAD without evidence of acute plaque disruption, suggesting that cardiac ischemia alone can also produce SCD during exercise (109). Plaque disruption during exercise is attributed to exercise-related increases in shear forces as well as increases in the bending and flexing of the epicardial coronary arteries during exercise (263). The flexing of the coronary arteries is increased during exercise by the increase in heart rate. In addition, the increase in left ventricular (LV) end-diastolic volume (EDV) and the reduction in LV end-systolic volume (ESV) require greater excursion and therefore bending of the epicardial coronaries during exercise. This bending of stiffened atherosclerotic arteries can produce or exacerbate plaque fissuring and rupture. In contrast to asymptomatic individuals, older individuals with prior CAD events can

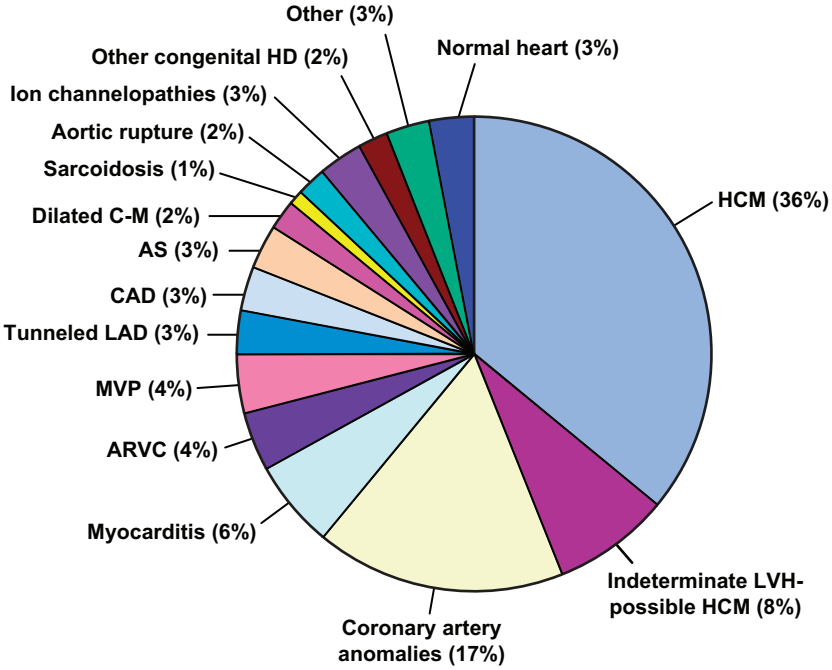

FIGURE 2. Distribution of cardiovascular causes of sudden death in 1,435 young competitive athletes. ARVC, arrhythmogenic right ventricular cardiomyopathy; AS, aortic stenosis; CAD, coronary artery disease; C-M, cardiomyopathy; HCM, hypertrophic cardiomyopathy; HD, heart disease; LAD, left anterior descending; LVH, left ventricular hypertrophy; MVP, mitral valve prolapse. [From Maron et al. (145), with permission from American Heart Association.]

suffer recurrent CAD events or SCD during exercise from plaque rupture or die from an arrhythmia originating from a myocardial scar (263) or induced by ischemia (109).

The absolute incidence of SCD during exercise is low, but not definitively defined because the low frequency of SCD produces large confidence limits for any estimate. The annual rate among young athletes in the United States has generally been estimated at ~1 death per 200,000 athletes (129), although a rate of 1 death per year per 3,100 National College Athletic Association Division I male basketball players (83) has been reported. This suggests that 1 in 800 of these players would die during a 4-yr college career, a frequency that appears improbable. The rate of exercise-related SCD in previously asymptomatic adults has been calculated as 1 per 15,000–18,000 (246, 264) individuals per year. These estimates are derived from studies in Rhode Island (264) and Seattle (246), but the estimates are based on only 10 and 9 deaths, respectively. Nearly all studies of exercise-related SCD identify few female victims. Exercise can also produce acute myocardial infarctions (AMI) by the same mechanical effects on the coronary arteries discussed above (155, 289). The absolute incidence of AMI with exercise is not clearly defined, but ~10% of AMIs in one series were associated with vigorous physical exertion (76).

B. Cardiac Dysfunction and Cardiac Fatigue

The performance of endurance exercise acutely increases the physiological demands on the heart. The initial sympathetic nervous system response to exercise is a withdrawal of parasympathetic vagal tone which produces the early increase in heart rate (203). Subsequently, the sympathetic nervous system is activated as evidenced by catecholamine release at nerve endings and "spill over" of epi- and norepinephrine into the systemic circulation. These hormones further increase heart rate and cardiac contractility, which increase stroke volume and cardiac output. These responses increase cardiac output during the initial phases of endurance exercise, but prolonged endurance exercise can produce decreases in cardiac function, known as "cardiac fatigue" (43). This possibility was, to our knowledge, first suggested by Bengt Saltin, one of the pioneers of exercise physiology, who in 1964 reported decreases in stroke volume after 3 h of exercise despite preserved blood volume (212). This decrease in stroke volume with preserved blood volume distinguishes cardiac fatigue from cardiovascular drift which refers to further increases in heart rate and decreases in stroke volume decrease during prolonged exercise due to loss of fluids and circulating blood volume (292).

A meta-analysis including 294 cases from 23 studies reported a relative 2% reduction in left ventricular ejection fraction (LVEF) following endurance exercise (151). Reductions in LVEF with exercise are reported most frequently in untrained subjects performing moderate duration exercise (≤3 h) and in trained athletes performing ultra-endurance events (≥10.5 h) (151). The reduction in LVEF in these two groups was on average −5.5% and −4%, respectively (151). Trained athletes performing moderate (≤3 h) or long duration (≤6 h) exercise do not typically demonstrate changes in LVEF, but LVEF reductions are frequently reported after exercising more than 6 h (27, 53, 125, 286). A recovery of LVEF to preexercise values is typically observed within 48 h after exercise (147).

The mechanisms producing the decrease in LVEF after exercise are not clear, but several possibilities (230) alone or in combination (236) have been proposed. Decreases in blood volume could reduce cardiac preload reducing ventricular performance without directly altering cardiac contractility (151). Alternatively, exercise may produce myocardial dysfunction independent of volume changes. Decreases in LV systolic strain and in absolute peak systolic twist have been reported postexercise (174, 175, 180). These findings indicate (transient) cardiac dysfunction. The cardiovascular response to infused catecholamines is reduced following prolonged exercise, suggesting decreased β-adrenoreceptor sensitivity (84, 229, 281). The decreased β-adrenoreceptor sensitivity could explain the decreases in LV systolic strain and absolute peak systolic twist (174, 175, 180). Other possible explanations for the acute decrease in LVEF are acute cardiac damage as discussed below and increases in oxidative stress (273). These possible explanations are not exclusionary so that multiple factor may contribute to the decrease (236) **(FIGURE 3)**.

Right ventricle (RV) function also acutely decreases with extreme endurance exercise (12, 125, 169), and the decrease in RV function increases with exercise duration (124). The acute effect of prolonged exercise on RV function appears to be greater than that on the LV (125, 169, 269). Wall stress is lower at rest in the RV than LV primarily because the pulmonary artery systolic pressure is lower than the systemic arterial pressure (126). The relative increase in RV stress with exercise, however, is remarkably greater in the RV because exercise produces a relatively greater increase in pulmonic than aortic systolic pressure (116, 126). This differential effect of exercise on the RV and LV has not been widely appreciated, but one study noted a 125 versus 4% increase in wall stress during exercise for the RV and LV, respectively (126). The thinner wall of the RV (216, 218) may allow this increase in wall stress to affect RV function more than the LV (126).

IV. EVIDENCE OF ACUTE MYOCARDIAL INJURY

A. Creatine Kinase

Creatine kinase (CK) catalyzes the transfer of a phosphate group from creatine phosphate to ADP producing ATP. There are two CK subunits, "M" and "B," reflecting their muscle and brain predominance, respectively. CK is composed of two subunits creating three isoforms: the homodimers CK-MM and CK-BB and the heterodimer CK-MB (31). Skeletal muscle contains 99% CK-MM and 1% CK-MB, cardiac muscle containing 79% CK-MM, 20% CK-MB, and 1% CK-BB and brain tissue contains 97% CK-BB and 3% CK-MB (210). The size of these proteins prevents that they are exiting the cell so that increased blood concentrations of CK indicate cell damage with membrane injury.

CK-MB was widely used in clinical practice to diagnose acute myocardial infarction (141, 204), but led to the overdiagnosis of AMI in endurance athletes after prolonged exercise. Boston Marathon runners had elevations in total CK and CK-MB immediately after the race (245). Such results raised the possibility that prolonged endurance exercise damaged the heart. Postexercise CK-MB elevations were confirmed by others after prolonged swimming (254) and running (48, 224), but the source of the CK-MB was not clear. Skeletal muscle biopsies performed 3 wk after the 1981 Boston Marathon demonstrated that marathon par-

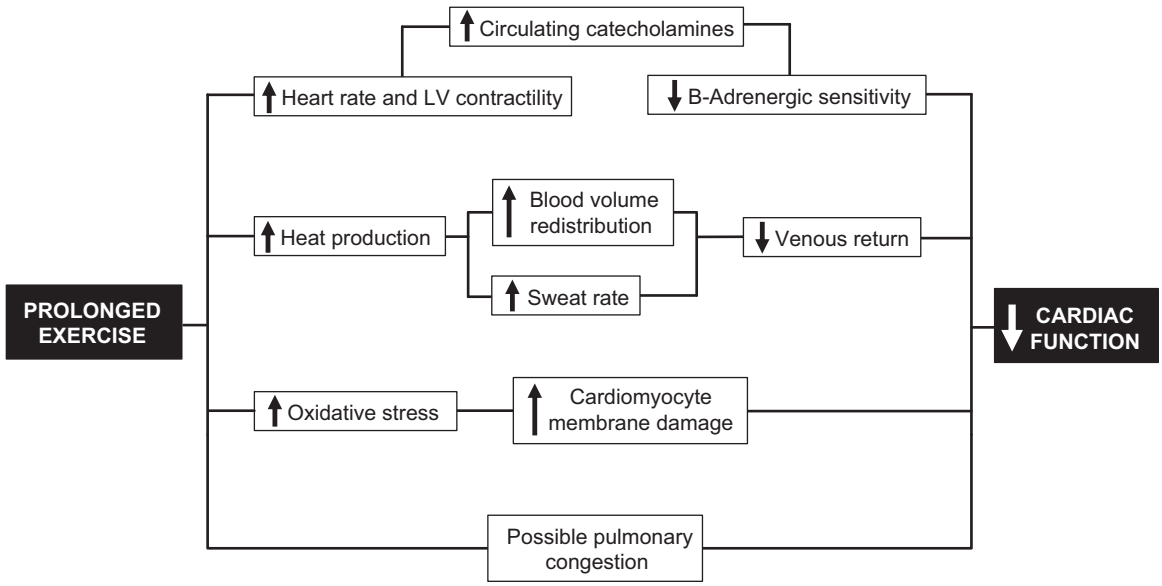

FIGURE 3. Schematic representation of potential mechanisms for impaired cardiac function after prolonged exercise. [Adapted from Shave et al. (235), with permission from Elsevier.]

ticipants had increased levels of CK-MB in their gastrocnemius muscles compared with sedentary controls (8,455 ± 1,235 vs. 3,993 ± 846 U/g) (244). Fetal skeletal muscle contains abundant concentrations of CK-MB prompting the authors to suggest that athletes are repetitively injuring their skeletal muscle, which is repaired by more embryonic satellite cells, which have a high, more fetal-like CK-MB content. These repair cells can also be injured by training and competition releasing CK-MB. Increased satellite cell concentration has also been demonstrated in runners' skeletal muscle (275). CK-MB typically constitutes ≤1% of the total CK in skeletal muscle tissue, but endurance athletes may have 8% of their CK as CK-MB form (8). Furthermore, the muscle CK-MB concentration increases with exercise training, demonstrating that higher CK-MB concentrations are not a constituent factor in endurance athletes, but an adaptation to training (8).

These multiple lines of evidence suggest that elevated CK-MB levels following endurance exercise originate from skeletal muscle damage, and do not represent acute myocardial injury. Cardiac troponin has replaced CK-MB as the preferred diagnostic marker for AMI, and many clinical laboratories no longer perform CK-MB measurements. Nevertheless, when evaluating these new markers, researchers and clinicians should remember that some "cardiac damage markers" like CK-MB can originate from exercise-training induced changes in skeletal muscle.

B. Cardiac Troponins

The contractile apparatus of striated muscle is composed of the troponin complex, the actin-based thin filament, the myosin-based thick filament, and tropomyosin. The troponin complex is tadpole-shaped and composed of subunits, troponin C, troponin T, and troponin I (55, 221). Approximately 90% of the troponin units are bound to the tropomyosin strand; the remaining 10% are within the cytosol of the cardiomyocyte (19). Skeletal and cardiac troponin C is identical, whereas the troponin I and T isoforms are specific for either skeletal or cardiac muscle. This specificity in cardiac troponin (cTn) I and T make these proteins suitable for detecting cardiac damage. Circulating cTn I and T concentrations are extremely low in healthy subjects, but markedly increase after cardiac injury. cTn is now the standard biomarker for diagnosing AMI (162, 259, 265).

Endurance exercise increases cTn, similar to the CK-MB experience, raising the possibility that exercise produces subtle myocardial injury. Initial reports using insensitive measures of cTn suggested that an increase in cTn was an infrequent phenomenon. For example, in what we believe is the first report of exercise-induced cTn elevations with exercise, cTn exceeded the normal reference range in only 1 of 19 marathon participants (113). Subsequent studies using more sensitive assays observed that 47–62% of athletes after marathons (67, 75, 169), triathlons (202, 270), endurance cycling (172, 238), and ultra-endurance races (125, 239) demonstrated cTn levels exceeding the value used to diagnose AMI (199, 235). Exercise-induced cTn elevations are not restricted to athletes or to prolonged endurance events. cTn elevations also occur in healthy individuals and those with cardiac disease after walking ≥30 km (56, 60), and in athletes after only 30 min of high intensity exercise (237). The recent introduction of "high-sensitivity cTn assays" has further increased detection of cTn in athletes, and we have shown exercise-induced cTnI increases in every athlete studied after the 2011 Boston marathon **(FIGURE 4)** (59).

The exercise-induced cTn elevations are greater with younger age (67), presence of cardiovascular risk factors (56), running inexperience (67), increased exercise duration and exercise intensity (56, 99, 153, 169, 231, 235), and increasing dehydration (95) with exercise. We combined these factors and found that only younger age and longer exercise duration predicted cTn increases in marathon runners competing at similar intensities (57), and that exercise intensity is the strongest single predictor of cTn release (58). This observation suggests that the cTn exercise response is directly related to the cardiac work of exercise since the cardiac demand during exercise is primarily determined by intensity.

The mechanisms mediating the exercise-induced cTn elevations are unknown, but there are several possibilities (284). Exercise could increase cardiomyocyte membrane permeability by mechanical stress (148), by the production of oxidative radicals, or by preload-induced increases in stretch-responsive integrins (64, 89). These changes in membrane permeability would be transient and not affect myocyte viability. Cardiac ischemia could cause proteolysis of the cTn complex (146), permitting troponin degradation products to pass through the cellular membrane (64) without

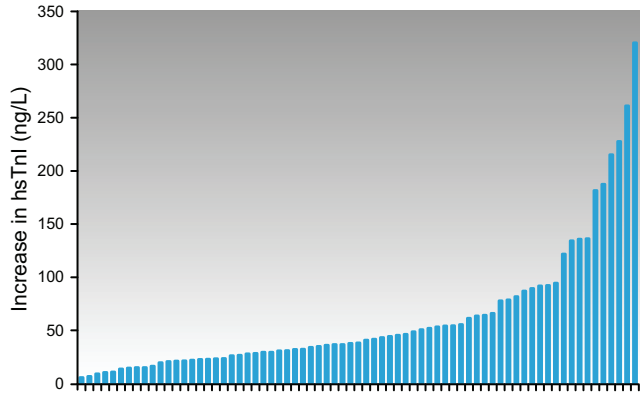

FIGURE 4. Exercise-induced increases in high-sensitive cardiac troponin I (hsTnI) levels in participants in the 2011 Boston marathon (n = 71). Each bar represents one subject, with all individuals demonstrating an increase in hsTnI postexercise. [Adapted from Eijsvogels et al. (59), with permission from Elsevier.]

changes in membrane permeability. Alternatively, temporary ischemia produces cell bubbles or blebs in hepatic cell membranes (78). These blebs are either reabsorbed or shed into the circulation with reperfusion. Blebs in the circulation could produce increases in plasma cTn, but it is not clear if this bleb formation occurs with temporary ischemia in cardiomyocytes (90). Furthermore, ischemia as a cause seems unlikely since cardiac ischemia is not thought to occur in healthy individuals during exercise (54).

Cardiomyocytes are estimated to die and be replaced at a rate of 0.5–1% per year depending on age (17). Recent animal (21) and human (61) studies suggest that endurance exercise training increases cardiomyocyte turnover making it possible that dying cardiomyocytes could release their cTn into the circulation. This process, if acutely accelerated by prolonged or intense exercise, could explain the acute increase in cTn. Cardiomyocyte apoptosis could also increase cTn levels (167), but it is unlikely that endurance exercise increases the rate of apoptosis since exercise training produces either no (102) or less (121) myocardial apoptosis.

Myocardial cell necrosis is the most frequent cause of cTn release in patients and could occur with endurance exercise. Indeed, rats forced to swim strenuously for 5 h demonstrated myocardial necrosis and inflammatory infiltrates at necropsy (30), but strenuous swim training in rodents is often accompanied by submergence and intermittent hypoxia, which may have produced or contributed to the myocardial necrosis. On the other hand, the magnitude and the kinetics of cTn levels differ between endurance exercise athletes and patients with myocardial injury. Athletes typically demonstrate a biphasic response of cTn release (150), starting within 60 min after the onset of exercise. The cTn elevations in athletes are only moderate (199, 235) and return to baseline within 72 h (222, 267). In contrast, the increases in cTn in patients with AMI occur ≥2 h after the onset of ischemia, greatly exceed the clinical cut-off value, and remain elevated for 4–10 days (107, 293), although milder cardiac ischemia could produce changes similar to those observed in athletes.

The increase in cTn after exercise could originate from noncardiac sources as with CK-MB. The cTnT concentration is increased in some patients with skeletal muscle disease without other evidence of cardiac injury (97). It is theorized that muscle injury causes expression of skeletal muscle fetal proteins, including cTnT, which enter the circulation after exercise-induced recurrent muscle damage (20, 201). Expression of the cTnT in skeletal muscle has not been documented in athletes, and current cTnT assays should not detect the regenerating isoform of cTnT (7). Furthermore, skeletal muscle repair should not increase cTnI (97), which may also increase after exercise and is more specific for cardiomyocyte injury. Thus a noncardiac origin for cTn increases postexercise is unlikely, but cannot be totally discounted given the experience with CK-MB.

