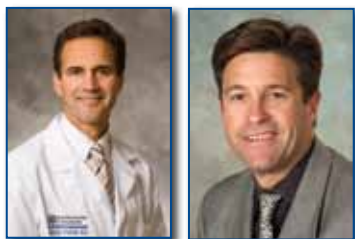**SPECIAL SERIES** *Preventive Cardiology*

Cardiovascular Damage Resulting from Chronic Excessive Endurance Exercise

by Harshal R. Patil, MD, James H. O'Keefe, MD, Carl J. Lavie, MD, Anthony Magalski, MD, Robert A. Vogel, MD & Peter A. McCullough, MD

Chronic, excessive sustained endurance exercise may cause adverse structural remodeling of the heart and large arteries.

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Abstract

A daily routine of physical activity is highly beneficial in the prevention and treatment of many prevalent chronic diseases, especially of the cardiovascular (CV) system. However, chronic, excessive sustained endurance exercise may cause adverse structural remodeling of the heart and large arteries. An evolving body of data indicates that chronically training for and participating in extreme endurance competitions such as marathons, ultra-marathons, Iron-man distance triathlons, very long distance bicycle racing, etc., can cause transient acute volume overload of the atria and right ventricle, with transient reductions in right ventricular ejection fraction and elevations of cardiac biomarkers, all of which generally return to normal within seven to ten days. In veteran extreme endurance athletes, this recurrent myocardial injury and repair may eventually result in patchy myocardial fibrosis, particularly in the atria, interventricular septum and right ventricle, potentially creating a substrate for atrial and ventricular arrhythmias. Furthermore, chronic, excessive, sustained, high-intensity endurance exercise may be associated with diastolic dysfunction, large-artery wall stiffening and coronary artery calcification. Not all veteran extreme endurance athletes develop pathological remodeling, and indeed lifelong exercisers generally have low mortality rates and excellent functional capacity. The aim of this review is to discuss the emerging understanding of the cardiac pathophysiology of extreme endurance exercise, and make suggestions about healthier fitness patterns for promoting optimal CV health and longevity.

Introduction

Although exercise is not a pharmacologic agent, in many ways its effects resemble those

Figure 1
Dose of physical activity and all-cause mortality reduction. The mortality benefits of exercise appear with even small amounts of daily exercise and peak at 50 minutes of vigorous exercise.[9]
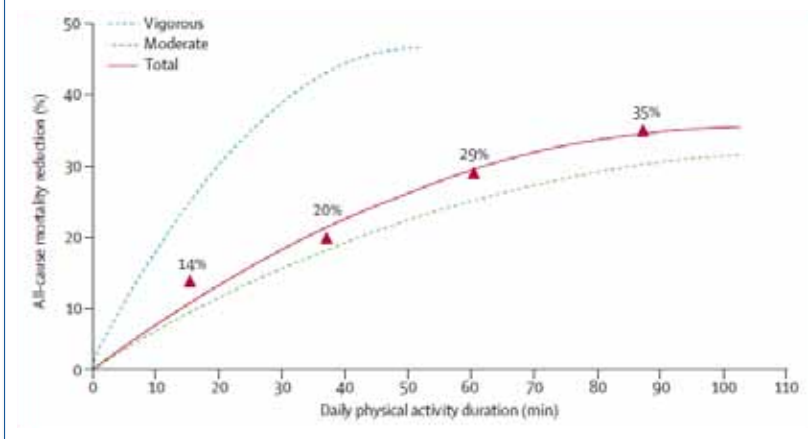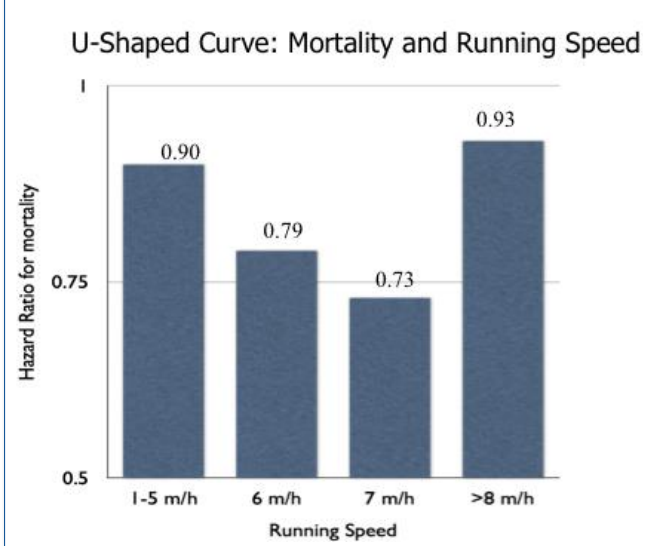