The prevalence and kinetics of cTn increases after exercise suggest that this is a physiological and not a pathological exercise response, but far fewer studies have examined the relationship between cTn changes and myocardial function. Most studies have not demonstrated a relationship between cTn levels and LV dysfunction (74, 131, 220), although at least one study has observed that higher cTnI levels are associated with increases in the LV wall motion index ($r = 0.77$, $P < 0.001$) and larger peak strain rates ($r = 0.45$, $P < 0.05$) (125). At least two other studies observed that increased postexercise cTnI (124) and cTnT (169) levels were related to RV dysfunction. These relationships were modest ($r = 0.49$, $P = 0.002$ and $r = 0.70$, $P < 0.001$, respectively), and correlation does not prove cause and effect. Furthermore, any dysfunction associated with increased cTn appears transient. Cardiac magnetic resonance imaging (MRI) with late gadolinium enhancement (LGE) performed ≤3 days after a marathon did not reveal any myocardial injury or scar, despite the fact that cTnT levels were still elevated in the athletes (163). Similarly, only 1 of 34 runners with elevated cTn levels following a marathon (272) was detected at 3 mo to have any cardiac abnormality after an assessment which included biomarkers, ECG, rest and exercise echocardiographic assessments (272), and MRI with LGE (220). The one athlete was found to have a previously unknown coronary artery stenosis (272). Consequently, available data suggest that the increases in cTn levels are not associated with permanent cardiac damage or dysfunction.

C. BNP and NT-proBNP

The family of natriuretic peptides include neurohormones that are predominantly produced in the heart. These peptides are not stored in cardiomyocytes so their production is a constant process (234). B-type natriuretic peptide (BNP) and its cleaved inactive NH_2-terminal fragment (NT-proBNP) are secreted by the ventricles in response to cardiomyocyte stress produced by volume or pressure overload (134). BNP increases natriuresis, vasodilation, and inhibition of sympathetic activity, thereby reducing ventricular wall stress (23). Elevated levels of BNP and NT-proBNP indicate cardiac dysfunction, making them valuable clinical biomarkers for diagnosis, management, and risk stratification of patients with cardiovascular disease (142, 266).

BNP and NT-proBNP levels at rest in endurance athletes are similar to their untrained and age-matched peers (5, 219), but increase 5- to 10-fold after exercise in subjects participating in endurance exercise events (88, 169, 171, 179, 217, 243). Some authors have attributed these increases to either impaired cardiac function or subclinical myocardial injury (179).

The pattern of the exercise-induced BNP and NT-proBNP release typically has the peak value immediately after exercise and a return to baseline values within 72 h (114, 222). As many as 65–77% of the participants in endurance events demonstrate acute increases in NT-proBNP to values exceeding the upper reference limits (99th percentile) of the assay (217, 220). The magnitude of the increase in BNP and NT-proBNP levels is primarily dependent on exercise duration (217, 231), but increasing age (114, 171), lower levels of fitness (88, 169, 220), and elevated baseline levels of these biomarkers (211, 231) also affect the ultimate value. In vitro models support the role of stress duration in determining the magnitude of BNP increases since the BNP release in stretched cardiomyocytes increases with the duration of the stretching (287). Exercise intensity does not affect BNP and NT-proBNP release (132, 231) in contrast to the observations with cTn release. Some have suggested a "ceiling effect" for the relationship between BNP levels and exercise intensity, meaning that BNP and NT-proBNP are maximized at a low exercise intensity level so that further increases in blood levels require accumulation over time (132).

The larger increase in BNP levels with exercise duration and in sicker cardiac patients suggested to early investigators that the BNP increase indicated acute cardiac injury or cardiac dysfunction (179). Early investigators also observed a direct relationship between increases in cTn and BNP (179), but this relationship has not been confirmed by others (88, 114, 217). The lack of a correlation between cTn and BNP suggests that these are independent physiological responses to exercise. An acute BNP release with exercise may be designed to produce natriuresis, vasodilation, and less sympathetic activity, thereby reducing ventricular wall stress.

Alternatively, BNP and NT-proBNP release may be involved in the cardiac adaptations to exercise training (219). Resting BNP levels increased in military cadets after 10 wk of a high-intensity strength and endurance exercise training program (158). These cadets also demonstrated an increase in LV mass with training, but changes in LV mass were not correlated with BNP levels. BNP and NT-proBNP levels increase the most with exercise in the least trained athletes, suggesting that the acute increase may help initiate a training response (88, 169, 220).

Few studies have examined the relationship between exercise-induced BNP changes and cardiac function. Studies using sample sizes of only $n = 14$ (131), $n = 17$ (291), and $n = 20$ subjects (220) did not find a relationship between BNP and a reduction in left ventricular function, whereas studies using larger sample sizes of $n = 27$ (125), $n = 40$ (124), and $n = 60$ (169) did suggest a weak but significant relationship. Only one study investigated the effects of exercise on BNP levels and both LV and RV function (124). There was a significant correlation between postrace BNP levels and the change in right ($r = 0.52$, $P < 0.001$) but not left ventricular ejection fraction ($r = 0.25$, $P = 0.13$). This suggests that the effects of exercise may be greater on the right ventricle (127) as discussed elsewhere in this review.

The clinical implications of exercise-induced increases in BNP and NT-proBNP levels are unknown, but elevations in athletes are transient (114, 222) and NT-proBNP levels are lower in collapsed marathon runners than in asymptomatic peers, who completed the race (169, 242). Also, 95 of 99 collapsed marathon runners demonstrated NT-proBNP levels within their age-adjusted limits (242), suggesting that exercise-induced elevations in BNP and NT-proBNP are a physiological phenomenon without direct clinical consequences.

V. CARDIAC ADAPTATIONS DUE TO LONG-TERM EXERCISE TRAINING

A. The Athlete's Heart

The term *athlete's heart* refers to the cardiac adaptations to endurance exercise training that can include enlargement of all four cardiac chambers (186). These cardiac adaptations have generally been considered benign, but this assumption may not be entirely correct (22, 72) as discussed below (see sect. VI*B*).

B. Endurance Exercise Versus Strength Training

Sports can be classified by the proportions of static and dynamic exercise required. Dynamic (also called aerobic, endurance, or isotonic) exercise primarily involves joint movement, changes in muscle length, multiple rhythmic contractions, and the generation of comparatively small intramuscular forces, whereas predominantly static or strength exercise generates larger intramuscular forces (154). Intense, prolonged endurance exercise increases skeletal muscle oxygen demand which requires a systemic increase in oxygen uptake and delivery. Rearranging the Fick equation from cardiac output (CO) = oxygen uptake (V_{O_2})/arterial-venous oxygen difference (A–V O_2 Δ) to V_{O_2} = CO × A–V O_2 Δ demonstrates that the required increase in V_{O_2} can be satisfied by increases in both CO and the A–V O_2 Δ. Both increase acutely with exercise. Blood flow or CO increases because of increases in heart rate and stroke volume. Peripheral vascular resistance generally decreases, but systolic blood pressure usually increases because of the increase in CO (208, 209). Chronic endurance training predominantly produces a volume load on the left and right ventricles because of the increased blood flow with endurance exercise. In contrast, the acute cardiovascular responses to strength exercise are a modest increase in V_{O_2} and CO, but substantial increases

in peripheral vascular resistance and systolic blood pressure. The increased peripheral vascular resistance and increased blood pressure produced by strength exercise predominantly produces a pressure load on the left and right ventricles (160).

C. Cardiac Dimension Changes in Endurance Athletes and With Exercise Training

Echocardiographic studies confirm that the cardiac adaptations to chronic endurance and strength exercise training mimic the cardiac response to volume and pressure overload, respectively. Prospective exercise training studies demonstrate that endurance training increases left ventricular internal dimensions with little change in LV wall thickness (10). In contrast, strength exercise training increases LV wall thickness with little effect on LV cavity dimensions (193). The duration of most prospective exercise training studies cannot, however, replicate the effects of prolonged exercise training, such as that performed by endurance athletes, on cardiac dimensions.

Elite Italian athletes are required to undergo periodic cardiovascular screening (188). Researchers have used the echocardiographic results obtained from these evaluations to examine the upper limits of cardiac adaptations to exercise training. Athletes competing in endurance sports demonstrated markedly enlarged LV and left atrial (LA) diameters but little increase in LV wall thickness. Among 1,300 Italian athletes, 45% had LV end-diastolic internal diameters (LVEDD) $\geq$55 mm, the upper limit of normal (ULN) used in most clinical echocardiographic laboratories, and 14% had an LVEDD $\geq$60 mm (186). Also, among 1,777 Italian athletes, 20% had a LA diameter $\geq$40 mm, the ULN, and 2% had values $\geq$45 mm (189). In contrast to the increases in chamber diameter, among 738 male and 209 female Italian athletes, only 16 men had an LV wall thickness $>$12 mm, the ULN used for this parameter (190). The increase in LVEDD was greater in athletes participating in endurance sports and correlated inversely with heart rate ($r = -0.37$, $P < 0.001$) and directly with BSA ($r = 0.76$, $P < 0.001$) (186). The direct relationship with BSA indicates that not all of the increases in chamber dimensions in these cross-sectional studies are due to exercise training alone and that some of the enlargement may be due to characteristics that selected individuals for athletic achievement.

Gender and race affect the cardiac dimensions in athletes. Female athletes have smaller LV and LA diameters and are less likely to demonstrate LV wall thickness $>$ULN (187, 189, 268). LV wall thickness is also greater in black athletes (14, 185).

Fewer studies have examined RV size in athletes and prospectively with exercise training in part because echocardiographic examination of the RV is more difficult than with the LV. Right ventricular size and volume also increase with exercise training (38, 218), and the changes in RV size may be relatively greater than the LV changes (126) **(FIGURE 5)**. The ratio of RV and LV end-systolic volumes is greater in endurance athletes than in sedentary controls, suggesting that RV enlargement with exercise training is proportionally greater than the LV enlargement. Similarly, the ratio of RV to LV mass is also greater in the endurance athletes. This may reflect the relatively greater RV than LV wall stress produced acutely by exercise that was discussed above (see sect. III*B*). Only modest increases in RV dimensions are reported in strength-trained athletes (39). LV diastolic dysfunction may contribute to increased pulmonary artery pressure and the decrease in RV systolic function seen postexercise (180). These changes resolve, however, within a week after exertion (124).

Very few studies have examined the right atrial (RA) size, but those that are available also demonstrate larger RA dimensions in endurance-trained athletes than in age- and sex-matched strength athletes and controls (38).

D. Cardiac Performance in Athletes and With Exercise Training

As presented above, V_{O_2} requirements increase with the exercise work rate. V_{O_2} is determined by CO or the systolic volume (SV) and heart rate, and by the A–V O_2 Δ. Maximal exercise capacity, or $V_{O_{2max}}$, is therefore a surrogate marker of maximal SV or cardiac performance. The SV in athletes, and after exercise training, is increased because of the increased LVEDD also mentioned above.

Cardiac function depends not only on systolic function, but also on how readily the ventricles fill during diastole. The speed with which the ventricles fill depends on their ability to relax rapidly, but also on other factors such as pericardial and pulmonary mechanical restraint (68). In fact, removing the pericardium in dogs increases end-diastolic volume during exercise, maximal cardiac output, and therefore maximal aerobic power (252). The development of novel diastolic measurements has increased the understanding of the processes involved in LV filling and the changes in endurance athletes. LV filling is intrinsically related to systolic function. In fact, systolic twisting of the myocardium is necessary prior to untwisting and the initiation of diastolic suction. The untwisting of the LV during the isovolumic relaxation and early filling phases releases elastic energy stored by the preceding systolic twisting and contributes to the initial atrioventricular pressure gradient. This untwisting has been related to LV pressure decay in dogs subjected to pacing and dobutamine infusion (173). The storage of energy during LV twisting appears to be fundamental to supporting diastolic filling during maximal exercise by

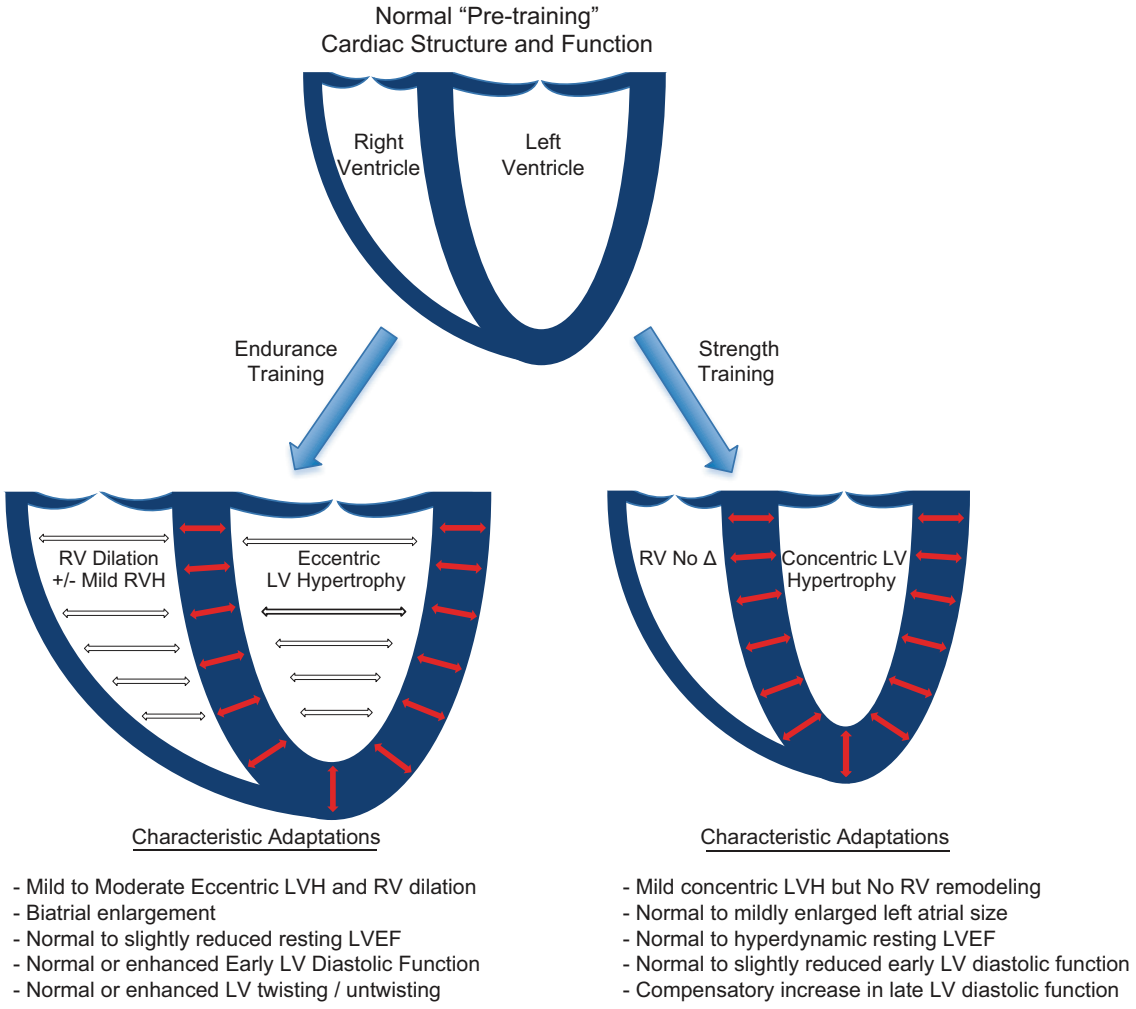

FIGURE 5. Summary of exercise-induced remodeling of the left and right ventricle. Endurance training increases left ventricular internal dimensions with little change in LV wall thickness (10), whereas strength training increases LV wall thickness with little effect on LV cavity dimensions (193). [From Weiner and Baggish (279), with permission from Elsevier.]

creating a suction-aided filling effect (213). Recent studies demonstrated increased untwisting rates in endurance athletes participating in kayaking, canoeing, and rowing compared with patients with hypertrophic cardiomyopathy (115), suggesting that this also could help distinguish physiological adaptations from pathology.

Endurance athletes tend to have longer isovolumic-relaxation times (28) leading to rapid ventricular filling that is represented by the E wave measured by Doppler echocardiography. Diastasis occurs after early diastolic filling. This tends to be quite long in athletes with slow heart rates, but it progressively shortens as the HR increases. The rate at which the LV filling pressure rises during late diastole depends on the myocardial compliance. Finally, atrial contraction occurs generating an additional pressure gradient depending on the cardiac output, the blood remaining in the atria at the end of diastole, and myocardial and pericardial compliance. The A wave measured by Doppler echocardiography represents the atrial contraction contribution to the LV filling. Historically, the E/A mitral inflow velocity ratio has been used to evaluate diastolic function. The E/A ratio of virtually all endurance athletes is >1.0, but can be as high as 4.8 in some athletes. The increased ratio is mainly due to a decrease in the A wave velocity. This implies that at rest, the relative contribution of the atrial contraction is lower in trained athletes, since most of the LV filling occurs in the early diastole and during diastasis particularly at slower HR (28). These filling patterns could mimic the restrictive filling pattern seen in cardiomyopathies, but should not raise suspicion of pathology even in the presence of left atrial enlargement. In contrast, E/A ratio values <1.0 suggest a nonphysiological condition in a trained athlete. The E/A ratio, however, is not specific and is affected by heart rate, loading conditions, and pressure gradients. The normal Doppler tissue imaging (DTI), a normal calculated pulmonary artery systolic pressure, and the over-

all clinical picture should be used to avoid misclassifying diastolic indexes in athletes as pathological.

DTI can sample areas of the myocardium near the mitral annulus and determine myocardial velocities both during systole and diastole. It is particularly helpful when other diastolic indexes are indeterminate. A ratio of transmitral *E* velocity to the tissue Doppler *e′* velocity directly correlates with invasive measurements of the pulmonary capillary wedge pressure, such that an *E/e′* greater than 15 predicts an LV end-diastolic pressure of more than 15 mmHg (166).

Few studies have examined longitudinally the effect of exercise training on RV and LV diastolic function (10, 168, 280). Studies of collegiate rowers and American football players before and after training demonstrate that rowers developed biventricular dilation with enhanced diastolic function, whereas football players developed isolated, concentric left ventricular hypertrophy with diminished diastolic relaxation (10). Similarly, cross-sectional studies comparing endurance athletes with matched controls demonstrate increased early diastolic velocities (29), a shift in the pattern of ventricular filling towards early diastole despite LV hypertrophy (40, 52), and an association of peak LV inflow velocity with LVEDD (37) and stroke volume (77). These findings are all consistent with enhanced diastolic function. The limited data examining diastolic function in strength-trained athletes suggest that there is either no change or relative impairment of LV relaxation (10).

Several lines of evidence suggest that LV diastolic function is reduced after ≥1 h of endurance exercise (151). The magnitude of the diastolic dysfunction does not seem to be related to changes in heart rate, blood pressure, or LVEDD (151), and it has been suggested by the a few echocardiographic indexes of diastolic dysfunction (74, 174, 175, 181). Most studies (105, 111, 233, 286), but not all (170), demonstrate normalization of diastolic function within 24 h after exercise. Thus the decrease in LVEF and diastolic function appear to be transient. Consequently, the effect of exercise on LV function appears to be a physiological response with limited, if any, clinical significance (285).

Athletes have more compliant and distensible ventricles than nonathletes. The increased distensibility observed in athletes affects the pressure-volume loop allowing filling of the ventricle at lower-than-normal pressures because the lower part of the loop is shifted downward because of increased chamber compliance. This permits a lesser pressure rise at greater volumes. It also shifts the LV end-diastolic pressure (LVEDP)/SV (Frank-Starling) curve leftward so that small increases in LVEDP translate into large changes in SV during submaximal exercise. This has been demonstrated in studies using direct invasive measurements of filling pressures and rapid increases and decreases in ventricular filling using saline infusions and lower body negative pressure, respectively (133).

E. Implications of the Changes in Cardiac Dimensions and Function

A fundamental question that emanates from this review is whether exposure to lifelong endurance exercise and the cardiac adaptation that it engenders can deleteriously affect cardiovascular health. Case series and cross-sectional studies of cardiac function, albeit important in the understanding of these adaptations, do not provide cause and effect evidence to answer this question. More epidemiological and longitudinal studies on cardiovascular risk in endurance athletes exposed to the highest intensity of endurance exercise over prolonged period of time are required to resolve this issue.

The increases in cardiac dimensions and function discussed above are required for superior exercise performance and are not associated with deleterious side-effects. The possibility that increased LV and RV dimensions from exercise training contribute to cardiac disease in a minority of susceptible individuals and that increases in atrial size contributes to atrial fibrillation are discussed subsequently.

VI. POTENTIAL MALADAPTATIONS TO LIFELONG EXERCISE

A. Atherosclerosis and Coronary Artery Calcification

Atherosclerosis is a complex process in the arterial wall that involves a large number of growth factors, cytokines, and vasoregulatory molecules (207). The deposit of fatty streaks in the intima layer of the vessel wall is the earliest recognizable lesion and precedes plaque formation and expansion of the lesion (276). Atherosclerotic plaques have two common phenotypes with different potential clinical sequelae. Stable plaques are characterized by a small lipid pool, low concentrations of inflammatory cells, and a thick fibrous cap (135). Such plaques may progress leading to coronary narrowing and conditions such as angina pectoris or exercise-induced cardiac ischemia. These plaques are less vulnerable to plaque disruption and therefore less likely to produce thrombosis and an acute coronary syndrome (ACS) such as unstable angina pectoris, AMI, or SCD. Vulnerable plaques are characterized by a large lipid pool, high inflammatory activity covered by a thin fibrous cap, and are more likely to rupture and produce ACS (42, 65). The progression of plaques usually takes decades, and the presence of atherosclerosis does not necessarily cause clinical symptoms (135). Atherosclerotic coronary artery disease (ASCAD) is the leading cause of cardiovascular events and death worldwide. The arterial injury produced by atherosclerosis often

leads to calcification of the plaques, and osteogenic proteins have been detected in atherosclerotic lesions (2). The extent of coronary artery calcification is, therefore, a marker of ASCAD and is used both to assess the degree of atherosclerosis and to predict prognosis (24, 255).

Exercise training reduces all of the major risk factors for CAD (262) and physical activity reduces morbidity and mortality from ASCAD (194, 262). Despite strong risk factor evidence that exercise should reduce ASCAD (215, 262) and overwhelming evidence that physical activity reduces ASCAD clinical events (94, 159), there has long been controversy whether habitual physical activity levels actually reduce or retard the atherosclerotic process (103). A 1960 autopsy study of 207 white men aged 30–60 yr demonstrated that the degree of coronary atherosclerosis increased with age, but that there was no difference in the degree of ASCAD between physically active and sedentary men (248). Recent studies have demonstrated that atherosclerotic plaques are present in the carotid or peripheral arteries of 90% of marathon runners 50–75 yr old (118) and that carotid intima media thickness (cIMT), a marker of atherosclerosis, is not different in young, middle-aged, and veteran endurance-trained athletes and age-matched sedentary controls (18–77 yr old) (256) or physically inactive spouses (46 ± 12 yr old) (257). Such results, suggesting no reduction in the atherosclerotic process, contrast with studies showing reduced markers of ASCVD. These studies include evidence that 6 mo of exercise training reduces cIMT (249) and that vigorous exercise reduces the rate of cIMT progression compared with less active controls after 3 (117) and 6 (198) yr of exercise training.

Coronary artery calcification (CAC) scoring provides a more direct assessment of coronary artery atherosclerosis than measures of peripheral vascular disease such as cIMT. CAC can be determined by computed tomography (CT) and scored using Agatston units. A CAC score of zero indicates a very low 10-yr risk of an ACS event (18), whereas increasing CAC scores are linearly related to an increased risk of a cardiac event (47). Increased physical activity is associated with reduced CAC scores in most (44, 45, 251), but not all (81), cross-sectional studies in the general population. At least one longitudinal study has also confirmed that increased physical activity is associated with reduced CAC scores (70). Studies demonstrating reductions in CAC scores have generally examined mild to moderate levels of exertion. Paradoxically, several studies have suggested that CAC may be increased in long-term, middle-aged endurance athletes. A comparison of 108 German men ≥50 yr of age, who had participated in ≥5 marathons, had CAC scores greater than 216 controls, matched for age and Framingham risk factor score (FRS) (157). This difference was absent when men were not matched for FRS, raising the possibility that the marathoners relatively recently adopted an active lifestyle, which improved their risk factors and FRS, whereas their CAC scores reflected their prior exposure to higher risk factors. Against this explanation is the observation that American men who completed ≥1 marathon/yr over the previous 25 years demonstrated larger CAC volumes than a sedentary control group (83.8 ± 67.7 vs. 44.0 ± 36.8 mm^3, $P < 0.01$) (228). The runners were older, however (59 ± 7 vs. 55 ± 10 yr, $P < 0.05$), which could account for some of the difference.

Several possibilities could explain the higher CAC scores in the marathoners. The marathoners could have higher values of unmeasured risk factors or could have been exposed to higher risk factor levels prior to their exercise training as suggested by the German study. Alternatively, the faster heart rate and SBP during exercise training could have accelerated the atherosclerotic process in the runners. It is also possible that increased CAC may not reflect increased risk in the runners. Coronary calcification may stabilize the coronary plaque raising the possibility that the exercise training increases plaque stability. Supporting this concept is the recent observation that the extent of CAC measure by the CAC score increases the risk of a cardiac event, whereas increased density of the CAC deposit actually reduces risk (35). The CVD risk is considerably lower in individuals with densely calcified plaques compared with non- or partially calcified plaques (35, 93). This hypothesis is supported by the finding that statins promote calcification of atherosclerotic plaques even though they reduce plaque burden and thereby promote plaque stability (196). Exercise may cause similar effects on plaque composition, suggesting that the higher CAC scores in athletes contribute to plaque stabilization and subsequent risk reduction for cardiovascular morbidity and mortality. Finally, it is possible that the same amount of atherosclerosis in an athlete produces more CAC. Exercise acutely increases parathyroid hormone levels (13, 138). Parathyroid hormone increases circulating calcium levels, which could accelerate the calcification of atherosclerotic lesions (80).

B. Myocardial Fibrosis

Myocardial fibrosis is characterized by the accumulation of collagen in the extracellular matrix of the heart (49). Myocardial fibrosis most commonly occurs after myocyte injury from ischemia, but can have nonischemic causes (100). Myocardial fibrosis is divided into reactive interstitial fibrosis, infiltrative interstitial fibrosis, and replacement fibrosis (see **FIGURE 6**) (149). In reactive interstitial fibrosis, myocytes synthesize collagen in response to cardiac stress that can be produced by aging, cardiac conditions causing LV pressure or volume overload, and metabolic factors including increased activity of reactive oxygen species, the renin-angiotensin aldosterone system, and the β-adrenergic system (149). In infiltrative interstitial fibrosis, insoluble proteins such as amyloid in amyloidosis (232) or glycosphingolipids in Anderson-

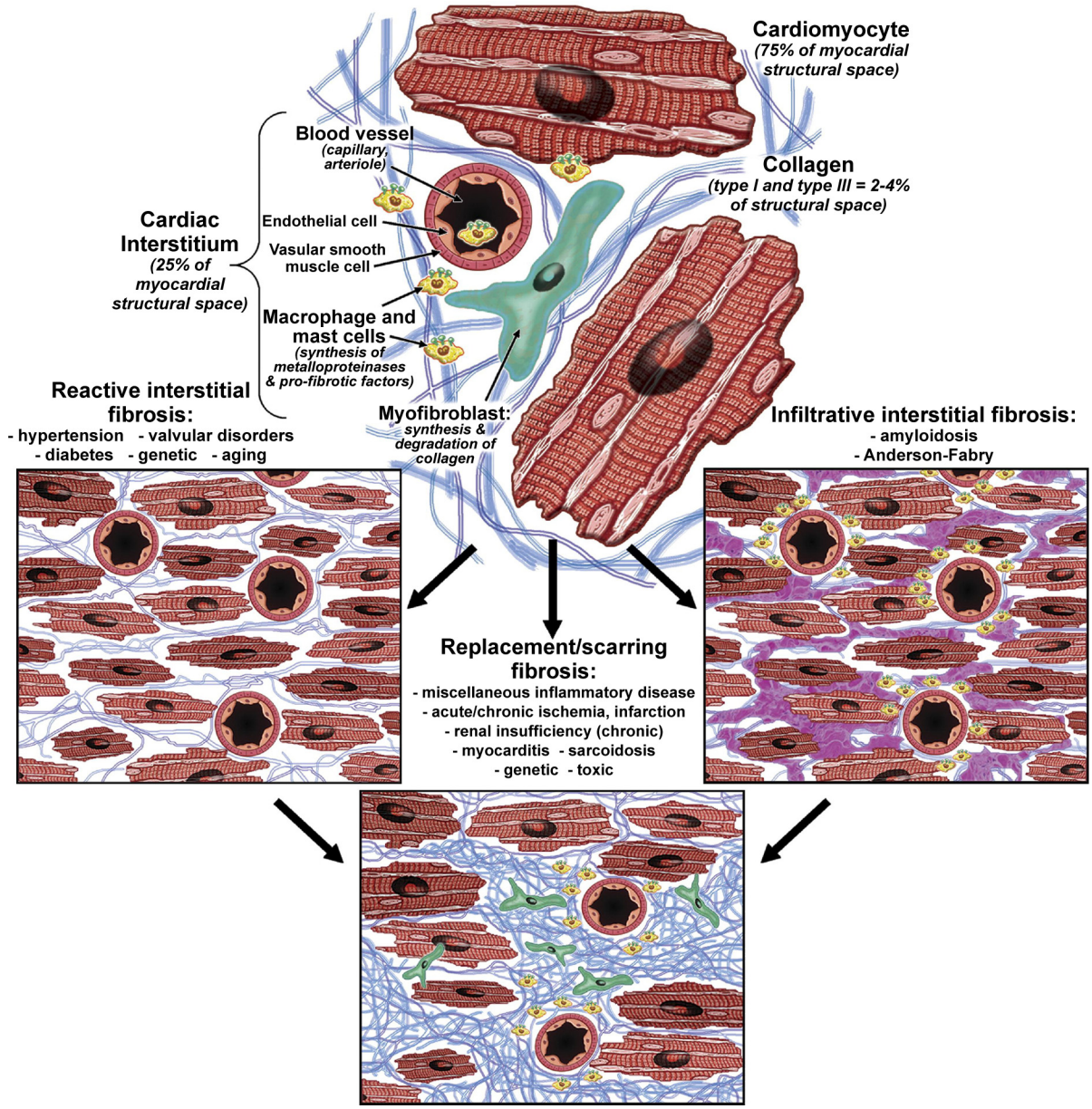

FIGURE 6. Pathophysiology of myocardial fibrosis. [From Mewton et al. (149), with permission from Elsevier.]

Fabry disease (295) deposit in the cardiac interstitium. In replacement fibrosis, myocytes damaged by such factors as ischemia or viral infection are replaced by collagen (253). Both reactive and infiltrative interstitial fibrosis may progress to replacement fibrosis (277). Replacement fibrosis can be localized when produced by cardiac ischemia following a myocardial infarction (MI) resulting in a "scar" formation, or it can be diffuse following conditions such a viral myocarditis.

Myocardial fibrosis reduces ventricular compliance leading to heart failure with a preserved ejection fraction (HFpEF), atrial enlargement, and atrial fibrillation. Myocardial fibrosis is also present in systolic heart failure. Several studies demonstrated that the presence of myocardial fibrosis increases the risk for future cardiac events and mortality (122, 152, 176, 278).

At least one animal study suggests that prolonged or lifelong exercise may produce or accelerate myocardial fibrosis. Rats forced to run for 16 wk, a time deemed equivalent to 10 yr of endurance exercise training in humans, developed eccentric cardiac hypertrophy, diastolic dysfunction, atrial dilation, and collagen deposition at the right ventricle and both atria (16).

Elite middle-aged and veteran endurance athletes (45–75 yr old), who have exercised ≥10 yr at a competitive level and currently run ≥30 miles/wk, demonstrate increased plasma markers of collagen syntheses and degradation,

including tissue inhibitor of matrix metalloproteinase type I (TIMP-1), carboxy-terminal telopeptide of collagen type I (CITP), and carboxy-terminal propeptide of collagen type I (PICP), compared with age-matched sedentary controls (136). The TIMP-1 levels were greatest in those athletes with LV hypertrophy. This biochemical evidence of abnormal collagen turnover suggests that myocardial fibrosis may be present in these veteran endurance athletes (136).

Myocardial fibrosis can be directly visualized in humans using MRI after the injection of gadolinium. Fibrotic areas of the heart entrap the gadolinium so that it can be visualized on late imaging in a process called late gadolinium enhancement (LGE). LGE was detected in 12 of 102 German marathon runners (12%) compared with only 4 of 102 age-matched controls (4%), but this was not statistically different ($P = 0.077$) (22). Five of the runners had an LGE pattern typically found in CAD patients, despite being asymptomatic, and seven had a non-CAD pattern. The presence of fibrosis in endurance exercise athletes was confirmed in studies from Australia (5/40, 13%) (124) and the United Kingdom (6/12, 50%) (290). Not all studies have supported the hypothesis that life-long endurance athletes have increased LGE (82, 163, 177, 269). Differences in age, habitual physical activity levels, and study size may contribute to the discrepancy between studies. For example, athletes with LGE tend to be older than athletes without LGE (124). The prevalence of LGE increases with years of competitive exercise training (290) and the number of completed marathons [odds ratio (OR) = 1.65, 95% confidence interval (CI) = 1.08–2.52] (157). This increase could be a factor of age or represent a potentially deleterious effect of exercise training.

The significance of myocardial fibrosis in athletes is currently unknown. Athletes with LGE have higher CAC scores than runners without LGE (CAC score = 192 vs. 26, $P = 0.005$) (157) and a lower coronary event free survival during 25 mo of follow-up (75 vs. 99%, $P < 0.001$) (22). The fibrosis in several of these studies is located where the right ventricle attaches to the intraventricular septum and could represent mild fibrosis from constant flexing at this "hinge" point produced by both exercise and the right ventricular enlargement that attends long-term endurance exercise training (123). This is discussed further in section VIG.

The animal study note above observed that most markers of myocardial fibrosis returned to baseline after discontinuation of exercise training (16). This suggests that the fibrosis is of the reactive phenotype, which is an intermediate marker of disease severity and is reversible in patient populations (50, 139, 140). Additional studies in humans are required to determine if the fibrosis is reversible with exercise cessation and to determine the clinical significance of persistent fibrosis in athletes.

C. Atrial Fibrillation

Atrial fibrillation (AF) refers to chaotic electrical activity that replaces normal sinus rhythm and eliminates the contribution of atrial contraction to LV filling. AF is the most common arrhythmia in the United States and affects ~6 million individuals. (156) The risk of AF increases with age, and the incidence of AF in individuals ≥65 yr of age is ~2% per year (104, 206). The prevalence of AF will increase with the increasing age of the population (206).

AF can be classified as paroxysmal, persistent, or permanent (69). Paroxysmal AF is defined as AF that reverts to normal sinus rhythm within 7 days, and ~50% of paroxysmal AF patients do so within 24 h. Persistent AF is defined as AF that persists beyond 7 days. Permanent AF is defined as AF that is long-standing, usually defined as >1 yr and which can either not be converted to sinus rhythm or when cardioversion has not been attempted (69). These three forms of AF generally progress from one to the other if the patient does not receive medical intervention.

Risk factors for AF include any condition that increases left atrial size or pressure (247), such as hypertension, left systolic or diastolic heart failure, and stenosis or regurgitation of the mitral valve. Increases in both parasympathetic and sympathetic tone also increase the risk of AF (247). Increased parasympathetic tone shortens the atrial refractory period by decreasing the inward current of the L-type calcium channels (294). Shortening the atrial refractory period shortens the excitation wavelength and facilitates atrial reentry. Increased sympathetic activity, such as that produced by exercise, shortens the atrial action potential, thereby increasing the risk of AF. Increased adrenergic tone may also produce micro reentry atrial circuits, which can initiate the AF (34). Hyperthyroidism increases cardiac sensitivity to catecholamines and can provoke AF. Drugs that mimic increased sympathetic activity such as cocaine and caffeine can also produce AF.

AF decreases the atrial contribution to LV filling and decreases CO. The decrease in CO can decrease exercise tolerance especially in those with resistance to LV filling such as patients with mitral valve stenosis or LV hypertrophy. AF can also cause "tachycardia mediated cardiomyopathy" if the ventricular response rate is not controlled (79). Tachycardia-mediated cardiomyopathy refers to a reversible decrease in cardiac systolic function produced by persistently rapid heart rates.

The most devastating complication of AF is systemic thromboembolism. Clots form in the left atrium, and specifically in the left atrial appendage, because of the blood stasis

produced by the AF. Approximately 15% of strokes in the United States are associated with AF (200). These strokes tend to be large and therefore devastating. For this reason, many patients with AF are placed on anticoagulant therapy depending on a risk/benefit analysis of the patient. Notably, the risk of thromboembolism exists in all AF categories including paroxysmal AF probably because patients with paroxysmal AF have more and longer episodes than they appreciate and because clots are ejected when sinus rhythm is restored.

The relationship between physical activity and atrial fibrillation is complex and suggests a U-shaped relationship (250). Low levels of exercise are associated with a reduced prevalence of AF possibly by reducing factors producing AF such as hypertension. Physical activity is associated with reduced incidence of AF in women (62), but this relationship is not significant after controlling for body mass index. Similarly, light to moderate exercise was associated with a lower relative risk of new-onset AF in the cardiovascular health study (164). In contrast, long-term high levels of endurance exercise appear to increase the incidence of AF. Among participants in the Physicans Health Study, the risk of AF increased with the number of days per week of vigorous physical activity (3). There are also a systematic review (247) and a meta-analysis (1) showing an increase in AF among endurance athletes with the relative risk in the athletes increased fivefold (OR = 5.29, 95% CI = 3.57–7.85, $P = 0.0001$) (1). This risk seems to be higher in men than in women (288). The systematic review (247) and meta-analysis (1) were based on the same studies and compared athletes with the general population. Even among athletes, however, the risk appears to increase with the amount of endurance activity. Participants in a 90-km Nordic ski race (the Vasaloppet) during 1989–1998 were followed until December 2005 using national health registries (6). There were 52,755 Vasaloppet participants of whom 919 were hospitalized for an arrhythmia during follow-up. Those completing five or more races were more likely to experience any arrhythmia compared with those completing only one (OR = 1.3, 95% CI = 1.08–1.58). This result was largely due to more frequent AF (OR = 1.29, 95% CI = 1.04–1.61) and bradyarrhythmias (OR = 2.1, 95% CI = 1.28–3.47). Those with the fastest finishing times relative to the winner were also more likely to be hospitalized for any arrhythmia (OR = 1.3, 95% CI = 1.04–1.62) again due to more frequent AF and bradyarrhythmias, but separately the AF and bradyarrythmias were not statistically significant (OR = 1.2, 95% CI = 0.93–1.55; OR = 1.85, 95% CI = 0.97–3.54, respectively). AF was not more frequent in a study of young, elite Italian athletes (189), but this observation suggests that AF requires either increased age, persistent athletic participation, or probably both.

The mechanism increasing AF in endurance athletes is not defined, but probably is a combination of increased parasympathetic tone and left atrial enlargement especially in older endurance athletes. AF can also be provoked by exercise via sympathetic stimulation. This may be produced by intense exercise alone, but is often exacerbated by other sympathomimetic agents.