Figure 2
Relationship between running speed and mortality.[10]

of a powerful drug. Daily physical activity (PA) and exercise produces numerous favorable changes in gene expression, with improvements in physiological function, structure, and body composition.[1-4] A regimen of regular exercise training (ET) is extremely efficacious in the prevention and treatment of many of our most common and deadly chronic diseases including: coronary artery disease (CAD), diabetes, obesity, high blood pressure, heart failure (HF) and depression.[5] Individuals who regularly engage in more PA have markedly lower rates of disability, and an average life expectancy that is about seven years longer than sedentary people.[6,7] For this reason, enlightened health care providers routinely recommend to patients regular PA as an indispensable element of their day-to-day routine.
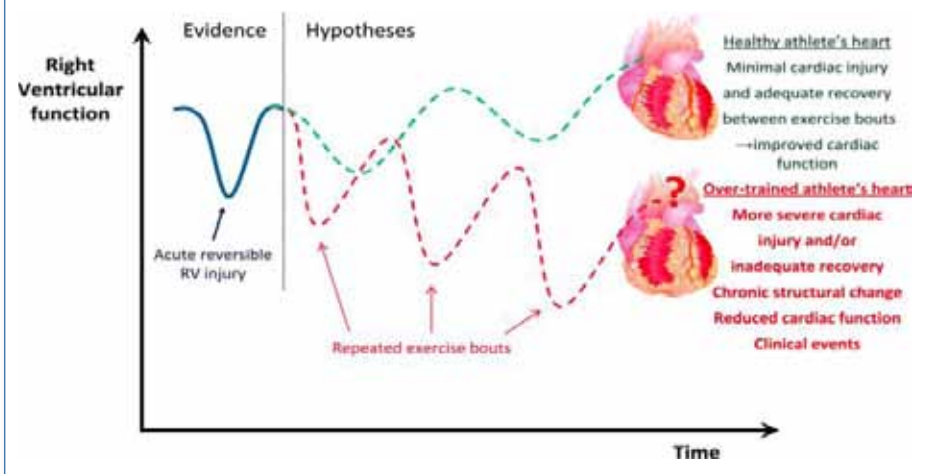
As can be expected with any drug, a safe upper range dose of ET may exist, above which the adverse effects of sustained intense PA and exercise may outweigh its benefits. Even a modest dose of regular PA, as little as 15 minutes daily, can confer substantial health benefits, as shown in a recent observational long-term study in involving 416,000 individuals.[9] That study also found that exercise improved overall survival in a dose-dependent fashion up to about 60 minutes of daily vigorous PA; beyond that a point of diminishing returns was apparent (See Figure 1). Similarly, a 15-year observational study of 52,000 adults reported that long-term runners had a 19% lower risk of all-cause mortality compared with non-runners. However, U-shaped mortality curves were apparent for running distances, speeds, and frequencies (See Figure 2). Running speeds of six to seven miles/hour, running distances of about one to twenty miles/week, and frequencies of runs of two to five days/week were associated with lower rates of all-cause mortality; while higher weekly mileage, faster running paces, and more frequent runs diminished some of the survival benefits noted with more moderate running.[10] From this large study, more not only did not appear to be better, but actually more running appeared to be worse, in that there was a loss of the survival benefit that was noted at lower levels of running. A recently published trial randomized 60 male CAD patients to regular vigorous exercise training sessions of either 30 or 60 minutes. The 30-minute physical activity sessions produced less oxidant stress and augmented arterial elasticity; sixty-minute workouts increased oxidant stress and worsened vascular stiffness as assessed by pulse wave velocity. These adverse effects were mainly apparent in older subjects.[11]

Thus, exercise confers benefits even with relatively modest levels of regular PA. Competitive ultra-endurance athletes often engage in daily vigorous aerobic exercise for anywhere from 90 to 300 minutes per day, commonly accumulating workloads of 200

Figure 3
Potential impact of repeated bouts of ultra-endurance exercise on right ventricular structure and function.[13]

and ultra-marathons, Iron-man distance triathlons, and very long distance bicycling can exact a toll on the health and integrity of the heart and blood vessels.[26]

Sudden Death and Endurance Exercise

Over the past 35 years, the number of Americans participating in a marathon annually has risen twenty-fold. In 2010, there were an estimated half million marathon finishers.[29] Recent analyses[30,31a] estimated the rate of sudden cardiac death (SCD) among marathoners as approximately 1 per 100,000-200,000 participants; while that per participant risk has not changed over the decades, absolute mortality has increased as the number of participants has risen. The final mile of the 26.2 mile marathon run represents less than 5% of the total distance yet accounts for almost 50% of the SCDs.[31]

The fatality rate for triathlons is approximately twice that of marathons, largely due to increased CV events and drowning during the swim portion of the races.[32] The incidence of SCD among collegiate athletes during competition is about 1 per 40,000 participants per year for all athletes, but rises to 1 per 3,000 for Division I male basketball players.[33] However, the rare occurrence of sudden cardiac death during marathons, triathlons, and collegiate athletic events does not convey the full spectrum of potential adverse effects induced by chronic EEE training and racing.