D. Other Arrhythmias

AF is the arrhythmia that appears most consistently to be associated with life-long physical activity. Atrial flutter is a right-sided macro-reentrant atrial arrhythmia that most commonly originates from the cavotricuspid isthmus in the right atrium. Paroxysmal atrial flutter has been reported in 10% of former endurance athletes (92), but is often combined with AF in analyses of arrhythmias in athletes (11).

A slower resting heart rate (sinus bradycardia) is a well-known cardiac adaptation to endurance training and athletes may develop first- and second-degree heart block (101). Third-degree heart block is unusual in athletes and requires a careful evaluation (137), but some athletes may develop transient third-degree heart block during sleep when vagal tone is high. First-degree heart block refers to an increase in the AV conduction time, second to intermittent AV block of electrical conduction from originating the atrium, and third to complete blockage of the passage of all atrial beats to the ventricles. Several studies suggest that these bradyarrhythmias persist after the athlete stops active exercise training (6, 11). For example, the average heart rate was lower among 62 former professional cyclists who participated in the Tour de Suisse from 1955–1972 than in golfers matched for age, weight, blood pressure, and cardiac medications [66 ± 9 vs. 70 ± 8 beats per minute (BPM), $P = 0.004$] (11). The cyclists had participated in the Tour de Suisse 38 ± 6 yr earlier. Evidence of sinus node dysfunction, defined as a heart rate <40 BPM, atrial flutter, placement of a pacemaker for bardycardia, or an R-R interval >2.5 s, was present in 16% of the former cyclists but in only 2% of the golfers ($P = 0.006$). A similar percentage of cyclists and golfers spent >4 h weekly in aerobic exercise (52 % vs. 44%, $P = 0.47$), but the cyclists did slightly more endurance training. These results are similar to those from the Vasaloppet study mentioned above, which observed an increase in hospitalizations for bradyarrhythmias among those skiers who participated in the most races (6).

Persistence of bradycardia and evidence of sinus node abnormalities after the cessation of intense exercise training imply that either endurance athletes have innately different cardiac electrophysiology before exercise training or that prolonged endurance exercise remodels the cardiac electrical system. These studies cannot, however, totally exclude a persistently more active lifestyle and therefore more continued exercise training in the former endurance athletes.

E. Long QT

The QT interval is an electrocardiographic measurement of the time between depolarization and repolarization of the cardiac ventricles. The QT interval is generated by currents produced by the passage of potassium, calcium, and sodium ions through cardiac ion channels (226). Both decreases in the repolarizing K^+ outward current and increases in the depoloarizing sodium and calcium currents can increase the QT interval (226). Abnormal increases in the QT interval produce the long QT syndrome (LQTS), which can produce polymorphic ventricular tachycardia, syncope, and SCD. LQTS does not produce any structural cardiac changes and is the likely cause of many SCDs in young people when there are no pathological findings at autopsy. LQTS and other defects in cardiac ion channel function are referred to clinically as "channelopathies."

Defects in at least 10 genes affecting cardiac ion channels have been associated with LQTS, but 90% of LQTS patients have defects in one of three genes: *KCNQ1*, *KCNH2*, and *SCN5A* (226). Defects in *KCNQ1* are most prevalent and produce LQTS-1 (226). Defects in *KCNH2* and *SCN5A* produce LQTS-2 and LQTS-3, respectively. Loss-of-function mutations in *KCNQ1* affect the I_{KS} potassium channel reducing the current generated by I_{KS} (165). The I_{KS} channel is sensitive to adrenergic stimulation (165). A normally functioning I_{KS} channel shortens the QT interval during increased adrenergic states such as physical exertion, whereas patients with defective I_{KS} channels cannot shorten their QT duration during exercise and other situations with increased adrenergic tone (36, 165). LQTS-1-3 differ not only in terms of their genetic cause, but also in their phenotypic presentation. Approximately 75% of cardiac events in individuals with LQTS-1 occur during exercise, whereas <5% of these events occur during exercise in LQTS-2&3 patients **(FIGURE 7)** (226). Thus exercise is a trigger for cardiac arrhythmic event in LQTS-1 patients.

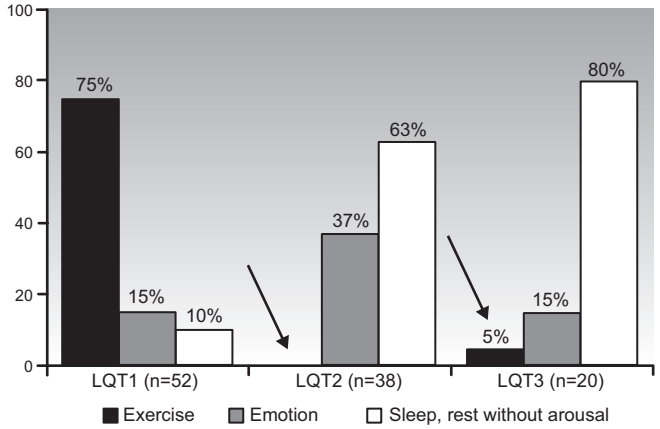

FIGURE 7. The bars present frequency of activities associated with the onset of all fatal and nonfatal cardiac events in individuals with the three most common long QT genotypes. [From Schwartz et al. (226).]

Increased vagal tone appears to be a risk factor for cardiac arrhythmia in patients with LQTS-1. LQTS-1 patients with increased baroreflex sensitivity, a marker of increased vagal tone, are more likely to have experienced at least one cardiac arrhythmic event compared with those with less vagal tone (227). Similarly, a greater reduction in heart rate in the first minute after exercise is a marker of enhanced vagal tone (36). LQTS-1 patients with the greatest reduction in heart rate after exercise are more likely to have experienced at least one cardiac arrhythmic event (36). Only patients with defects in genes affecting the adrenergically sensitive I_{KS} potassium channel are affected (36, 227). Both studies suggest that enhanced vagal tone increases the risk of ventricular tachycardia and SCD in LQTS-1 patients. Exercise training reduces heart rate in large part by increasing parasympathetic or vagal tone (26). Consequently, these studies (36, 227) suggest that increases in vagal tone from exercise training could increase arrhythmia risk in individuals with a genetic predilection for LQTS-1. This possibility requires more study, but some experts have recommended avoiding repetitive exercise capable of producing an exercise training effect in individuals with the mutations in *KCNQ1* and LQTS-1 (36).

F. Aortic Size and Root Dilatation

Exercise training increases the dimensions of all four muscular cardiac chambers, but few studies have examined the effect of exercise training on aortic diameter. Some have suggested that exercise training may increase aortic diameter (9, 296). This is an important consideration because aortic dissection and rupture are a rare (144) but recognized (87, 271) cause of sudden death during exercise, and the risk of these events increases with increasing aortic diameter. A meta-analysis examined aortic root diameters from 23 echocardiographic studies including 5,580 elite athletes and 729 controls (96). The athletes included 1,506 endurance trained, 425 strength trained, 213 combined strength and endurance trained, and 3,436 mixed trained athletes. Aortic root size was 3.2 mm greater at the sinuses of Valsalva and 1.6 mm greater at the aortic annulus in the athletes than in controls ($P < 0.05$ for both). The aortic diameter at the annulus was 2.2 mm greater in the endurance trained athletes than in controls ($P < 0.05$) and 1.5 mm greater in strength trained athletes ($P = 0.13$). Too few studies were available to perform similar measurements at the sinuses of Valsalva. These results suggest that exercise training increases aortic diameter, but longitudinal studies are required to confirm these largely cross-sectional data (96). Furthermore, these differences are small and unlikely to have clinical significance. On the other hand, this effect probably does have clinical significance in patients with genetic connective tissue defects that predispose them to aortic dilatation such as patients with Marfan syndrome (197) who may experience an augmented effect from exercise training. Also, the effect of long-term exercise training

on individuals with bicuspid aortic valves, which has an associated aortopathy (46), has not been examined to our knowledge.

G. Arrhythmogenic RV Dysplasia

Arrhythmogenic RV dysplasia/cardiomyopathy (ARVC) produces RV enlargement, reduced RV systolic function, RV arrhythmias, and SCD (15). ARVC is responsible for up to 20% of SCD in all young individuals (240) and for ~4% of SCDs in young athletes in the United States (145). ARVC is the predominant cause of exercise-related sudden deaths in the Padua region of Italy (260). Pathologically ARVC is characterized by fibrous fatty replacement of normal myocytes, primarily in the RV, although pathological changes can be found in the intraventricular septum and LV (73). Fatty infiltration can be seen with magnetic resonance imaging, which is used to help diagnose the condition (15).

Genetically ARVC has most consistently been related to mutations in genes producing proteins involved in desmosomes and the adherens junction, those areas responsible for myocyte to myocyte binding (110). Dysfunctional desmosomal proteins lead to cell breakdown and replacement of myocardial cells by fat and fibrous tissue. Genetic defects in desmosomal proteins including plakophilin, plakoglobin, desmoglein, and desmoplain have been identified as causes of ARVC (110). Predilection of the disease for the RV is likely related to the thinner walls of this structure compared with the LV, which permits stretching of the RV and injury to the desmosomal myocyte connections.

The penetrance of ARVC within families is variable, suggesting that environmental factors may affect manifestation of the disease (98). There are at least two studies examining the effect of exercise training on the development of ARVC in animals (110) or humans (98) with genetic susceptibility to the disease, and both suggest that exercise training accelerates appearance and progression of ARVC. Plakoglobin connects the cytoplasmic component of the desmosome and adherens junction to the intracellular cytoskeleton and contractile myofilaments such as actin (110). Heterozygous plakoglobin-deficient mice develop larger RV diameters, reduced RV function, and more RV arrhythmias mimicking the clinical picture of ARVC **(FIGURE 8)** (110). Endurance exercise training in this mouse model accelerates the appearance of RV enlargement and dysfunction (110).

Exercise training also appears to increase the penetrance of ARVC in humans. Known carriers of a desmosomal mutation (87 subjects, 46 men) with a mean age of 44 ± 18 yr were queried about their exercise habits after age 10 (98). There were 56 endurance athletes in the cohort, defined as participating in a sport requiring >70% of maximal aerobic capacity for ≥50 h/yr. The endurance athletes developed symptoms at a younger age (30.1 ± 13 vs. 40.6 ± 21.2 yr, $P = 0.05$). Also, more of the athletes with a genetic abnormality met established criteria for the diagnosis of ARVC (82 vs. 35%, $P < 0.001$). The athletes had a lower lifetime survival free of heart failure ($P = 0.004$) and of ventricular tachycardia (VT)/ventricular fibrillation (VF) ($P = 0.013$) than the nonathletes. When evaluated by quartiles of physical activity, individuals in the second, third, and fourth quartiles had a 6.64-, 16.7-, and 25.3-fold greater risk, respectively, of meeting the diagnostic criteria for ARVC compared with the least active group ($P < 0.05$ for all). Furthermore, those individuals in the most active group who reduced their activity levels had a reduced risk of subsequent VT and VF compared with those who maintained a high level of activity.

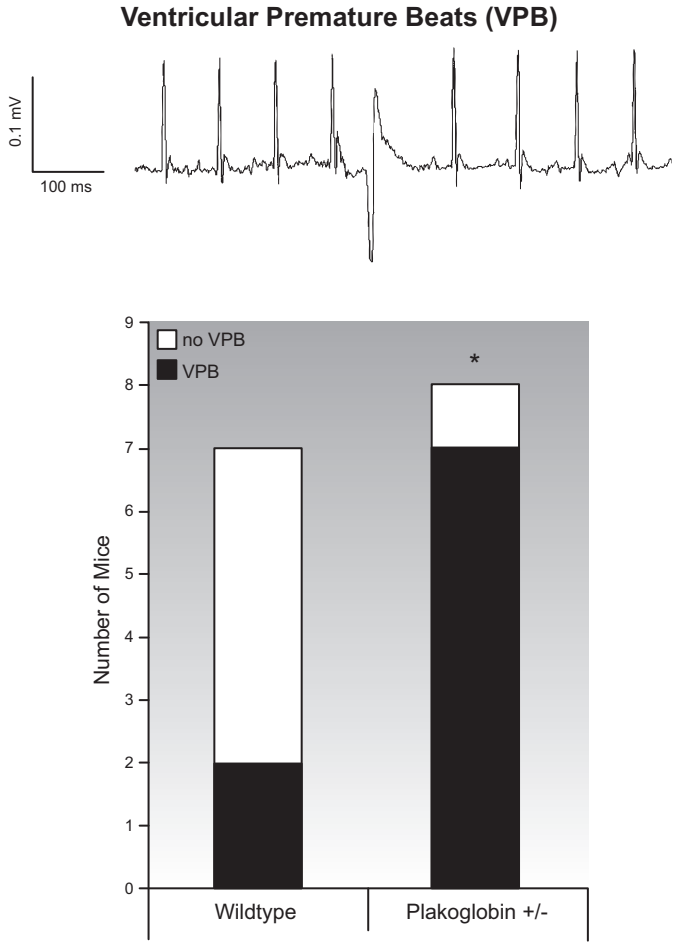

FIGURE 8. ECG rhythm strip at top shows a spontaneous ventricular premature beat (VPB) in a heterozygous plakoglobin-deficient mouse model of arrythmogenic right ventricular dysplasia/cardiomyopathy. Lower bar graphs show the number of mice with spontaneous VPDs/ARVC. *Statistically significant difference between the number of mice in the plakogblobin +/- and wildtype group demonstrating VPBs. [From Kirchhof et al. (110).]

Both studies require confirmation, but are consistent with the concept that exercise training increases RV dimensions, and that this enlargement stresses myocardial junctions. This produces cellular damage in those with genetic defects in proteins involved in cell to cell junctions.

These results are also consistent with studies suggesting that prolonged exercise training may produce RV cardiac changes that mimic ARVC. As discussed in section IIIC, the acute increases in pulmonary artery systolic pressure with exercise is greater than the increase in systemic arterial pressure producing relatively greater increases in RV than LV wall stress (126). Also, the increases in RV volume and mass appear to be proportionately greater than those in the LV (126), again suggesting a larger effect of exercise training on the RV. It has long been known that prolonged endurance exercise such as a full-length triathlon (3.9 km swim, 180.2 km bicycle ride, and 42.2 km run) produces acute increases in RV diameter measured by echocardiography, whereas LV volume decreases (51). Recent studies have confirmed these changes in RV diameter after endurance events, but have also documented reductions in RV ejection fraction (EF) without change in LV function (124). BNP and cTnI increased with exercise, and the magnitude of the increase correlated directly with the decrease in RV ejection fraction ($r = 0.52$ and 0.49, $P < 0.002$ for both) (124). The reduction in RVEF also correlated directly with the race duration and the athletes' estimated maximal oxygen uptake, suggesting that the time and absolute intensity of exertion affect RV function. The presence of myocardial scarring in these athletes was assessed using MRI and LGE. Five of 39 athletes had LGE. These five athletes had practiced sports for an average of 20 ± 16 versus only 8 ± 6 yr in those without LGE ($P < 0.05$). LGE in the athletes was located where the RV attaches to the intraventricular septum.

An animal model (16), referred to as the marathon rat (274), also suggests that exercise training preferentially produces worrisome changes in the RV. Rats forced to run on a treadmill for 18 wk at high intensity, which the authors equate to 10 yr of endurance training, developed collagen deposits and biochemical markers of myocardial fibrosis in the RV, but not in the LV (16). Furthermore, programmed electrical stimulation, a technique designed to evaluate susceptibility to lethal arrhythmias, produced sustained ventricular tachycardia, in 42% (5 of 12) of exercise-trained animals but in only 6% (1 of 16) of sedentary controls ($P = 0.05$).

In sum, these articles suggest that prolonged exercise training facilitates the development of ARVC in susceptible individuals. Studies of prolonged exercise and lifelong endurance athletes suggest that prolonged exercise training may even create scarring, fibrosis, and myocardial injury in individuals without a genetic predisposition to RV cardiomyopathy (124).

VII. LONGEVITY

It is well established that moderate-intensity exercise reduces the risk of CVD mortality and morbidity (282). Vigorous exercise, however, can transiently increase the risk of sudden cardiac death (263). The impact of chronic endurance exercise on the longevity of elite athletes is controversial. Early studies in university rowers report a 15% reduction in mortality compared with the general population (85) and a 6-yr increase in life expectancy compared with nonathletic classmates (195). However, others reported reduced mortality rates below the age of 50 but not later in life (223), or no difference in longevity among athletic and nonathletic university students (205).

More recent studies largely support a beneficial effect of vigorous exercise on longevity. A large American study, including 13,016 runners and 42,121 controls, demonstrated that that leisure-time running reduced all-cause mortality rates by 30% [hazard ratio (HR) = 0.70, 95% CI = 0.64–0.77] and cardiovascular mortality by 45% (HR = 0.55, 95% CI = 0.46–0.65) (130). Persistent running further improved the health benefits of exercise. Interestingly, mortality rates were largely independent of weekly running distance, frequency, speed, and number of MET-min (130). These findings are in contrast with the Copenhagen City Heart Study (225). Although the authors reported a 6-yr increased life expectancy in joggers ($n = 1,129$) versus nonjoggers ($n = 16,423$), the results suggested a U-shaped relationship between jogging time and mortality (225). Whereas jogging 60–150 min/wk significantly reduced mortality (HR = 0.58, 95% CI = 0.41–0.82), jogging 150–240 min/wk or >240 min/wk did not (HR = 0.79, 95% CI = 0.52–1.19 and HR = 0.86, 95% CI = 0.59, 1.24, respectively) (225). There were only 166 joggers in the highest jogging group, however.

Several studies assessed longevity in elite athletes. Finish champion skiers ($n = 396$) demonstrated 2.8–4.3 yr of increased life expectancy compared with a comparison group of Finnish men (106). Two other Finnish studies found 5–6 yr of increased life expectancy in world-class endurance athletes ($n = 303$ and $n = 437$) compared with a military reference cohort ($n = 1,712$) (108, 214). A reduction of the risks for cardiovascular mortality (OR = 0.49, 95% CI = 0.26–0.93) and cancer (OR = 0.36, 95% CI = 0.12–0.92) were the major contributors to the increased survival rates in the athletic population (108, 214). These findings were recently confirmed by a meta-analysis including data from 42,807 elite athletes (71). Athletes reported a 33% reduced risk for all-cause mortality [standardized mortality rate (SMR) = 0.67, 95% CI = 0.55–0.81]. Both cardiovascular (SMR = 0.73, 95% CI = 0.65–0.82) and cancer (SMR = 0.60, 95% CI = 0.38–0.94) mortality rates were significantly lower in athletes versus controls (71). Similarly, a large Swedish study ($n = 73,622$) reported a 52% decrease in overall mortality (SMR = 0.48, 95% CI = 0.44–0.53) and a 57% decrease in cardiovascular mortality (SMR = 0.43, 95% CI = 0.35–0.51) among participants of the Vasaloppet cross-country ski race (63). Health benefits were stronger in older skiers and those that participated in

multiple races (63). A study including 15,174 Olympic athletes who won medals between 1896 and 2010 reported 2.8 yr of increased life expectancy compared with matched cohorts in the general population (32). Finally, French elite cyclists competing in the Tour de France (n = 786) experienced a 41% lower all-cause mortality (SMR = 0.59, 95% CI = 0.42–0.72) and a 33% lower cardiovascular mortality (SMR = 0.67, 95% CI = 0.50–0.88) compared with males from the general population (143).

Consequently, there is in general strong evidence that vigorous endurance exercise reduces all-cause and cardiovascular mortality in amateur and elite athletes. Thus doses of habitual exercise above the recommended physical activity guidelines may improve health and stimulate longevity in the long run. On the other hand, such studies cannot separate the effects of exercise training from innate characteristics that facilitated these individuals becoming athletes in the first place. Also, lifestyle differences such as smoking, diet, and socioeconomic status between athletes and control cohorts may confound assessment of the benefits of lifelong exercise training on longevity (120).