The etiologies of sudden cardiac death during or after extreme exertion in individuals younger than age 40 most commonly include genetic causes such as hypertrophic cardiomyopathy, anomalous coronary arteries, dilated cardiomyopathy, and congenital long QT syndrome. In athletes over age 30, CAD and acute myocardial ischemia are the predominant causes of exercise related SCD.[34-40] All of these causes should be excluded, and in the remaining cases with sudden cardiac death and no discernable cause, an acquired structural cardiac abnormality due to chronic and repetitive sessions of extreme exertion should be considered.

to 300 metabolic equivalent hours (METS X hours) weekly; this is about five to ten times more than the weekly cumulative exercise workload recommended by consensus guidelines for prevention of CAD.[5,12] The purpose of this review is to explore the possibility that chronic intense sustained endurance exercise may cause adverse structural and electrical remodeling of the heart and large arteries that could attenuate some of the benefits conferred by more moderate intensities and durations of exercise training.

In the environment of our evolution, our ancient ancestors performed a wide variety of PA usually done intermittently, at moderate intensities, for moderate durations; when high intensity exercise was performed, it was typically performed for short or intermediate bursts.[1-3] Humans are not genetically adapted for protracted, sustained, and extreme aerobic exercise efforts.[1,2]

Even in highly trained individuals, high-intensity, sustained multi-hour endurance exercise efforts are often associated with cardiac strain, elevated levels of troponin and B-type natriuretic peptide (BNP), and subsequent patchy myocardial fibrosis.[13-17] Especially, right ventricular (RV) function may be more profoundly affected by chronic excessive endurance exercise (EEE)[17-20] and, in some cases, RV recovery may be incomplete[20-22] which may represent a substrate for proarrhythmic RV remodeling in some highly trained athletes[23,24] even in the absence of a known familial disposition[25] (See Figure 3). Long-term exercise training and racing involving marathons

Pheidippides: First Marathon Runner and Its First Casualty, Too

During the Greco-Persian War in 490 BC, Pheidippides, a 40-year-old Greek herald, presumably a veteran long-distance runner, ran about 150 miles during a 48-hour period to deliver urgent critical military messages. On the third day, he ran the 26 miles from a battlefield near Marathon to Athens to deliver news of a momentous Greek victory. According to legend, upon arriving, Pheidippides exclaimed to the Athenians, "Victory is ours!", then immediately collapsed, and died. Now, 2,500 years later, with the rise in popularity of endurance sports, concerning evidence is mounting suggesting that extreme endurance training and competition may promote adverse cardiac structural remodeling, and predispose to acute and chronic CV problems.[1]

Born to Run

In the best-selling book, Born to Run, (Christopher McDougall, Knopf Publishing, 2009) Micah True is the mythic long distance runner, Caballo Blanco, who runs as far as 100 miles in a day. Recently, this legendary ultra-marathoner died suddenly while out on a routine 12-mile training run March 27, 2012. On autopsy his heart was enlarged and scarred; he died of a lethal arrhythmia.[2] Although speculative, the pathologic changes in the heart of this 58-year-old veteran extreme endurance athlete were likely manifestations of Pheidippides' cardiomyopathy—a condition caused by chronic excessive endurance exercise.[28]

Animal Studies

In an animal study Benito et al. compared rats that were trained to run strenuously and without resting for 60 minutes daily for 16 weeks to sedentary rats.[41] The running rats developed bi-ventricular hypertrophy, diastolic dysfunction, bi-atrial dilation and had increased collagen deposition and fibrosis in the RV and in both atria. Ventricular tachycardia was inducible in 42% of the running rats versus only 6% of the sedentary rats ($P=0.05$). Importantly, the fibrotic changes caused by 16 weeks of intensive ET had largely regressed back to normal by eight weeks after the daily running regimen was ceased. Excessive strenuous daily running in this animal study replicated the adverse cardiac structural remodeling and pro-arrhythmia substrate noted in observational studies of extreme e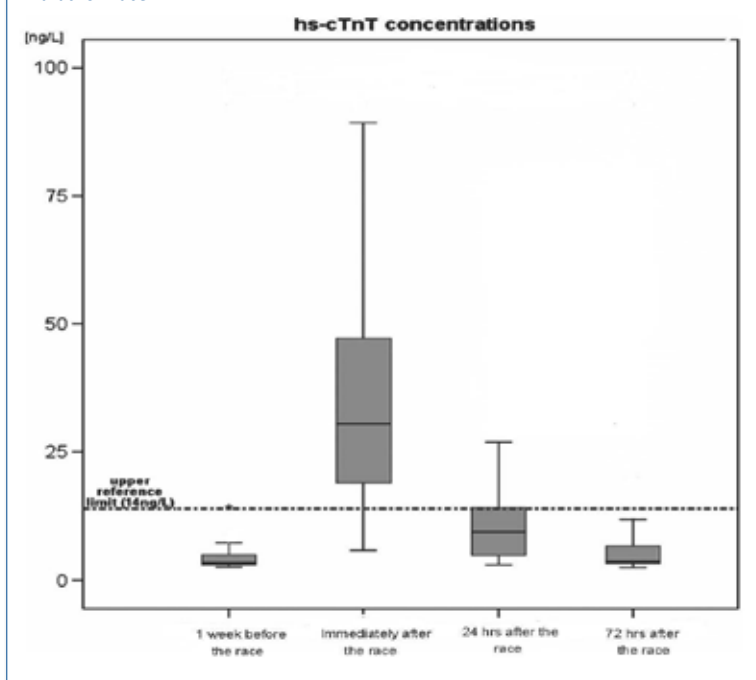ndurance human athletes. These findings support the hypothesis that long-term strenuous daily endurance ET such as marathon running or professional long-distance cycling may cause cardiac fibrosis (especially in the atria and the RV), diastolic dysfunction, and increased susceptibility to atrial and ventricular arrhythmias (VA). However, it should be noted that animal studies are of uncertain clinical relevance due to the excessively stressful nature of the imposed exercise.

Biomarker Evidence for Cardiac Damage with Excessive Endurance Exercise

Running is a prototypical natural physical activity and often plays an integral and important role in an active healthy lifestyle.[1,2] However, continuous running such as is required for training and participating in a marathon may be detrimental to cardiovascular health. Several serological markers of cardiac damage

Figure 4
Hs-cTnT concentrations before, immediately after, 24 hours and 72 hours after the marathon race.[42]

have been documented to rise during and after marathon running.[13, 17, 42] These markers include cardiac troponin-I, creatine kinase and creatine kinase myocardial band (CK-MB), myoglobin, and BNP (See Figure 4). Additionally, transient renal dysfunction has been observed with EEE efforts causing volume depletion and diminished renal filtration with elevations in blood urea nitrogen, serum creatine, and cystatin-C.[43] Abnormally increased levels of cardiac biomarkers including troponin after extreme aerobic endurance events, such as marathons, in all probability reflect myocardial cell damage and stretch at the sites of myocyte slippage of one cell along another due to loss of integrity of desmosomal connections.

Athlete's Heart

Chronic EEE imposes increased hemodynamic demands which alter the loading conditions of the heart, particularly among athletes participating in sports requiring sustained large elevations in cardiac work such as long-distance running, rowing, and cycling.[44] Highly trained individuals develop cardiac adaptations including enlarged left ventricular (LV) and RV volumes, increased LV wall thickness and cardiac mass, and increased left atrial (LA) size.[38-40] These structural alterations, together with a preserved LV ejection fraction (EF), have been considered typical

findings of the "athlete's heart."[35-37] Accumulating information suggest that some of the remodeling that occurs in endurance athletes may be pathological rather than entirely benign and adaptive.[34]

Adverse Structural Remodeling

Repetitive sustained intense aerobic exercise induces remodeling of the RV with dilation of RV end diastolic dimension, however, the RVEF remains normal in asymptomatic athletes without evidence for arrhythmia.[25,26] In a recent study,[13] forty athletes were studied at baseline, immediately following an endurance race (three to eleven hours duration) and one week after the race (See Figures 5, 6). Relative to baseline, RV volumes increased and all functional measures decreased post-race; RVEF decreased with increasing race duration. RV function was mostly recovered by one week. On cardiac magnetic resonance imaging (CMR), delayed gadolinium enhancement (a marker of myocardial fibrosis) localized to the interventricular septum was identified in athletes who had greater cumulative exercise exposure and lower RVEF than those with normal CMR (See Figure 7).

In a study of 102 ostensibly healthy male runners ranging from 50 to 72 years old, who had completed at least five marathons during the past three years compared to 102 age-matched control subjects, CMR was used to assess the effects of chronic long distance running on myocardial structure.[45] Approximately 12% of these apparently healthy marathon runners showed evidence for patchy myocardial scarring, a rate three-fold higher than that in age-matched control subjects. This study indicates that in endurance athletes, CMR with late gadolinium enhancement can reliably detect areas of patchy fibrosis.[45] Of additional concern, the CAD event rate during two-year follow up was significantly higher in the marathon runners than in controls (P < .0001).