VIII. PERSPECTIVES AND CONCLUSIONS

Physically active individuals experience approximately half the risk of ASCVD, and most studies suggest that the benefits of physical activity increase progressively with increasing activity. Few studies, however, have examined the effects of life-long extreme endurance exercise on cardiac risk or the possibility that there may be deleterious cardiac effects of extreme exercise and prolonged exercise training **(FIGURE 9)**.

Some of the risk of exercise is well-known, since it is accepted that exercise and physical activity acutely, albeit transiently, increase the risk for both AMI and SCD. This risk is small for the general population and further reduced, but still present, even in habitually active individuals. Exercise also acutely increases serum biomarkers for cardiovascular disease including CK-MB, cTn, and BNP. The increase in CKMB appears to result from skeletal muscle damage from exercise-trained skeletal muscle whose CKMB content has increased with exercise training. The source of the increases in cTn and BNP is less clear, but both probably are emitted from cardiac muscle in response to the physical stress of exercise. These increases are of some concern because several studies have demonstrated that a prolonged bout of exercise reduces ventricular function, primarily of the right ventricle, supporting the hypothesis that prolonged exercise acutely injures cardiac muscle and produces "cardiac fatigue." These reductions in cardiac function are transient, and probably of no physiologic consequence, but there are several studies documenting myocardial fibrosis in lifelong endurance athletes. It is not clear if the increases in cardiac biomarkers, reductions in ventricular function, and cardiac fibrosis are interrelated. There is also preliminary evidence that middle-aged endurance athletes have increased coronary artery calcification scores, a marker of atherosclerosis. This is surprising given the generally low levels of atherosclerotic risk factors in the runners. The significance of this calcification is unknown especially given the overwhelming evidence that physical activity is related to lower ASCVD risk, but it is possible that the increases in heart rate and SBP produced by exercise alter coronary artery flow dynamics and ultimately accelerate atherosclerosis.

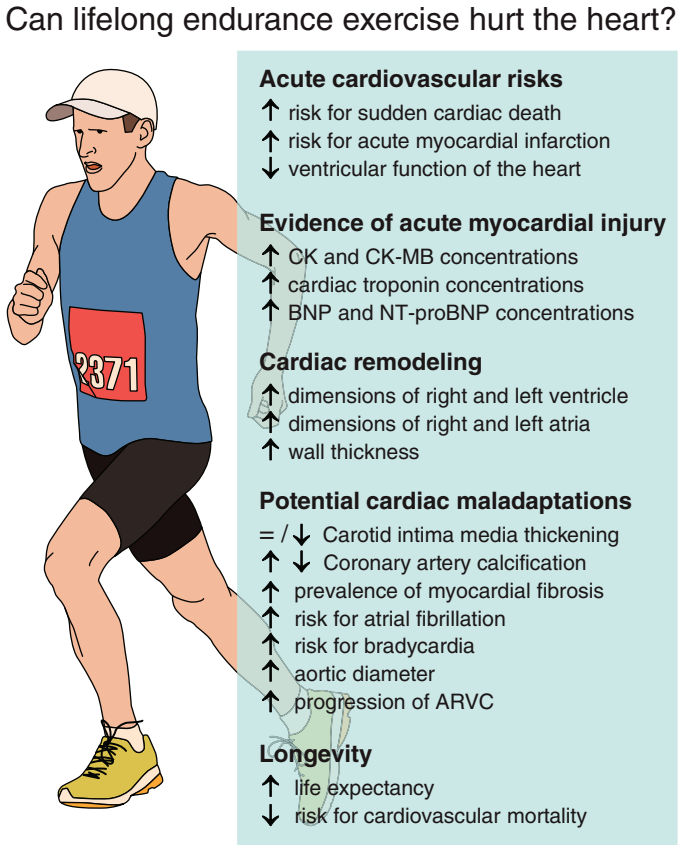

FIGURE 9. An overview of potential deleterious cardiac effects of the performance of acute and chronic endurance exercise.

Exercise training produces profound changes in cardiac physiology and structure collectively referred to as the "athlete's heart." There are increases in cardiac parasympathetic or vagal tone and reductions in sympathetic tone producing the well-recognized reductions in resting heart rate. There is also enlargement of all four cardiac chambers. These adaptations that facilitate exercise performance may have adverse cardiac effects. Atrial fibrillation appears to be more common in older athletes possibly because of increased vagal tone and left atrial size. The RV increases in size with exercise training and appears to be more vulnerable to the acute effects of exercise possibly because the increase in pulmonary artery systolic blood pressure with exercise and therefore RV wall stress is relatively greater in the right than left sides of the heart. Remarkably, physically

active individuals with genetic defects in the desmosomal proteins known to cause RVCM/D have an earlier and more severe presentation of the disease than their sedentary counterparts who also have the genetic defects. This strongly suggests that exercise can hasten cardiac disease in susceptible individuals. One can speculate that exercise and physical activity could similarly hasten phenotypic expression of other inherited cardiac conditions such as LQTS, HCM, genetic defects of aortic tissue, and other diseases.

This review does not intend to defame exercise, but to praise it. Exercise and physical activity appear to have remarkably beneficial effects for the majority of the population. The problem for most developed societies is too little and not too much exercise. Nevertheless, the possibility that prodigious amounts of exercise could adversely affect cardiac function and disease risk in some individuals or populations should be scientifically considered and examined.

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REFERENCES

1. Abdulla J, Nielsen JR. Is the risk of atrial fibrillation higher in athletes than in the general population? A systematic review and meta-analysis. *Europace* 11: 1156–1159, 2009.

2. Aikawa E, Nahrendorf M, Figueiredo JL, Swirski FK, Shtatland T, Kohler RH, Jaffer FA, Aikawa M, Weissleder R. Osteogenesis associates with inflammation in early-stage atherosclerosis evaluated by molecular imaging in vivo. *Circulation* 116: 2841–2850, 2007.

3. Aizer A, Gaziano JM, Cook NR, Manson JE, Buring JE, Albert CM. Relation of vigorous exercise to risk of atrial fibrillation. *Am J Cardiol* 103: 1572–1577, 2009.

4. Albert CM, Mittleman MA, Chae CU, Lee IM, Hennekens CH, Manson JE. Triggering of sudden death from cardiac causes by vigorous exertion. *N Engl J Med* 343: 1355–1361, 2000.

5. Almeida S, Azevedo A, Castro A, Frioes F, Freitas J, Ferreira A, Bettencourt P. B-type natriuretic peptide is related to left ventricular mass in hypertensive patients but not in athletes. *Cardiology* 98: 113–115, 2002.

6. Andersen K, Farahmand B, Ahlbom A, Held C, Ljunghall S, Michaelsson K, Sundstrom J. Risk of arrhythmias in 52 755 long-distance cross-country skiers: a cohort study. *Eur Heart J* 34: 3624–3631, 2013.

7. Apple FS, Collinson PO, Biomarkers ITFoCAoC. Analytical characteristics of high-sensitivity cardiac troponin assays. *Clin Chem* 58: 54–61, 2012.

8. Apple FS, Rogers MA, Sherman WM, Costill DL, Hagerman FC, Ivy JL. Profile of creatine kinase isoenzymes in skeletal muscles of marathon runners. *Clin Chem* 30: 413–416, 1984.

9. Babaee Bigi MA, Aslani A. Aortic root size and prevalence of aortic regurgitation in elite strength trained athletes. *Am J Cardiol* 100: 528–530, 2007.

10. Baggish AL, Wang F, Weiner RB, Elinoff JM, Tournoux F, Boland A, Picard MH, Hutter AM Jr, Wood MJ. Training-specific changes in cardiac structure and function: a prospective and longitudinal assessment of competitive athletes. *J Appl Physiol* 104: 1121–1128, 2008.

11. Baldesberger S, Bauersfeld U, Candinas R, Seifert B, Zuber M, Ritter M, Jenni R, Oechslin E, Luthi P, Scharf C, Marti B, Attenhofer Jost CH. Sinus node disease and arrhythmias in the long-term follow-up of former professional cyclists. *Eur Heart J* 29: 71–78, 2008.

12. Banks L, Sasson Z, Busato M, Goodman JM. Impaired left and right ventricular function following prolonged exercise in young athletes: influence of exercise intensity and responses to dobutamine stress. *J Appl Physiol* 108: 112–119, 2010.

13. Barry DW, Kohrt WM. Acute effects of 2 hours of moderate-intensity cycling on serum parathyroid hormone and calcium. *Calcified Tissue Int* 80: 359–365, 2007.

14. Basavarajaiah S, Boraita A, Whyte G, Wilson M, Carby L, Shah A, Sharma S. Ethnic differences in left ventricular remodeling in highly-trained athletes relevance to differentiating physiologic left ventricular hypertrophy from hypertrophic cardiomyopathy. *J Am Coll Cardiol* 51: 2256–2262, 2008.

15. Basso C, Corrado D, Marcus FI, Nava A, Thiene G. Arrhythmogenic right ventricular cardiomyopathy. *Lancet* 373: 1289–1300, 2009.

16. Benito B, Gay-Jordi G, Serrano-Mollar A, Guasch E, Shi Y, Tardif JC, Brugada J, Nattel S, Mont L. Cardiac arrhythmogenic remodeling in a rat model of long-term intensive exercise training. *Circulation* 123: 13–22, 2011.

17. Bergmann O, Bhardwaj RD, Bernard S, Zdunek S, Barnabe-Heider F, Walsh S, Zupicich J, Alkass K, Buchholz BA, Druid H, Jovinge S, Frisen J. Evidence for cardiomyocyte renewal in humans. *Science* 324: 98–102, 2009.

18. Blaha M, Budoff MJ, Shaw LJ, Khosa F, Rumberger JA, Berman D, Callister T, Raggi P, Blumenthal RS, Nasir K. Absence of coronary artery calcification and all-cause mortality. *JACC Cardiovasc Imaging* 2: 692–700, 2009.

19. Bleier J, Vorderwinkler KP, Falkensammer J, Mair P, Dapunt O, Puschendorf B, Mair J. Different intracellular compartmentations of cardiac troponins and myosin heavy chains: a causal connection to their different early release after myocardial damage. *Clin Chem* 44: 1912–1918, 1998.

20. Bodor GS, Survant L, Voss EM, Smith S, Porterfield D, Apple FS. Cardiac troponin T composition in normal and regenerating human skeletal muscle. *Clin Chem* 43: 476–484, 1997.

21. Bostrom P, Mann N, Wu J, Quintero PA, Plovie ER, Panakova D, Gupta RK, Xiao C, MacRae CA, Rosenzweig A, Spiegelman BM. C/EBPbeta controls exercise-induced cardiac growth and protects against pathological cardiac remodeling. *Cell* 143: 1072–1083, 2010.

22. Breuckmann F, Mohlenkamp S, Nassenstein K, Lehmann N, Ladd S, Schmermund A, Sievers B, Schlosser T, Jockel KH, Heusch G, Erbel R, Barkhausen J. Myocardial late gadolinium enhancement: prevalence, pattern, and prognostic relevance in marathon runners. *Radiology* 251: 50–57, 2009.

23. Brunner-La Rocca HP, Kaye DM, Woods RL, Hastings J, Esler MD. Effects of intravenous brain natriuretic peptide on regional sympathetic activity in patients with chronic

heart failure as compared with healthy control subjects. *J Am Coll Cardiol* 37: 1221–1227, 2001.

24. Budoff MJ, Shaw LJ, Liu ST, Weinstein SR, Mosler TP, Tseng PH, Flores FR, Callister TQ, Raggi P, Berman DS. Long-term prognosis associated with coronary calcification: observations from a registry of 25,253 patients. *J Am Coll Cardiol* 49: 1860–1870, 2007.

25. Burfoot A. The history of the marathon: 1976-present. *Sports Medicine* 37: 284–287, 2007.

26. Carnevali L, Sgoifo A. Vagal modulation of resting heart rate in rats: the role of stress, psychosocial factors, and physical exercise. *Front Physiol* 5: 118, 2014.

27. Carrio I, Serra-Grima R, Berna L, Estorch M, Martinez-Duncker C, Ordonez J. Transient alterations in cardiac performance after a six-hour race. *Am J Cardiol* 65: 1471–1474, 1990.

28. Caselli S, Di Paolo FM, Pisicchio C, Pandian NG, Pelliccia A. Patterns of left ventricular diastolic function in Olympic athletes. *J Am Soc Echocardiography* 28: 236–244, 2015.

29. Caso P, D'Andrea A, Galderisi M, Liccardo B, Severino S, De Simone L, Izzo A, D'Andrea L, Mininni N. Pulsed Doppler tissue imaging in endurance athletes: relation between left ventricular preload and myocardial regional diastolic function. *Am J Cardiol* 85: 1131–1136, 2000.

30. Chen Y, Serfass RC, Mackey-Bojack SM, Kelly KL, Titus JL, Apple FS. Cardiac troponin T alterations in myocardium and serum of rats after stressful, prolonged intense exercise. *J Appl Physiol* 88: 1749–1755, 2000.

31. Christenson RH, Azzazy HM. Biochemical markers of the acute coronary syndromes. *Clin Chem* 44: 1855–1864, 1998.

32. Clarke PM, Walter SJ, Hayen A, Mallon WJ, Heijmans J, Studdert DM. Survival of the fittest: retrospective cohort study of the longevity of Olympic medallists in the modern era. *BMJ* 345: e8308, 2012.

33. Corrado D, Basso C, Rizzoli G, Schiavon M, Thiene G. Does sports activity enhance the risk of sudden death in adolescents and young adults? *J Am Coll Cardiol* 42: 1959–1963, 2003.

34. Coumel P. Autonomic influences in atrial tachyarrhythmias. *J Cardiovasc Electrophysiol* 7: 999–1007, 1996.

35. Criqui MH, Denenberg JO, Ix JH, McClelland RL, Wassel CL, Rifkin DE, Carr JJ, Budoff MJ, Allison MA. Calcium density of coronary artery plaque and risk of incident cardiovascular events. *JAMA* 311: 271–278, 2014.

36. Crotti L, Spazzolini C, Porretta AP, Dagradi F, Taravelli E, Petracci B, Vicentini A, Pedrazzini M, La Rovere MT, Vanoli E, Goosen A, Heradien M, George AL Jr, Brink PA, Schwartz PJ. Vagal reflexes following an exercise stress test: a simple clinical tool for gene-specific risk stratification in the long QT syndrome. *J Am Coll Cardiol* 60: 2515–2524, 2012.

37. D'Andrea A, Cocchia R, Riegler L, Scarafile R, Salerno G, Gravino R, Golia E, Pezzullo E, Citro R, Limongelli G, Pacileo G, Cuomo S, Caso P, Russo MG, Bossone E, Calabro R. Left ventricular myocardial velocities and deformation indexes in top-level athletes. *J Am Soc Echocardiogr* 23: 1281–1288, 2010.

38. D'Andrea A, Riegler L, Golia E, Cocchia R, Scarafile R, Salerno G, Pezzullo E, Nunziata L, Citro R, Cuomo S, Caso P, Di Salvo G, Cittadini A, Russo MG, Calabro R, Bossone E. Range of right heart measurements in top-level athletes: the training impact. *Int J Cardiol* 164: 48–57.

39. D'Andrea A, Riegler L, Morra S, Scarafile R, Salerno G, Cocchia R, Golia E, Martone F, Di Salvo G, Limongelli G, Pacileo G, Bossone E, Calabro R, Russo MG. Right ventricular morphology and function in top-level athletes: a three-dimensional echocardiographic study. *J Am Soc Echocardiogr* 25: 1268–1276, 2012.

40. D'Ascenzi F, Cameli M, Zaca V, Lisi M, Santoro A, Causarano A, Mondillo S. Supernormal diastolic function and role of left atrial myocardial deformation analysis by 2D speckle tracking echocardiography in elite soccer players. *Echocardiography* 28: 320–326, 2011.

41. Davies EJ, Moxham T, Rees K, Singh S, Coats AJ, Ebrahim S, Lough F, Taylor RS. Exercise training for systolic heart failure: Cochrane systematic review and meta-analysis. *Eur J Heart Fail* 12: 706–715, 2010.

42. Davies MJ. Stability and instability: two faces of coronary atherosclerosis. The Paul Dudley White Lecture 1995. *Circulation* 94: 2013–2020, 1996.

43. Dawson E, George K, Shave R, Whyte G, Ball D. Does the human heart fatigue subsequent to prolonged exercise? *Sports Medicine* 33: 365–380, 2003.

44. Delaney JA, Jensky NE, Criqui MH, Whitt-Glover MC, Lima JA, Allison MA. The association between physical activity and both incident coronary artery calcification and ankle brachial index progression: the multi-ethnic study of atherosclerosis. *Atherosclerosis* 230: 278–283, 2013.

45. Desai MY, Nasir K, Rumberger JA, Braunstein JB, Post WS, Budoff MJ, Blumenthal RS. Relation of degree of physical activity to coronary artery calcium score in asymptomatic individuals with multiple metabolic risk factors. *Am J Cardiol* 94: 729–732, 2004.

46. Detaint D, Michelena HI, Nkomo VT, Vahanian A, Jondeau G, Sarano ME. Aortic dilatation patterns and rates in adults with bicuspid aortic valves: a comparative study with Marfan syndrome and degenerative aortopathy. *Heart* 100: 126–134, 2014.

47. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, Liu K, Shea S, Szklo M, Bluemke DA, O'Leary DH, Tracy R, Watson K, Wong ND, Kronmal RA. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med* 358: 1336–1345, 2008.

48. Diamond TH, Smith R, Goldman AP, Myburgh DP, Bloch JM, Visser F. The dilemma of the creatine kinase cardiospecific iso-enzyme (CK-MB) in marathon runners. *S African Med J* 63: 37–41, 1983.

49. Diez J. Mechanisms of cardiac fibrosis in hypertension. *J Clin Hypertens* 9: 546–550, 2007.

50. Diez J, Querejeta R, Lopez B, Gonzalez A, Larman M, Martinez Ubago JL. Losartan-dependent regression of myocardial fibrosis is associated with reduction of left ventricular chamber stiffness in hypertensive patients. *Circulation* 105: 2512–2517, 2002.

51. Douglas PS, O'Toole ML, Hiller WD, Reichek N. Different effects of prolonged exercise on the right and left ventricles. *J Am Coll Cardiol* 15: 64–69, 1990.

52. Douglas PS, O'Toole ML, Hiller WD, Reichek N. Left ventricular structure and function by echocardiography in ultraendurance athletes. *Am J Cardiol* 58: 805–809, 1986.

53. Douglas PS, O'Toole ML, Woolard J. Regional wall motion abnormalities after prolonged exercise in the normal left ventricle. *Circulation* 82: 2108–2114, 1990.

54. Duncker DJ, Bache RJ. Regulation of coronary blood flow during exercise. *Physiol Rev* 88: 1009–1086, 2008.

55. Ebashi S. Separation of troponin into its three components. *J Biochem* 72: 787–790, 1972.

56. Eijsvogels T, George K, Shave R, Gaze D, Levine BD, Hopman MT, Thijssen DH. Effect of prolonged walking on cardiac troponin levels. *Am J Cardiol* 105: 267–272, 2010.

57. Eijsvogels TM, Hoogerwerf MD, Maessen MF, Seeger JP, George KP, Hopman MT, Thijssen DH. Predictors of cardiac troponin release after a marathon. *J Sci Med Sport* 18: 88–92, 2015.

58. Eijsvogels TM, Hoogerwerf MD, Oudegeest-Sander MH, Hopman MT, Thijssen DH. The impact of exercise intensity on cardiac troponin I release. *Int J Cardiol* 171: e3–4, 2014.

59. Eijsvogels TM, Januzzi JL, Taylor BA, Isaacs SK, D'Hemecourt P, Zaleski A, Dyer S, Troyanos C, Weiner RB, Thompson PD, Baggish AL. Impact of statin use on exercise-induced cardiac troponin elevations. *Am J Cardiol* 114: 624–628, 2014.

60. Eijsvogels TM, Veltmeijer MT, George K, Hopman MT, Thijssen DH. The impact of obesity on cardiac troponin levels after prolonged exercise in humans. *Eur J Appl Physiol* 112: 1725–1732, 2012.

61. Ellison GM, Waring CD, Vicinanza C, Torella D. Physiological cardiac remodelling in response to endurance exercise training: cellular and molecular mechanisms. *Heart* 98: 5–10, 2012.

62. Everett BM, Conen D, Buring JE, Moorthy MV, Lee IM, Albert CM. Physical activity and the risk of incident atrial fibrillation in women. *Circulation Cardiovasc Quality Outcomes* 4: 321–327, 2011.

63. Farahmand BY, Ahlbom A, Ekblom O, Ekblom B, Hallmarker U, Aronson D, Brobert GP. Mortality amongst participants in Vasaloppet: a classical long-distance ski race in Sweden. *J Internal Med* 253: 276–283, 2003.

64. Feng J, Schaus BJ, Fallavollita JA, Lee TC, Canty JM Jr. Preload induces troponin I degradation independently of myocardial ischemia. *Circulation* 103: 2035–2037, 2001.

65. Finn AV, Nakano M, Narula J, Kolodgie FD, Virmani R. Concept of vulnerable/unstable plaque. *Arterioscler Thromb Vasc Biol* 30: 1282–1292, 2010.

66. Fletcher GF, Balady G, Blair SN, Blumenthal J, Caspersen C, Chaitman B, Epstein S, Sivarajan Froelicher ES, Froelicher VF, Pina IL, Pollock ML. Statement on exercise: benefits and recommendations for physical activity programs for all Americans. A statement for health professionals by the Committee on Exercise and Cardiac Rehabilitation of the Council on Clinical Cardiology, American Heart Association. *Circulation* 94: 857–862, 1996.

67. Fortescue EB, Shin AY, Greenes DS, Mannix RC, Agarwal S, Feldman BJ, Shah MI, Rifai N, Landzberg MJ, Newburger JW, Almond CS. Cardiac troponin increases among runners in the Boston Marathon. *Ann Emerg Med* 49: 137–143, 2007.

68. Fujimoto N, Shibata S, Hastings JL, Carrick-Ranson G, Bhella PS, Palmer D, Fu Q, Levine BD. Effects of pericardial constraint and ventricular interaction on left ventricular hemodynamics in the unloaded heart. *Am J Physiol Heart Circ Physiol* 300: H1688–H1695, 2011.

69. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Kay GN, Le Huezey JY, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann LS, Smith SC Jr, Priori SG, Estes NA, 3rd, Ezekowitz MD, Jackman WM, January CT, Lowe JE, Page RL, Slotwiner DJ, Stevenson WG, Tracy CM, Jacobs AK, Anderson JL, Albert N, Buller CE, Creager MA, Ettinger SM, Guyton RA, Halperin JL, Hochman JS, Kushner FG, Ohman EM, Stevenson WG, Tarkington LG, Yancy CW, and American College of Cardiology Foundation/American Heart Association Task Force. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 123: e269–367, 2011.

70. Gabriel KP, Matthews KA, Perez A, Edmundowicz D, Kohl HW 3rd, Hawkins MS, Janak JC, Kriska AM, Kuller LH. Self-reported and accelerometer-derived physical activity levels and coronary artery calcification progression in older women: results from the Healthy Women Study. *Menopause* 20: 152–161, 2013.

71. Garatachea N, Santos-Lozano A, Sanchis-Gomar F, Fiuza-Luces C, Pareja-Galeano H, Emanuele E, Lucia A. Elite athletes live longer than the general population: a meta-analysis. *Mayo Clinic Proc* 89: 1195–1200, 2014.

72. Gaudreault V, Tizon-Marcos H, Poirier P, Pibarot P, Gilbert P, Amyot M, Rodes-Cabau J, Despres JP, Bertrand O, Larose E. Transient myocardial tissue and function changes during a marathon in less fit marathon runners. *Can J Cardiol* 29: 1269–1276.

73. Gemayel C, Pelliccia A, Thompson PD. Arrhythmogenic right ventricular cardiomyopathy. *J Am Coll Cardiol* 38: 1773–1781, 2001.

74. George K, Shave R, Oxborough D, Cable T, Dawson E, Artis N, Gaze D, Hew-Butler T, Sharwood K, Noakes T. Left ventricular wall segment motion after ultra-endurance exercise in humans assessed by myocardial speckle tracking. *Eur J Echocardiogr* 10: 238–243, 2009.

75. George K, Whyte G, Stephenson C, Shave R, Dawson E, Edwards B, Gaze D, Collinson P. Postexercise left ventricular function and cTnT in recreational marathon runners. *Med Sci Sports Exercise* 36: 1709–1715, 2004.

76. Giri S, Thompson PD, Kiernan FJ, Clive J, Fram DB, Mitchel JF, Hirst JA, McKay RG, Waters DD. Clinical and angiographic characteristics of exertion-related acute myocardial infarction. *JAMA* 282: 1731–1736, 1999.

77. Gledhill N, Cox D, Jamnik R. Endurance athletes' stroke volume does not plateau: major advantage is diastolic function. *Med Sci Sports Exercise* 26: 1116–1121, 1994.

78. Gores GJ, Herman B, Lemasters JJ. Plasma membrane bleb formation and rupture: a common feature of hepatocellular injury. *Hepatology* 11: 690–698, 1990.

79. Gupta S, Figueredo VM. Tachycardia mediated cardiomyopathy: pathophysiology, mechanisms, clinical features and management. *Int J Cardiol* 172: 40–46, 2014.

80. Hagstrom E, Michaelsson K, Melhus H, Hansen T, Ahlstrom H, Johansson L, Ingelsson E, Sundstrom J, Lind L, Arnlov J. Plasma-parathyroid hormone is associated with subclinical and clinical atherosclerotic disease in 2 community-based cohorts. *Arterioscler Thromb Vasc Biol* 34: 1567–1573, 2014.

81. Hamer M, Venuraju SM, Lahiri A, Rossi A, Steptoe A. Objectively assessed physical activity, sedentary time, and coronary artery calcification in healthy older adults. *Arterioscler Thromb Vasc Biol* 32: 500–505, 2012.

82. Hanssen H, Keithahn A, Hertel G, Drexel V, Stern H, Schuster T, Lorang D, Beer AJ, Schmidt-Trucksass A, Nickel T, Weis M, Botnar R, Schwaiger M, Halle M. Magnetic resonance imaging of myocardial injury and ventricular torsion after marathon running. *Clin Sci* 120: 143–152, 2011.

83. Harmon KG, Asif IM, Klossner D, Drezner JA. Incidence of sudden cardiac death in National Collegiate Athletic Association athletes. *Circulation* 123: 1594–1600, 2011.

84. Hart E, Dawson E, Rasmussen P, George K, Secher NH, Whyte G, Shave R. Beta-adrenergic receptor desensitization in man: insight into post-exercise attenuation of cardiac function. *J Physiol* 577: 717–725, 2006.

85. Hartley PH, Llewellyn GF. Longevity of Oarsmen. *Br Med J* 1: 657–662, 1939.

86. Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, Macera CA, Heath GW, Thompson PD, Bauman A. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation* 116: 1081–1093, 2007.

87. Hatzaras I, Tranquilli M, Coady M, Barrett PM, Bible J, Elefteriades JA. Weight lifting and aortic dissection: more evidence for a connection. *Cardiology* 107: 103–106, 2007.

88. Herrmann M, Scharhag J, Miclea M, Urhausen A, Herrmann W, Kindermann W. Post-race kinetics of cardiac troponin T and I and N-terminal pro-brain natriuretic peptide in marathon runners. *Clin Chem* 49: 831–834, 2003.

89. Hessel MH, Atsma DE, van der Valk EJ, Bax WH, Schalij MJ, van der Laarse A. Release of cardiac troponin I from viable cardiomyocytes is mediated by integrin stimulation. *Pflügers Arch* 455: 979–986, 2008.

90. Hickman PE, Potter JM, Aroney C, Koerbin G, Southcott E, Wu AH, Roberts MS. Cardiac troponin may be released by ischemia alone, without necrosis. *Clin Chim Acta* 411: 318–323, 2010.

91. Hoffman MD, Wegelin JA. The Western States 100-Mile Endurance Run: participation and performance trends. *Med Sci Sports Exercise* 41: 2191–2198, 2009.

92. Hoogsteen J, Schep G, Van Hemel NM, Van Der Wall EE. Paroxysmal atrial fibrillation in male endurance athletes. A 9-year follow up. *Europace* 6: 222–228, 2004.

93. Hou ZH, Lu B, Gao Y, Jiang SL, Wang Y, Li W, Budoff MJ. Prognostic value of coronary CT angiography and calcium score for major adverse cardiac events in outpatients. *JACC Cardiovascular Imaging* 5: 990–999, 2012.

94. Hu FB, Stampfer MJ, Solomon C, Liu S, Colditz GA, Speizer FE, Willett WC, Manson JE. Physical activity and risk for cardiovascular events in diabetic women. *Ann Internal Med* 134: 96–105, 2001.

95. Hubble KM, Fatovich DM, Grasko JM, Vasikaran SD. Cardiac troponin increases among marathon runners in the Perth Marathon: the Troponin in Marathons (TRIM) study. *Medical J Australia* 190: 91–93, 2009.

96. Iskandar A, Thompson PD. A meta-analysis of aortic root size in elite athletes. *Circulation* 127: 791–798, 2013.

97. Jaffe AS, Vasile VC, Milone M, Saenger AK, Olson KN, Apple FS. Diseased skeletal muscle: a noncardiac source of increased circulating concentrations of cardiac troponin T. *J Am Coll Cardiol* 58: 1819–1824, 2011.

98. James CA, Bhonsale A, Tichnell C, Murray B, Russell SD, Tandri H, Tedford RJ, Judge DP, Calkins H. Exercise increases age-related penetrance and arrhythmic risk in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated desmosomal mutation carriers. *J Am Coll Cardiol* 62: 1290–1297, 2013.

99. Jassal DS, Moffat D, Krahn J, Ahmadie R, Fang T, Eschun G, Sharma S. Cardiac injury markers in non-elite marathon runners. *Int J Sports Med* 30: 75–79, 2009.

100. Jellis C, Martin J, Narula J, Marwick TH. Assessment of nonischemic myocardial fibrosis. *J Am Coll Cardiol* 56: 89–97, 2010.

101. Jensen-Urstad K, Saltin B, Ericson M, Storck N, Jensen-Urstad M. Pronounced resting bradycardia in male elite runners is associated with high heart rate variability. *Scand J Med Sci Sports* 7: 274–278, 1997.

102. Jin H, Yang R, Li W, Lu H, Ryan AM, Ogasawara AK, Van Peborgh J, Paoni NF. Effects of exercise training on cardiac function, gene expression, and apoptosis in rats. *Am J Physiol Heart Circ Physiol* 279: H2994–H3002, 2000.

103. Kadoglou NP, Iliadis F, Liapis CD. Exercise and carotid atherosclerosis. *Eur J Vasc Endovasc Surg* 35: 264–272, 2008.

104. Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *Am J Cardiol* 82: 2N–9N, 1998.

105. Karlstedt E, Chelvanathan A, Da Silva M, Cleverley K, Kumar K, Bhullar N, Lytwyn M, Bohonis S, Oomah S, Nepomuceno R, Du X, Melnyk S, Zeglinski M, Ducas R, Sefidgar M, Mackenzie S, Sharma S, Kirkpatrick ID, Jassal DS. The impact of repeated marathon running on cardiovascular function in the aging population. *J Cardiovasc Magn Reson* 14: 58, 2012.

106. Karvonen MJ, Klemola H, Virkajarvi J, Kekkonen A. Longevity of endurance skiers. *Med Sci Sports* 6: 49–51, 1974.

107. Katus HA, Remppis A, Scheffold T, Diederich KW, Kuebler W. Intracellular compartmentation of cardiac troponin T and its release kinetics in patients with reperfused and nonreperfused myocardial infarction. *Am J Cardiol* 67: 1360–1367, 1991.

108. Kettunen JA, Kujala UM, Kaprio J, Backmand H, Peltonen M, Eriksson JG, Sarna S. All-cause and disease-specific mortality among male, former elite athletes: an average 50-year follow-up. *Br J Sports Med* 49: 893–897, 2015.

109. Kim JH, Malhotra R, Chiampas G, d'Hemecourt P, Troyanos C, Cianca J, Smith RN, Wang TJ, Roberts WO, Thompson PD, Baggish AL, Race Associated Cardiac Arrest Event Registry Study. Cardiac arrest during long-distance running races. *N Engl J Med* 366: 130–140, 2012.

110. Kirchhof P, Fabritz L, Zwiener M, Witt H, Schafers M, Zellerhoff S, Paul M, Athai T, Hiller KH, Baba HA, Breithardt G, Ruiz P, Wichter T, Levkau B. Age- and training-dependent development of arrhythmogenic right ventricular cardiomyopathy in heterozygous plakoglobin-deficient mice. *Circulation* 114: 1799–1806, 2006.

111. Knebel F, Spethmann S, Schattke S, Dreger H, Schroeckh S, Schimke I, Hattasch R, Makauskiene R, Kleczka J, Sanad W, Lock J, Brechtel L, Baumann G, Borges AC. Exercise-induced changes of left ventricular diastolic function in postmenopausal amateur marathon runners: assessment by echocardiography and cardiac biomarkers. *Eur J Prevent Cardiol* 21: 782–790, 2014.

112. Knechtle B, Knechtle P, Lepers R. Participation and performance trends in ultra-triathlons from 1985 to 2009. *Scand J Med Sci Sports* 21: e82–90, 2011.

113. Koller A, Mair J, Mayr M, Calzolari C, Larue C, Puschendorf B. Diagnosis of myocardial injury in marathon runners. *Ann NY Acad Sci* 752: 234–235, 1995.

114. Konig D, Schumacher YO, Heinrich L, Schmid A, Berg A, Dickhuth HH. Myocardial stress after competitive exercise in professional road cyclists. *Med Sci Sports Exercise* 35: 1679–1683, 2003.

115. Kovacs A, Apor A, Nagy A, Vago H, Toth A, Nagy AI, Kovats T, Sax B, Szeplaki G, Becker D, Merkely B. Left ventricular untwisting in athlete's heart: key role in early diastolic filling? *Int J Sports Med* 35: 259–264, 2014.

116. Kovacs G, Berghold A, Scheidl S, Olschewski H. Pulmonary arterial pressure during rest and exercise in healthy subjects: a systematic review. *Eur Respir J* 34: 888–894, 2009.

117. Kozakova M, Palombo C, Morizzo C, Nolan JJ, Konrad T, Balkau B, Investigators R. Effect of sedentary behaviour and vigorous physical activity on segment-specific carotid wall thickness and its progression in a healthy population. *Eur Heart J* 31: 1511–1519, 2010.

118. Kroger K, Lehmann N, Rappaport L, Perrey M, Sorokin A, Budde T, Heusch G, Jockel KH, Thompson PD, Erbel R, Mohlenkamp S. Carotid and peripheral atherosclerosis in male marathon runners. *Med Sci Sports Exercise* 43: 1142–1147, 2011.

119. Kujala UM, Kaprio J, Sarna S, Koskenvuo M. Relationship of leisure-time physical activity and mortality: the Finnish twin cohort. *JAMA* 279: 440–444, 1998.

120. Kujala UM, Tikkanen HO, Sarna S, Pukkala E, Kaprio J, Koskenvuo M. Disease-specific mortality among elite athletes. *JAMA* 285: 44–45, 2001.

121. Kwak HB, Song W, Lawler JM. Exercise training attenuates age-induced elevation in Bax/Bcl-2 ratio, apoptosis, and remodeling in the rat heart. *FASEB J* 20: 791–793, 2006.

122. Kwong RY, Chan AK, Brown KA, Chan CW, Reynolds HG, Tsang S, Davis RB. Impact of unrecognized myocardial scar detected by cardiac magnetic resonance imaging on event-free survival in patients presenting with signs or symptoms of coronary artery disease. *Circulation* 113: 2733–2743, 2006.

123. La Gerche A. Can intense endurance exercise cause myocardial damage and fibrosis? *Curr Sports Med Reports* 12: 63–69, 2013.

124. La Gerche A, Burns AT, Mooney DJ, Inder WJ, Taylor AJ, Bogaert J, Macisaac AI, Heidbuchel H, Prior DL. Exercise-induced right ventricular dysfunction and structural remodelling in endurance athletes. *Eur Heart J* 33: 998–1006, 2012.

125. La Gerche A, Connelly KA, Mooney DJ, MacIsaac AI, Prior DL. Biochemical and functional abnormalities of left and right ventricular function after ultra-endurance exercise. *Heart* 94: 860–866, 2008.

126. La Gerche A, Heidbuchel H, Burns AT, Mooney DJ, Taylor AJ, Pfluger HB, Inder WJ, Macisaac AI, Prior DL. Disproportionate exercise load and remodeling of the athlete's right ventricle. *Med Sci Sports Exercise* 43: 974–981, 2011.

127. La Gerche A, MacIsaac AI, Burns AT, Mooney DJ, Inder WJ, Voigt JU, Heidbuchel H, Prior DL. Pulmonary transit of agitated contrast is associated with enhanced pulmonary vascular reserve and right ventricular function during exercise. *J Appl Physiol* 109: 1307–1317, 2010.

128. Lamppa R, Yoder T. *State of the Sport - Part III: U. S.* Race Trends Running USA. http://www.runningusa.org/state-of-sporte-2013-part-III. [January 21, 2014].

129. Lawless CE. Minnesota high school athletes 1993–2012: evidence that American screening strategies and sideline preparedness are associated with very low rates of sudden cardiac deaths. *J Am Coll Cardiol* 62: 1302–1303, 2013.

130. Lee DC, Pate RR, Lavie CJ, Sui X, Church TS, Blair SN. Leisure-time running reduces all-cause and cardiovascular mortality risk. *J Am Coll Cardiol* 64: 472–481, 2014.

131. Leetmaa TH, Dam A, Glintborg D, Markenvard JD. Myocardial response to a triathlon in male athletes evaluated by Doppler tissue imaging and biochemical parameters. *Scand J Med Sci Sports* 18: 698–705, 2008.

132. Legaz-Arrese A, George K, Carranza-Garcia LE, Munguia-Izquierdo D, Moros-Garcia T, Serrano-Ostariz E. The impact of exercise intensity on the release of *cardiac biomarkers in marathon runners*. *Eur J Appl Physiol* 111: 2961–2967, 2011.

133. Levine BD, Lane LD, Buckey JC, Friedman DB, Blomqvist CG. Left ventricular pressure-volume and Frank-Starling relations in endurance athletes. Implications for orthostatic tolerance and exercise performance. *Circulation* 84: 1016–1023, 1991.

134. Liang F, Gardner DG. Mechanical strain activates BNP gene transcription through a p38/NF-kappaB-dependent mechanism. *J Clin Invest* 104: 1603–1612, 1999.

135. Libby P. Mechanisms of acute coronary syndromes and their implications for therapy. *N Engl J Med* 368: 2004–2013, 2013.

136. Lindsay MM, Dunn FG. Biochemical evidence of myocardial fibrosis in veteran endurance athletes. *Br J Sports Med* 41: 447–452, 2007.