A recent study also reported that long-term marathon runners had increased aortic stiffness compared with recreational exercisers.[46] This study assessed blood pressure and aortic elasticity among 47 individuals who chronically trained for and competed in marathons, and compared them to 46 others who

Figure 5
Duration-dependent effect of endurance events on right ventricular (RV) ejection fraction.[13]
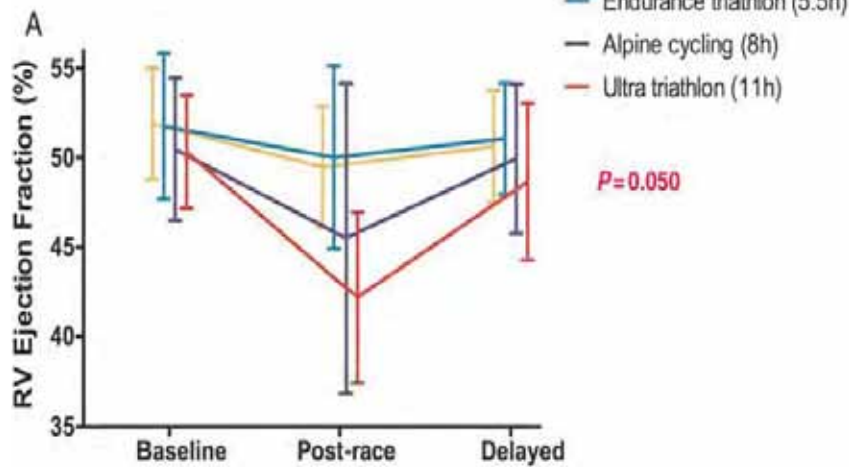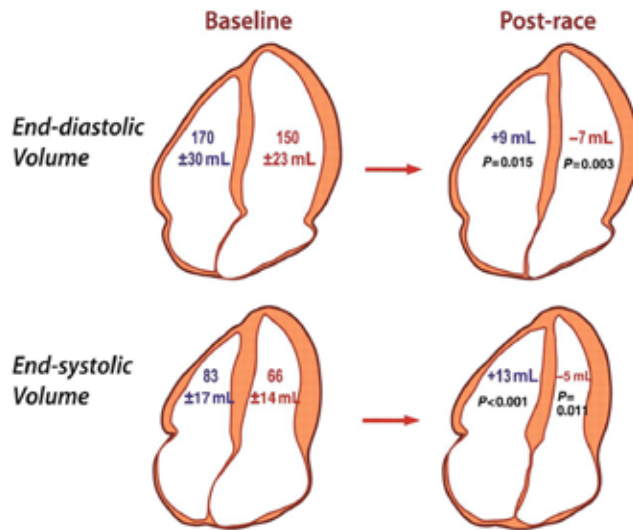

Figure 6
Differential effect of prolonged intense exercise on right and left ventricular volumes. Baseline volumes are shown on the left, and the changes in volume post-race are shown on the right. Right ventricular volumes increased in the post-race setting, whereas left ventricular volumes decreased, resulting in a decrease in right ventricular ejection fraction but not left ventricular ejection fraction.[13]

La Gerche A et al. Eur Heart J 2011;eurheartj.ehr397

Accelerated Coronary Atherosclerosis

Schwartz et al. reported that long-term marathon runners, defined as individuals who have completed at least 25 marathons over the past 25 years, showed higher than expected levels of coronary artery calcium (CAC) and calcified coronary plaque volume.[26] This study, utilizing CT coronary angiography, found that the chronic marathoners had significantly more calcified plaque volume, 274 mm³, versus 169 mm³ for the sedentary controls. CV risk factors such as age, systolic blood pressure, total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels were similar between the marathoners and controls, but heart rate and weight were lower, and high-density lipoprotein cholesterol levels were higher in the runners. A similar study in a different population found increased CAC in 108 middle-aged marathon runners compared with non-runners who had matched risk factors,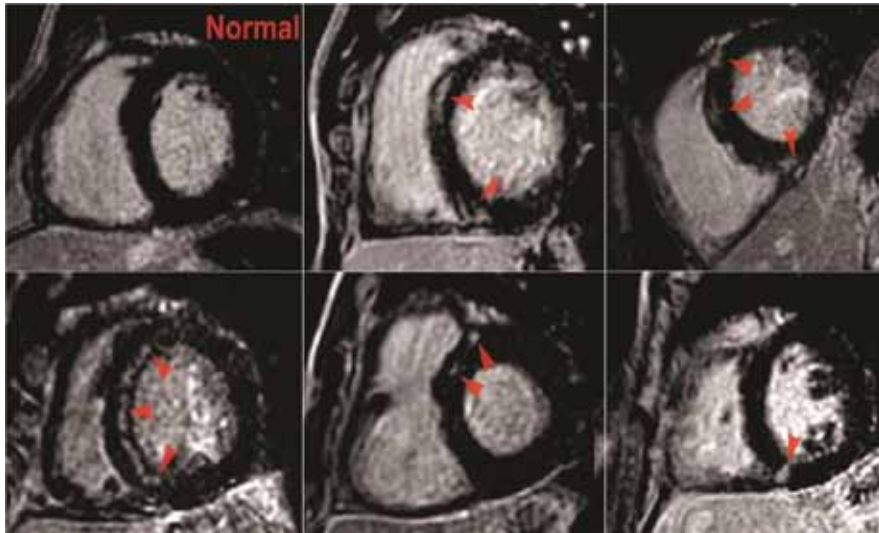 and CV event rates in the marathoners were equivalent to a CAD population.[48] In a case report, Goel et al.[49] observed a 49-year-old marathoner who had significant obstructions in all three major epicardial coronary arteries with no associated risk factors, and who generated protracted oxidative stress with prolonged running.