137. Link MS, Homoud MK, Wang PJ, Estes NA 3rd. Cardiac arrhythmias in the athlete: the evolving role of electrophysiology. *Curr Sports Med Reports* 1: 75–85, 2002.

138. Lippi G, Schena F, Montagnana M, Salvagno GL, Banfi G, Guidi GC. Acute variation of osteocalcin and parathyroid hormone in athletes after running a half-marathon. *Clin Chem* 54: 1093–1095, 2008.

139. Lopez B, Gonzalez A, Beaumont J, Querejeta R, Larman M, Diez J. Identification of a potential cardiac antifibrotic mechanism of torasemide in patients with chronic heart failure. *J Am Coll Cardiol* 50: 859–867, 2007.

140. Lopez B, Querejeta R, Gonzalez A, Sanchez E, Larman M, Diez J. Effects of loop diuretics on myocardial fibrosis and collagen type I turnover in chronic heart failure. *J Am Coll Cardiol* 43: 2028–2035, 2004.

141. Lott JA, Stang JM. Serum enzymes and isoenzymes in the diagnosis and differential diagnosis of myocardial ischemia and necrosis. *Clin Chem* 26: 1241–1250, 1980.

142. Mant J, Al-Mohammad A, Swain S, Laramee P, Guideline Development. Management of chronic heart failure in adults: synopsis of the National Institute For Health and clinical excellence guideline. *Ann Intern Med* 155: 252–259, 2011.

143. Marijon E, Tafflet M, Antero-Jacquemin J, El Helou N, Berthelot G, Celermajer DS, Bougouin W, Combes N, Hermine O, Empana JP, Rey G, Toussaint JF, Jouven X.

Mortality of French participants in the Tour de France (1947–2012). *Eur Heart J* 34: 3145–3150, 2013.

144. Maron BJ, Doerer JJ, Haas TS, Tierney DM, Mueller FO. Sudden deaths in young competitive athletes: analysis of 1866 deaths in the United States, 1980–2006. *Circulation* 119: 1085–1092, 2009.

145. Maron BJ, Thompson PD, Ackerman MJ, Balady G, Berger S, Cohen D, Dimeff R, Douglas PS, Glover DW, Hutter AM Jr, Krauss MD, Maron MS, Mitten MJ, Roberts WO, Puffer JC, American Heart Association Council on Nutrition and Metabolism. Recommendations and considerations related to preparticipation screening for cardiovascular abnormalities in competitive athletes: 2007 update: a scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism: endorsed by the American College of Cardiology Foundation. *Circulation* 115: 16.43–1455, 2007.

146. McDonough JL, Arrell DK, Van Eyk JE. Troponin I degradation and covalent complex formation accompanies myocardial ischemia/reperfusion injury. *Circ Res* 84: 9–20, 1999.

147. McGavock JM, Warburton DE, Taylor D, Welsh RC, Quinney HA, Haykowsky MJ. The effects of prolonged strenuous exercise on left ventricular function: a brief review. *Heart Lung* 31: 279–292, 2002.

148. McNeil PL, Khakee R. Disruptions of muscle fiber plasma membranes. Role in exercise-induced damage. *Am J Pathol* 140: 1097–1109, 1992.

149. Mewton N, Liu CY, Croisille P, Bluemke D, Lima JA. Assessment of myocardial fibrosis with cardiovascular magnetic resonance. *J Am Coll Cardiol* 57: 891–903, 2011.

150. Middleton N, George K, Whyte G, Gaze D, Collinson P, Shave R. Cardiac troponin T release is stimulated by endurance exercise in healthy humans. *J Am Coll Cardiol* 52: 1813–1814, 2008.

151. Middleton N, Shave R, George K, Whyte G, Hart E, Atkinson G. Left ventricular function immediately following prolonged exercise: A meta-analysis. *Med Sci Sports Exercise* 38: 681–687, 2006.

152. Milano AD, Faggian G, Dodonov M, Golia G, Tomezzoli A, Bortolotti U, Mazzucco A. Prognostic value of myocardial fibrosis in patients with severe aortic valve stenosis. *J Thoracic Cardiovasc Surg* 144: 830–837, 2012.

153. Mingels A, Jacobs L, Michielsen E, Swaanenburg J, Wodzig W, van Dieijen-Visser M. Reference population and marathon runner sera assessed by highly sensitive cardiac troponin T and commercial cardiac troponin T and I assays. *Clin Chem* 55: 101–108, 2009.

154. Mitchell JH, Haskell W, Snell P, Van Camp SP. Task Force 8: classification of sports. *J Am Coll Cardiol* 45: 1364–1367, 2005.

155. Mittleman MA, Maclure M, Tofler GH, Sherwood JB, Goldberg RJ, Muller JE. Triggering of acute myocardial infarction by heavy physical exertion. Protection against triggering by regular exertion Determinants of Myocardial Infarction Onset Study Investigators. *N Engl J Med* 329: 1677–1683, 1993.

156. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, Seward JB, Tsang TS. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation* 114: 119–125, 2006.

157. Mohlenkamp S, Lehmann N, Breuckmann F, Brocker-Preuss M, Nassenstein K, Halle M, Budde T, Mann K, Barkhausen J, Heusch G, Jockel KH, Erbel R. Running: the risk of coronary events: prevalence and prognostic relevance of coronary atherosclerosis in marathon runners. *Eur Heart J* 29: 1903–1910, 2008.

158. Montgomery HE, Clarkson P, Dollery CM, Prasad K, Losi MA, Hemingway H, Statters D, Jubb M, Girvain M, Varnava A, World M, Deanfield J, Talmud P, McEwan JR, McKenna WJ, Humphries S. Association of angiotensin-converting enzyme gene I/D polymorphism with change in left ventricular mass in response to physical training. *Circulation* 96: 741–747, 1997.

159. Mora S, Cook N, Buring JE, Ridker PM, Lee IM. Physical activity and reduced risk of cardiovascular events: potential mediating mechanisms. *Circulation* 116: 2110–2118, 2007.

160. Morganroth J, Maron BJ, Henry WL, Epstein SE. Comparative left ventricular dimensions in trained athletes. *Ann Intern Med* 82: 521–524, 1975.

161. Morris JN, Heady JA, Raffle PA, Roberts CG, Parks JW. Coronary heart-disease and physical activity of work. *Lancet* 265: 1111–1120, 1953.

162. Morrow DA, Cannon CP, Jesse RL, Newby LK, Ravkilde J, Storrow AB, Wu AH, Christenson RH. National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: clinical characteristics and utilization of biochemical markers in acute coronary syndromes. *Circulation* 115: e356–375, 2007.

163. Mousavi N, Czarnecki A, Kumar K, Fallah-Rad N, Lytwyn M, Han SY, Francis A, Walker JR, Kirkpatrick ID, Neilan TG, Sharma S, Jassal DS. Relation of biomarkers and cardiac magnetic resonance imaging after marathon running. *Am J Cardiol* 103: 1467–1472, 2009.

164. Mozaffarian D, Furberg CD, Psaty BM, Siscovick D. Physical activity and incidence of atrial fibrillation in older adults: the cardiovascular health study. *Circulation* 118: 800–807, 2008.

165. Nademanee K. Exercise and vagal reflex in long QT syndrome type 1. *J Am Coll Cardiol* 60: 2525–2526, 2012.

166. Nagueh SF, Kopelen HA, Quinones MA. Assessment of left ventricular filling pressures by Doppler in the presence of atrial fibrillation. *Circulation* 94: 2138–2145, 1996.

167. Narula J, Haider N, Virmani R, DiSalvo TG, Kolodgie FD, Hajjar RJ, Schmidt U, Semigran MJ, Dec GW, Khaw BA. Apoptosis in myocytes in end-stage heart failure. *N Engl J Med* 335: 1182–1189, 1996.

168. Naylor LH, Arnolda LF, Deague JA, Playford D, Maurogiovanni A, O'Driscoll G, Green DJ. Reduced ventricular flow propagation velocity in elite athletes is augmented with the resumption of exercise training. *J Physiol* 563: 957–963, 2005.

169. Neilan TG, Januzzi JL, Lee-Lewandrowski E, Ton-Nu TT, Yoerger DM, Jassal DS, Lewandrowski KB, Siegel AJ, Marshall JE, Douglas PS, Lawlor D, Picard MH, Wood MJ. Myocardial injury and ventricular dysfunction related to training levels among nonelite participants in the Boston marathon. *Circulation* 114: 2325–2333, 2006.

170. Neilan TG, Yoerger DM, Douglas PS, Marshall JE, Halpern EF, Lawlor D, Picard MH, Wood MJ. Persistent and reversible cardiac dysfunction among amateur marathon runners. *Eur Heart J* 27: 1079–1084, 2006.

171. Neumayr G, Pfister R, Mitterbauer G, Eibl G, Hoertnagl H. Effect of competitive marathon cycling on plasma N-terminal pro-brain natriuretic peptide and cardiac troponin T in healthy recreational cyclists. *Am J Cardiol* 96: 732–735, 2005.

172. Neumayr G, Pfister R, Mitterbauer G, Maurer A, Gaenzer H, Sturm W, Hoertnagl H. Effect of the "Race Across The Alps" in elite cyclists on plasma cardiac troponins I and T. *Am J Cardiol* 89: 484–486, 2002.

173. Notomi Y, Popovic ZB, Yamada H, Wallick DW, Martin MG, Oryszak SJ, Shiota T, Greenberg NL, Thomas JD. Ventricular untwisting: a temporal link between left ventricular relaxation and suction. *Am J Physiol Heart Circ Physiol* 294: H505–H513, 2008.

174. Nottin S, Doucende G, Schuster I, Tanguy S, Dauzat M, Obert P. Alteration in left ventricular strains and torsional mechanics after ultralong duration exercise in athletes. *Circulation Cardiovasc Imaging* 2: 323–330, 2009.

175. Nottin S, Menetrier A, Rupp T, Boussuges A, Tordi N. Role of left ventricular untwisting in diastolic dysfunction after long duration exercise. *Eur J Appl Physiol* 112: 525–533, 2012.

176. O'Hanlon R, Grasso A, Roughton M, Moon JC, Clark S, Wage R, Webb J, Kulkarni M, Dawson D, Sulaibeekh L, Chandrasekaran B, Bucciarelli-Ducci C, Pasquale F, Cowie MR, McKenna WJ, Sheppard MN, Elliott PM, Pennell DJ, Prasad SK. Prognostic significance of myocardial fibrosis in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 56: 867–874, 2010.

177. O'Hanlon R, Wilson M, Wage R, Smith G, Alpendurada FD, Wong J, Dahl A, Oxborough D, Godfrey R, Sharma S, Roughton M, George K, Pennell DJ, Whyte G, Prasad SK. Troponin release following endurance exercise: is inflammation the cause? A cardiovascular magnetic resonance study. *J Cardiovasc Magn Res* 12: 38, 2010.

178. Ogilvie D, Foster CE, Rothnie H, Cavill N, Hamilton V, Fitzsimons CF, Mutrie N. Interventions to promote walking: systematic review. *BMJ* 334: 1204, 2007.

179. Ohba H, Takada H, Musha H, Nagashima J, Mori N, Awaya T, Omiya K, Murayama M. Effects of prolonged strenuous exercise on plasma levels of atrial natriuretic peptide and brain natriuretic peptide in healthy men. *Am Heart J* 141: 751–758, 2001.

180. Oxborough D, Shave R, Warburton D, Williams K, Oxborough A, Charlesworth S, Foulds H, Hoffman MD, Birch K, George K. Dilatation and dysfunction of the right ventricle immediately after ultraendurance exercise: exploratory insights from conventional two-dimensional and speckle tracking echocardiography. *Circulation Cardiovasc Imaging* 4: 253–263, 2011.

181. Oxborough D, Whyte G, Wilson M, O'Hanlon R, Birch K, Shave R, Smith G, Godfrey R, Prasad S, George K. A depression in left ventricular diastolic filling following prolonged strenuous exercise is associated with changes in left atrial mechanics. *J Am Soc Echocardiography* 23: 968–976, 2010.

182. Paffenbarger RS Jr, Hyde RT, Wing AL, Hsieh CC. Physical activity, all-cause mortality, and longevity of college alumni. *N Engl J Med* 314: 605–613, 1986.

183. Paffenbarger RS Jr, Laughlin ME, Gima AS, Black RA. Work activity of longshoremen as related to death from coronary heart disease and stroke. *N Engl J Med* 282: 1109–1114, 1970.

184. Paffenbarger RS Jr, Wing AL, Hyde RT. Physical activity as an index of heart attack risk in college alumni. *Am J Epidemiol* 108: 161–175, 1978.

185. Papadakis M, Carre F, Kervio G, Rawlins J, Panoulas VF, Chandra N, Basavarajaiah S, Carby L, Fonseca T, Sharma S. The prevalence, distribution, and clinical outcomes of electrocardiographic repolarization patterns in male athletes of African/Afro-Caribbean origin. *Eur Heart J* 32: 2304–2313.

186. Pelliccia A, Culasso F, Di Paolo FM, Maron BJ. Physiologic left ventricular cavity dilatation in elite athletes. *Ann Internal Med* 130: 23–31, 1999.

187. Pelliccia A, Kinoshita N, Pisicchio C, Quattrini F, Dipaolo FM, Ciardo R, Di Giacinto B, Guerra E, De Blasiis E, Casasco M, Culasso F, Maron BJ. Long-term clinical consequences of intense, uninterrupted endurance training in olympic athletes. *J Am Coll Cardiol* 55: 1619–1625, 2010.

188. Pelliccia A, Maron BJ. Preparticipation cardiovascular evaluation of the competitive athlete: perspectives from the 30-year Italian experience. *Am J Cardiol* 75: 827–829, 1995.

189. Pelliccia A, Maron BJ, Di Paolo FM, Biffi A, Quattrini FM, Pisicchio C, Roselli A, Caselli S, Culasso F. Prevalence and clinical significance of left atrial remodeling in competitive athletes. *J Am Coll Cardiol* 46: 690–696, 2005.

190. Pelliccia A, Maron BJ, Spataro A, Proschan MA, Spirito P. The upper limit of physiologic cardiac hypertrophy in highly trained elite athletes. *N Engl J Med* 324: 295–301, 1991.

191. Physical Acitivity Guidelines Advisory Committe. Physical Activity Guidelines Advisory Committee Report http://www.health.gov/paguidelines/committeereport.aspx. [April 3rd, 2013].

192. Piepoli MF, Davos C, Francis DP, Coats AJ, ExTra MC. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). *BMJ* 328: 189, 2004.

193. Pluim BM, Zwinderman AH, van der Laarse A, van der Wall EE. The athlete's heart. A meta-analysis of cardiac structure and function. *Circulation* 101: 336–344, 2000.

194. Powell KE, Thompson PD, Caspersen CJ, Kendrick JS. Physical activity and the incidence of coronary heart disease. *Annu Rev Public Health* 8: 253–287, 1987.

195. Prout C. Life expectancy of college oarsmen. *JAMA* 220: 1709–1711, 1972.

196. Puri R, Nicholls SJ, Shao M, Kataoka Y, Uno K, Kapadia SR, Tuzcu EM, Nissen SE. Impact of statins on serial coronary calcification during atheroma progression and regression. *J Am Coll Cardiol* 65: 1273–1282, 2015.

197. Pyeritz RE. Heritable thoracic aortic disorders. *Curr Opin Cardiol* 29: 97–102, 2014.

198. Rauramaa R, Halonen P, Vaisanen SB, Lakka TA, Schmidt-Trucksass A, Berg A, Penttila IM, Rankinen T, Bouchard C. Effects of aerobic physical exercise on inflammation and atherosclerosis in men: the DNASCO Study: a six-year randomized, controlled trial. *Ann Internal Med* 140: 1007–1014, 2004.

199. Regwan S, Hulten EA, Martinho S, Slim J, Villines TC, Mitchell J, Slim AM. Marathon running as a cause of troponin elevation: a systematic review and meta-analysis. *J Intervent Cardiol* 23: 443–450, 2010.

200. Reiffel JA. Atrial fibrillation and stroke: epidemiology. *Am J Med* 127: e15–16, 2014.

201. Ricchiuti V, Apple FS. RNA expression of cardiac troponin T isoforms in diseased human skeletal muscle. *Clin Chem* 45: 2129–2135, 1999.

202. Rifai N, Douglas PS, O'Toole M, Rimm E, Ginsburg GS. Cardiac troponin T and I, echocardiographic [correction of electrocardiographic] wall motion analyses, and ejection fractions in athletes participating in the Hawaii Ironman Triathlon. *Am J Cardiol* 83: 1085–1089, 1999.

203. Robinson BF, Epstein SE, Beiser GD, Braunwald E. Control of heart rate by the autonomic nervous system. Studies in man on the interrelation between baroreceptor mechanisms and exercise. *Circ Res* 19: 400–411, 1966.

204. Roe CR, Limbird LE, Wagner GS, Nerenberg ST. Combined isoenzyme analysis in the diagnosis of myocardial injury: application of electrophoretic methods for the detection and quantitation of the creatine phosphokinase MB isoenzyme. *J Lab Clin Med* 80: 577–590, 1972.

205. Rook A. An investigation into the longevity of Cambridge sportsmen. *Br Med J* 1: 773–777, 1954.

206. Rosamond W, Flegal K, Friday G, Furie K, Go A, Greenlund K, Haase N, Ho M, Howard V, Kissela B, Kittner S, Lloyd-Jones D, McDermott M, Meigs J, Moy C, Nichol G, O'Donnell CJ, Roger V, Rumsfeld J, Sorlie P, Steinberger J, Thom T, Wasserthiel-Smoller S, Hong Y, American Heart Association Statistics, Stroke Statistics. Heart disease and stroke statistics–2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 115: e69–171, 2007.

207. Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s. *Nature* 362: 801–809, 1993.

208. Rowell LB. Muscle blood flow in humans: how high can it go? *Med Sci Sports Exercise* 20: S97–103, 1988.

209. Rowell LB, O'Leary DS. Reflex control of the circulation during exercise: chemoreflexes and mechanoreflexes. *J Appl Physiol* 69: 407–418, 1990.

210. Saenger AK. A tale of two biomarkers: the use of troponin and CK-MB in contemporary practice. *Clin Lab Sci* 23: 134–140, 2010.

211. Sahlen A, Winter R, Lind B, Jacobsen PH, Stahlberg M, Marklund T, Fux T, Svensson J, Braunschweig F. Magnitude, reproducibility, and association with baseline cardiac function of cardiac biomarker release in long-distance runners aged $>$ or $=$ 55 years. *Am J Cardiol* 102: 218–222, 2008.

212. Saltin B, Stenberg J. Circulatory response to prolonged severe exercise. *J Appl Physiol* 19: 833–838, 1964.

213. Santoro A, Alvino F, Antonelli G, Cameli M, Bertini M, Molle R, Mondillo S. Left ventricular strain modifications after maximal exercise in athletes: a speckle tracking study. *Echocardiography* 32:920–927, 2015.

214. Sarna S, Sahi T, Koskenvuo M, Kaprio J. Increased life expectancy of world class male athletes. *Med Sci Sports Exercise* 25: 237–244, 1993.

215. Sattelmair J, Pertman J, Ding EL, Kohl HW 3rd, Haskell W, Lee IM. Dose response between physical activity and risk of coronary heart disease: a meta-analysis. *Circulation* 124: 789–795, 2011.

216. Scharf M, Brem MH, Wilhelm M, Schoepf UJ, Uder M, Lell MM. Atrial and ventricular functional and structural adaptations of the heart in elite triathletes assessed with cardiac MR imaging. *Radiology* 257: 71–79, 2010.