Increases in LV mass typically develop in response to high-level, intense long-term ET, particularly in cyclists, cross-country skiers, and rowers.[50] The "physiological" LV hypertrophy that is a common feature of "athlete's heart" is thought to be a functional adaptation to chronic ET. LV mass, as

did not participate in chronic endurance ET. The chronic marathoners showed significantly higher systolic blood pressures compared with the control group (126 mm Hg vs. 115 mm Hg). Pulse-wave velocity, utilized to assess aortic stiffness, was significantly higher in the marathoner group compared to controls.[20,46] Thus, sustained shear stress over a long period of time may induce fibrotic changes in the arterial wall, potentially similar to that in the myocardium, and over time leads to decreases in compliance. It should be noted that aortic stiffness and atrial pulse wave reflections have been established as independent predictors of CV risk.[47]

Figure 7
Delayed gadolinium enhancement in five athletes.[13] Images of five athletes in whom focal delayed gadolinium enhancement (DGE) was identified in the interventricular septum (indicated with arrows) when compared with an athlete with a normal study (top left).

La Gerche A et al. Eur Heart J 2011;eurheartj.ehr397

Figure 8
Proposed pathogenesis of endurance athlete's cardiomyopathy.

RA=Right atrium, RV= Right ventricle, LV= Left ventricle, SCD= Sudden Cardiac Death

found a mismatch between the risk-factor profiles and the amount CAC particularly in those with a LV muscle mass above 150 grams.
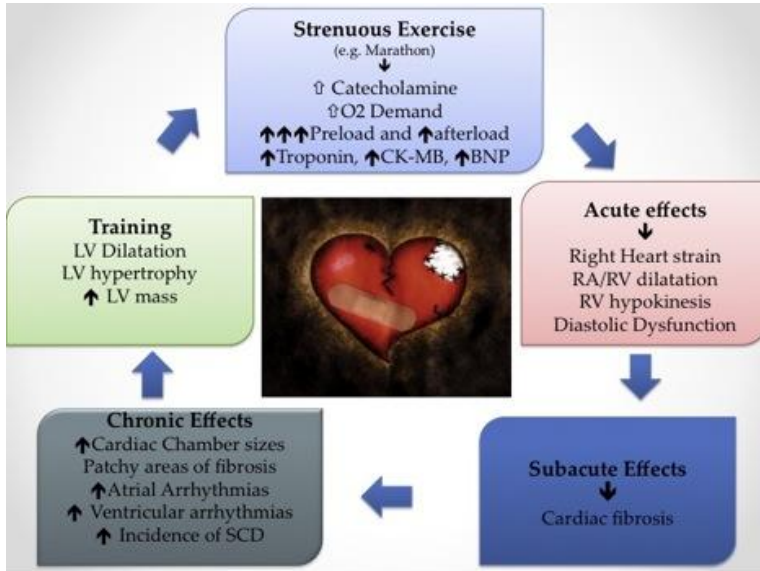
Pathophysiology of Chronic Extreme Exercise

Figure 8 describes the pathophysiology and adverse CV consequences (fibrosis, atrial arrhythmias, VA, and SCD) associated with endurance exercise training and competition, such as marathon running. Although the accelerated atherosclerosis in chronic marathoners is somewhat surprising and counterintuitive, the metabolic and mechanical stresses involved in chronic extreme endurance efforts may be playing a critical pathophysiological role. Individuals who chronically train and race over very long-distances have sustained elevations in heart rates, blood pressures, cardiac output, and cardiac chamber volumes for as much as several hours daily. Heavy and sustained exercise training generates large quantities of free-radicals that likely outstrip the buffering capacity of the system, leaving these individuals susceptible to oxidative stress and transient myocyte dysfunction, perhaps inducing adverse changes in the quality and quantity of desmosomes and other cell anchoring structures. This process causes dilation of the RA and RV resulting from hours of strenuous physical activity and increased cardiac demands. This repetitive cycle may stimulate immune cells including lymphocytes, macrophages, and mast cells to secrete cytokines that signal the myofibroblasts to proliferate and secrete procollagen which is then cross-linked to form mature collagen.

determined by CMR, was significantly greater in the marathoners.[51] In this study, increased LV mass correlated with higher CAC scores. Specifically, marathon runners with a mass above 150 grams had a significantly higher CAC score than those with LV masses below 150 grams.[51] These investigators also

This eventually results in fibrosis deposited in patches in the myocardium and more diffusely in the large arteries.

Pro-arrhythmic Effects of Excessive Endurance Exercise

Although it has been recognized that elite-level athletes commonly develop abnormal electrocardiograms and benign atrial and ventricular ectopy[52-54] the "athlete's heart" adaptations to long-term, high-level exercise training traditionally have not been thought to predispose to serious arrhythmias, HF, myocardial infarction, or sudden cardiac death. However, recent data indicate that adverse cardiac remodeling induced by EEE can, among other issues, create an arrhythmogenic substrate[17, 26, 45, 54] Indeed, chronic sustained vigorous aerobic ET such as marathon or ultra-marathon running or professional cycling has been associated with increased risk of atrial fibrillation,[17, 36, 45, 48-50, 55-60, 67] and complex ventricular ectopy including ventricular tachycardia and SCD[30] even in very fit individuals.[52] Despite the fact that these studies excluded athletes with findings to suggest arrhythmogenic RV dysplasia, the VA typically originate from a mildly dysfunctional RV,[23,24,54,61] that may be the result of prior myocardial injury from excessive and sustained aerobic exercise training. Myocardial fibrosis (fibrillary collagen deposition) develops as a reparative process in response to damaged myocardium. This patchy myocardial scarring can favor reentry and is well established as a substrate for arrhythmia susceptibility.[62, 63]

Chronic excessive endurance exercise training and competition also stimulates multiple other disruptions within the system including episodic release of excessive catecholamine and resultant coronary vasoconstriction, chronic elevations of heart rate during sessions of protracted aerobic ET leading to decreased diastolic filling time of the coronary arteries, increased demand for oxygen, changes in free fatty acid metabolism, lactic acidosis, and metabolic derangements.[43] During an extreme endurance event, in susceptible individuals the heart may not be able to cope with the prolonged and sustained excessive physiological demands, thus increasing right heart preload and afterload, which initiates stretch and subsequent chamber dilatation in response to these hemodynamic changes.[58] Right heart dilation and hypokinesis following protracted exhaustive exercise training has been documented using both CMR and echocardiography.[23,45] Diastolic dysfunction of both the RV and LV has also been observed in individuals doing chronic EEE and racing.[64]

During the post-endurance exercise period, the cardiac geometric dimensions are restored and many athletes continue this cycle with long distance exercise training, marathon running, transient chamber enlargement, and subsequent myocardial recovery. With this recurrent stretch of the chambers and re-establishment of the chamber geometry, some individuals may be prone to the development of chronic structural changes including dilation of the heart chambers and patchy myocardial scarring in response to the recurrent volume overload and excessive cardiac strain.[59] Approximately one in three finishers of a marathon, irrespective of baseline fitness level or the time it took to complete the race, will have a post-race spike and fall in cardiac troponin and BNP.[60] It is logical to hypothesize that a subset of these individuals eventually go on to develop patchy cardiac fibrosis. These abnormalities are often asymptomatic and probably accrue over many years; and may predispose to serious arrhythmias and/or sudden cardiac death.

Risk Stratification of Endurance Athletes

Currently, we have no proven screening methods for detecting the CV pathology associated with EEE. A logical strategy for now would deploy post-competition cardiac biomarkers, echocardiography and/or advanced imaging such as CMR to identify individuals at risk for and with subclinical adverse structural remodeling and the substrate for arrhythmias.[61] For any individual who is considering EEE efforts such as marathons or day long aerobic races for any other activity that elevates cardiac output for a sustained period of time (continuously over several hours), it may be reasonable to obtain a maximal treadmill exercise test to screen for ischemia and/or exercise induced arrhythmias[24] and Heart CT for CAC scoring, particularly for those who are over age 50 and who have been chronically training for and competing in EEE events. Aortic pulse wave velocity could give an inference into the development of vascular stiffness that may not be readily appreciated by cuff blood pressure measurement.