217. Scharhag J, Herrmann M, Urhausen A, Haschke M, Herrmann W, Kindermann W. Independent elevations of N-terminal pro-brain natriuretic peptide and cardiac troponins in endurance athletes after prolonged strenuous exercise. *Am Heart J* 150: 1128–1134, 2005.

218. Scharhag J, Schneider G, Urhausen A, Rochette V, Kramann B, Kindermann W. Athlete's heart: right and left ventricular mass and function in male endurance athletes and untrained individuals determined by magnetic resonance imaging. *J Am Coll Cardiol* 40: 1856–1863, 2002.

219. Scharhag J, Urhausen A, Herrmann M, Schneider G, Kramann B, Herrmann W, Kindermann W. No difference in N-terminal pro-brain natriuretic peptide (NT-proBNP) concentrations between endurance athletes with athlete's heart and healthy untrained controls. *Heart* 90: 1055–1056, 2004.

220. Scharhag J, Urhausen A, Schneider G, Herrmann M, Schumacher K, Haschke M, Krieg A, Meyer T, Herrmann W, Kindermann W. Reproducibility and clinical significance of exercise-induced increases in cardiac troponins and N-terminal pro brain natriuretic peptide in endurance athletes. *Eur J Cardiovasc Prev Rehabil* 13: 388–397, 2006.

221. Schaub MC, Perry SV. The relaxing protein system of striated muscle. Resolution of the troponin complex into inhibitory and calcium ion-sensitizing factors and their relationship to tropomyosin. *Biochem J* 115: 993–1004, 1969.

222. Scherr J, Braun S, Schuster T, Hartmann C, Moehlenkamp S, Wolfarth B, Pressler A, Halle M. 72-h kinetics of high-sensitive troponin T and inflammatory markers after marathon. *Med Sci Sports Exercise* 43: 1819–1827, 2011.

223. Schnohr P. Longevity and causes of death in male athletic champions. *Lancet* 2: 1364–1366, 1971.

224. Schnohr P, Grande P, Christiansen C. Enzyme activities in serum after extensive exercise, with special reference to creatine kinase MB. *Acta Med Scand* 208: 229–231, 1980.

225. Schnohr P, Marott JL, Lange P, Jensen GB. Longevity in male and female joggers: the Copenhagen City Heart Study. *Am J Epidemiol* 177: 683–689, 2013.

226. Schwartz PJ, Crotti L, Insolia R. Long-QT syndrome: from genetics to management. *Circulation Arrhythmia Electrophysiol* 5: 868–877, 2012.

227. Schwartz PJ, Vanoli E, Crotti L, Spazzolini C, Ferrandi C, Goosen A, Hedley P, Heradien M, Bacchini S, Turco A, La Rovere MT, Bartoli A, George AL Jr, Brink PA. Neural control of heart rate is an arrhythmia risk modifier in long QT syndrome. *J Am Coll Cardiol* 51: 920–929, 2008.

228. Schwartz RS, Merkel-Kraus S, Schwartz JG, Wickstrom KK, Peichel G, Garberich RF, Lesser JR, Oesterle SN, Knickelbine T, Harris KM, Duval S, Roberts WO, O'Keefe JH. Increased coronary artery plaque volume among male marathon runners. *Missouri Med* 111: 85–90, 2014.

229. Scott JM, Esch BT, Haykowsky MJ, Isserow S, Koehle MS, Hughes BG, Zbogar D, Bredin SS, McKenzie DC, Warburton DE. Sex differences in left ventricular function and beta-receptor responsiveness following prolonged strenuous exercise. *J Appl Physiol* 102: 681–687, 2007.

230. Scott JM, Warburton DE. Mechanisms underpinning exercise-induced changes in left ventricular function. *Med Sci Sports Exercise* 40: 1400–1407, 2008.

231. Serrano-Ostariz E, Terreros-Blanco JL, Legaz-Arrese A, George K, Shave R, Bocos-Terraz P, Izquierdo-Alvarez S, Bancalero JL, Echavarri JM, Quilez J, Aragones MT, Carranza-Garcia LE. The impact of exercise duration and intensity on the release of cardiac biomarkers. *Scand J Med Sci Sports* 21: 244–249, 2011.

232. Shah KB, Inoue Y, Mehra MR. Amyloidosis and the heart: a comprehensive review. *Arch Internal Med* 166: 1805–1813, 2006.

233. Shave R, Dawson E, Whyte G, George K, Nimmo M, Layden J, Collinson P, Gaze D. The impact of prolonged exercise in a cold environment upon cardiac function. *Med Sci Sports Exercise* 36: 1522–1527, 2004.

234. Shave R, George K, Gaze D. The influence of exercise upon cardiac biomarkers: a practical guide for clinicians and scientists. *Curr Med Chem* 14: 1427–1436, 2007.

235. Shave R, George KP, Atkinson G, Hart E, Middleton N, Whyte G, Gaze D, Collinson PO. Exercise-induced cardiac troponin T release: a meta-analysis. *Med Sci Sports Exercise* 39: 2099–2106, 2007.

236. Shave R, Oxborough D. Exercise-induced cardiac injury: evidence from novel imaging techniques and highly sensitive cardiac troponin assays. *Prog Cardiovasc Dis* 54: 407–415, 2012.

237. Shave R, Ross P, Low D, George K, Gaze D. Cardiac troponin I is released following high-intensity short-duration exercise in healthy humans. *Int J Cardiol* 145: 337–339, 2010.

238. Shave RE, Dawson E, Whyte G, George K, Gaze D, Collinson P. Effect of prolonged exercise in a hypoxic environment on cardiac function and cardiac troponin T. *Br J Sports Med* 38: 86–88, 2004.

239. Shave RE, Dawson E, Whyte PG, George K, Ball D, Gaze CD, Collinson P. Cardiac troponin T in female athletes during a two-day mountain marathon. *Scott Med J* 48: 41–42, 2003.

240. Shen WK, Edwards WD, Hammill SC, Bailey KR, Ballard DJ, Gersh BJ. Sudden unexpected nontraumatic death in 54 young adults: a 30-year population-based study. *Am J Cardiol* 76: 148–152, 1995.

241. Shiroma EJ, Lee IM. Physical activity and cardiovascular health: lessons learned from epidemiological studies across age, gender, and race/ethnicity. *Circulation* 122: 743–752, 2010.

242. Siegel AJ, Januzzi J, Sluss P, Lee-Lewandrowski E, Wood M, Shirey T, Lewandrowski KB. Cardiac biomarkers, electrolytes, and other analytes in collapsed marathon runners: implications for the evaluation of runners following competition. *Am J Clin Pathol* 129: 948–951, 2008.

243. Siegel AJ, Lewandrowski EL, Chun KY, Sholar MB, Fischman AJ, Lewandrowski KB. Changes in cardiac markers including B-natriuretic peptide in runners after the Boston marathon. *Am J Cardiol* 88: 920–923, 2001.

244. Siegel AJ, Silverman LM, Evans WJ. Elevated skeletal muscle creatine kinase MB isoenzyme levels in marathon runners. *JAMA* 250: 2835–2837, 1983.

245. Siegel AJ, Silverman LM, Lopez RE. Creatine kinase elevations in marathon runners: relationship to training and competition. *Yale J Biol Med* 53: 275–279, 1980.

246. Siscovick DS, Weiss NS, Fletcher RH, Lasky T. The incidence of primary cardiac arrest during vigorous exercise. *N Engl J Med* 311: 874–877, 1984.

247. Sorokin AV, Araujo CG, Zweibel S, Thompson PD. Atrial fibrillation in endurance-trained athletes. *Br J Sports Med* 45: 185–188, 2011.

248. Spain DM, Bradess VA. Occupational physical activity and the degree of coronary atherosclerosis in "normal" men. A postmortem study. *Circulation* 22: 239–242, 1960.

249. Spence AL, Carter HH, Naylor LH, Green DJ. A prospective randomized longitudinal study involving 6 months of endurance or resistance exercise. Conduit artery adaptation in humans. *J Physiol* 591: 1265–1275, 2013.

250. Stirbys P. How much exercise is too much. *J Atrial Fibrillation* 5: 5–6, 2013.

251. Storti KL, Pettee Gabriel KK, Underwood DA, Kuller LH, Kriska AM. Physical activity and coronary artery calcification in two cohorts of women representing early and late postmenopause. *Menopause* 17: 1146–1151, 2010.

252. Stray-Gundersen J, Musch TI, Haidet GC, Swain DP, Ordway GA, Mitchell JH. The effect of pericardiectomy on maximal oxygen consumption and maximal cardiac output in untrained dogs. *Circ Res* 58: 523–530, 1986.

253. Sutton MG, Sharpe N. Left ventricular remodeling after myocardial infarction: pathophysiology and therapy. *Circulation* 101: 2981–2988, 2000.

254. Symanski JD, McMurray RG, Silverman LM, Smith BW, Siegel AJ. Serum creatine kinase and CK-MB isoenzyme responses to acute and prolonged swimming in trained athletes. *Clin Chim Acta* 129: 181–187, 1983.

255. Tam LM, Kim J, Blumenthal RS, Nasir K, Al-Mallah MH, Blaha MJ. Absolute coronary artery calcium score is the best predictor of non-calcified plaque involvement in patients with low calcium scores (1–100). *Atherosclerosis* 230: 76–79, 2013.

256. Tanaka H, Seals DR, Monahan KD, Clevenger CM, DeSouza CA, Dinenno FA. Regular aerobic exercise and the age-related increase in carotid artery intima-media thickness in healthy men. *J Appl Physiol* 92: 1458–1464, 2002.

257. Taylor BA, Zaleski AL, Capizzi JA, Ballard KD, Troyanos C, Baggish AL, D'Hemecourt PA, Dada MR, Thompson PD. Influence of chronic exercise on carotid atherosclerosis in marathon runners. *BMJ* 4: e004498, 2014.

258. Taylor RS, Brown A, Ebrahim S, Jolliffe J, Noorani H, Rees K, Skidmore B, Stone JA, Thompson DR, Oldridge N. Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. *Am J Med* 116: 682–692, 2004.

259. The Joint European Society of Cardiology/American College of Cardiology. Myocardial infarction redefined: a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction. *Eur Heart J* 21: 1502–1513, 2000.

260. Thiene G, Corrado D, Basso C. Arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Orphanet J Rare Dis* 2: 45, 2007.

261. Thiene G, Nava A, Corrado D, Rossi L, Pennelli N. Right ventricular cardiomyopathy and sudden death in young people. *N Engl J Med* 318: 129–133, 1988.

262. Thompson PD, Buchner D, Pina IL, Balady GJ, Williams MA, Marcus BH, Berra K, Blair SN, Costa F, Franklin B, Fletcher GF, Gordon NF, Pate RR, Rodriguez BL, Yancey AK,

Wenger NK,. American Heart Association Council on Clinical Cardiology Subcommittee on Exercise, Prevention, American Heart Association Council on Nutrition, and Metabolism Subcommittee on Physical Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity). *Circulation* 107: 3109–3116, 2003.

263. Thompson PD, Franklin BA, Balady GJ, Blair SN, Corrado D, Estes NA 3rd, Fulton JE, Gordon NF, Haskell WL, Link MS, Maron BJ, Mittleman MA, Pelliccia A, Wenger NK, Willich SN, Costa F. Exercise and acute cardiovascular events placing the risks into perspective: a scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism and the Council on Clinical Cardiology. *Circulation* 115: 2358–2368, 2007.

264. Thompson PD, Funk EJ, Carleton RA, Sturner WQ. Incidence of death during jogging in Rhode Island from 1975 through 1980. *JAMA* 247: 2535–2538, 1982.

265. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Joint Task Force for the Universal Definition of Myocardial Infarction, Katus HA, Lindahl B, Morrow DA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasche P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S. Joint Task Force for the Universal Definition of Myocardial Infarction, Katus HA, Lindahl B, Morrow DA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasche P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S. Third universal definition of myocardial infarction. *Circulation* 126: 2020–2035, 2012.

266. Thygesen K, Mair J, Mueller C, Huber K, Weber M, Plebani M, Hasin Y, Biasucci LM, Giannitsis E, Lindahl B, Koenig W, Tubaro M, Collinson P, Katus H, Galvani M, Venge P, Alpert JS, Hamm C, Jaffe AS, Study Group on Biomarkers in Cardiology of the ESCWGoACC. Recommendations for the use of natriuretic peptides in acute cardiac care: a position statement from the Study Group on Biomarkers in Cardiology of the ESC Working Group on Acute Cardiac Care. *Eur Heart J* 33: 2001–2006, 2012.

267. Tian Y, Nie J, Huang C, George KP. The kinetics of highly sensitive cardiac troponin T release after prolonged treadmill exercise in adolescent and adult athletes. *J Appl Physiol* 113: 418–425, 2012.

268. Toutouzas K, Trikas A, Pitsavos C, Barbetseas J, Androulakis A, Stefanadis C, Toutouzas P. Echocardiographic features of left atrium in elite male athletes. *Am J Cardiol* 78: 1314–1317, 1996.

269. Trivax JE, Franklin BA, Goldstein JA, Chinnaiyan KM, Gallagher MJ, deJong AT, Colar JM, Haines DE, McCullough PA. Acute cardiac effects of marathon running. *J Appl Physiol* 108: 1148–1153, 2010.

270. Tulloh L, Robinson D, Patel A, Ware A, Prendergast C, Sullivan D, Pressley L. Raised troponin T and echocardiographic abnormalities after prolonged strenuous exercise–the Australian Ironman Triathlon. *Br J Sports Med* 40: 605–609, 2006.

271. Uchida K, Imoto K, Yanagi H, Date K. Acute aortic dissection occurring during the butterfly stroke in a 12-year-old boy. *Interactive Cardiovasc Thoracic Surg* 9: 366–367, 2009.

272. Urhausen A, Scharhag J, Herrmann M, Kindermann W. Clinical significance of increased cardiac troponins T and I in participants of ultra-endurance events. *Am J Cardiol* 94: 696–698, 2004.

273. Vitiello D, Boissiere J, Doucende G, Gayrard S, Polge A, Faure P, Goux A, Tanguy S, Obert P, Reboul C, Nottin S. beta-Adrenergic receptors desensitization is not involved in exercise-induced cardiac fatigue: NADPH oxidase-induced oxidative stress as a new trigger. *J Appl Physiol* 111: 1242–1248, 2011.

274. Volders PG. Marathon rat: myocardial remodeling in an animal model of vigorous endurance exercise and implications for humans. *Circulation* 123: 5–7, 2011.

275. Warhol MJ, Siegel AJ, Evans WJ, Silverman LM. Skeletal muscle injury and repair in marathon runners after competition. *Am J Pathol* 118: 331–339, 1985.

276. Weber C, Noels H. Atherosclerosis: current pathogenesis and therapeutic options. *Nature Med* 17: 1410–1422, 2011.

277. Weber KT, Brilla CG. Pathological hypertrophy and cardiac interstitium. Fibrosis and renin-angiotensin-aldosterone system. *Circulation* 83: 1849–1865, 1991.

278. Weidemann F, Herrmann S, Stork S, Niemann M, Frantz S, Lange V, Beer M, Gattenlohner S, Voelker W, Ertl G, Strotmann JM. Impact of myocardial fibrosis in patients with symptomatic severe aortic stenosis. *Circulation* 120: 577–584, 2009.

279. Weiner RB, Baggish AL. Exercise-induced cardiac remodeling. *Prog Cardiovasc Dis* 54: 380–386, 2012.

280. Weiner RB, Hutter AM Jr, Wang F, Kim J, Weyman AE, Wood MJ, Picard MH, Baggish AL. The impact of endurance exercise training on left ventricular torsion. *J Am Coll Cardiol* 3: 1001–1009, 2010.

281. Welsh RC, Warburton DE, Humen DP, Taylor DA, McGavock J, Haykowsky MJ. Prolonged strenuous exercise alters the cardiovascular response to dobutamine stimulation in male athletes. *J Physiol* 569: 325–330, 2005.

282. Wen CP, Wai JP, Tsai MK, Yang YC, Cheng TY, Lee MC, Chan HT, Tsao CK, Tsai SP, Wu X. Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study. *Lancet* 378: 1244–1253, 2011.

283. Whang W, Manson JE, Hu FB, Chae CU, Rexrode KM, Willett WC, Stampfer MJ, Albert CM. Physical exertion, exercise, and sudden cardiac death in women. *JAMA* 295: 1399–1403, 2006.

284. White HD. Pathobiology of troponin elevations: do elevations occur with myocardial ischemia as well as necrosis? *J Am Coll Cardiol* 57: 2406–2408, 2011.

285. Whyte GP. Clinical significance of cardiac damage and changes in function after exercise. *Med Sci Sports Exercise* 40: 1416–1423, 2008.

286. Whyte GP, George K, Sharma S, Lumley S, Gates P, Prasad K, McKenna WJ. Cardiac fatigue following prolonged endurance exercise of differing distances. *Med Sci Sports Exercise* 32: 1067–1072, 2000.

287. Wiese S, Breyer T, Dragu A, Wakili R, Burkard T, Schmidt-Schweda S, Fuchtbauer EM, Dohrmann U, Beyersdorf F, Radicke D, Holubarsch CJ. Gene expression of brain natriuretic peptide in isolated atrial and ventricular human myocardium: influence of angiotensin II and diastolic fiber length. *Circulation* 102: 3074–3079, 2000.

288. Wilhelm M, Roten L, Tanner H, Wilhelm I, Schmid JP, Saner H. Gender differences of atrial and ventricular remodeling and autonomic tone in nonelite athletes. *Am J Cardiol* 108: 1489–1495, 2011.

289. Willich SN, Lewis M, Lowel H, Arntz HR, Schubert F, Schroder R. Physical exertion as a trigger of acute myocardial infarction. Triggers and Mechanisms of Myocardial Infarction Study Group. *N Engl J Med* 329: 1684–1690, 1993.

290. Wilson M, O'Hanlon R, Prasad S, Deighan A, Macmillan P, Oxborough D, Godfrey R, Smith G, Maceira A, Sharma S, George K, Whyte G. Diverse patterns of myocardial fibrosis in lifelong, veteran endurance athletes. *J Appl Physiol* 110: 1622–1626, 2011.

291. Wilson M, O'Hanlon R, Prasad S, Oxborough D, Godfrey R, Alpendurada F, Smith G, Wong J, Basavarajaiah S, Sharma S, Nevill A, Gaze D, George K, Whyte G. Biological markers of cardiac damage are not related to measures of cardiac systolic and diastolic function using cardiovascular magnetic resonance and echocardiography after an acute bout of prolonged endurance exercise. *Br J Sports Med* 45: 780–784, 2011.

292. Wingo JE, Ganio MS, Cureton KJ. Cardiovascular drift during heat stress: implications for exercise prescription. *Exercise Sport Sci Rev* 40: 88–94, 2012.

293. Wu AH, Apple FS, Gibler WB, Jesse RL, Warshaw MM, Valdes R Jr. National Academy of Clinical Biochemistry Standards of Laboratory Practice: recommendations for the use of cardiac markers in coronary artery diseases. *Clin Chem* 45: 1104–1121, 1999.

294. Yue L, Feng J, Gaspo R, Li GR, Wang Z, Nattel S. Ionic remodeling underlying action potential changes in a canine model of atrial fibrillation. *Circ Res* 81: 512–525, 1997.

295. Zarate YA, Hopkin RJ. Fabry's disease. *Lancet* 372: 1427–1435, 2008.

296. Zeppilli P, Bianco M, Bria S, Palmieri V. Bicuspid aortic valve: an innocent finding or a potentially life-threatening anomaly whose complications may be elicited by sports activity? *J Cardiovasc Med* 7: 282–287, 2006.