SCIENCE OF MEDICINE/SPECIAL REVIEW

Avoiding Exercise-Induced CV Damage

Suggestions for an exercise routine that will optimize heath, fitness and longevity without causing adverse cardiovascular structural and electrical remodeling:

- Avoid a daily routine of exhaustive strenuous exercise training for periods greater than one hour continuously. An ideal target might be not more than seven hours weekly of cumulative strenuous endurance ET.[1,2,9,51]

- When doing exhaustive aerobic ET, take intermittent rest periods (even for a few minutes at an easier pace, such slowing down to walk in the middle of a run). This allows the cardiac output normalize temporarily, providing a 'cardiac rest period' when the chamber dimensions, blood pressure and pulse come down closer to baseline resting parameters before resuming strenuous exercise again.[2]

- Accumulate a large amount of daily light-to-moderate physical activity, such as walking, gardening, housekeeping, etc. Avoid prolonged sitting. Walk intermittently throughout the day. Look for opportunities to take the stairs. [1, 2] Buy a pedometer and gradually try to build up to 10,000 steps per day.

- Once or twice weekly, perform high-intensity interval exercise training to improve or maintain peak aerobic fitness. This is more effective in improving overall fitness and peak aerobic capacity than is continuous aerobic exercise training, despite a much shorter total accumulated exercise time spent doing the interval workout.[65, 66]

- Incorporate cross training using stretching, for example, yoga, and strength training into the weekly exercise routine. This confers multi-faceted fitness and reduces the burden of cardiac work compared to a routine of daily long-distance endurance exercise training. [1, 2]

- Avoid chronically competing in very long distance races, such as marathons, ultra-marathons, Iron-man distance triathlons, 100-mile bicycle races, etc., especially after age 45 or 50.

- Individuals over 45 or 50 years of age should reduce the intensity and durations of endurance exercise training sessions, and allow more recovery time.

References

1. O'Keefe JH, Vogel R, Lavie CJ, Cordain L. Achieving hunter-gatherer fitness in the 21(st) century: back to the future. Am J Med 2010;123:1082-6.
2. O'Keefe JH, Vogel R, Lavie CJ, Cordain L. Exercise like a hunter-gatherer: a prescription for organic physical fitness. Prog Cardiovasc Dis 2011;53:471-9.
3. Lavie CJ, Milani RV, O'Keefe JH, Lavie TJ. Impact of exercise training on psychological risk factors. Prog Cardiovasc Dis 2011;53:464-70.
4. O'Keefe, JH, Patil HR, Lavie CJ, Magalski A, Vogel RA, McCullough PA. Potential adverse cardiovascular effects from excessive endurance exercise. Mayo Clin Proc. 2012;87(6):587-595.
5. Haskell WL, Lee IM, Pate RR, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Circulation 2007;116:1081-93.
6. Sarna S, Sahi T, Koskenvuo M, Kaprio J. Increased life expectancy of world class male athletes. Med Sci Sports Exerc 1993;25:237-44.
7. Chakravarty EF, Hubert HB, Lingala VB, Fries JF. Reduced disability and mortality among aging runners: a 21-year longitudinal study. Arch Intern Med 2008;168:1638-46.
8. Lavie CJ, Thomas RJ, Squires RW, Allison TG, Milani RV. Exercise training and cardiac rehabilitation in primary and secondary prevention of coronary heart disease. Mayo Clin Proc 2009;84:373-83.
9. Wen CP, Wai JP, Tsai MK, et al. Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study. Lancet 2011;378:1244-53.
10. Lee DC, Pate RR, Lavie CJ, Blair SN. Running and all-cause mortality risk - is more better? Medicine & Science in Sports & Exercise 2012 ;44(5): S699.
11. Michaelides AP, Soulis D, Antoniades C, et al. Exercise duration as a determinant of vascular function and antioxidant balance in patients with coronary artery disease. Heart 2011;97:832-7.
12. Sharma S, Zaidi A. Exercise-induced arrhythmogenic right ventricular cardiomyopathy: fact or fallacy? Eur Heart J 2011. DOI: 10.1093/eurheartj/ehr436.
13. La Gerche A, Burns AT, Mooney DJ, et al. Exercise-induced right ventricular dysfunction and structural remodelling in endurance athletes. Eur Heart J 2012;33:998-1006.
14. Hubble KM, Fatovich DM, Grasko JM, Vasikaran SD. Cardiac troponin increases among marathon runners in the Perth Marathon: the Troponin in Marathons (TRIM) study. The Medical journal of Australia 2009;190:91-3.
15. Jassal DS, Moffat D, Krahn J, et al. Cardiac injury markers in non-elite marathon runners. International journal of sports medicine 2009;30:75-9.
16. Middleton N, Shave R, George K, et al. Altered left ventricular diastolic filling following a marathon is a reproducible phenomenon. Int J Cardiol 2007;122:87-9.
17. Neilan TG, Januzzi JL, Lee-Lewandrowski E, et al. Myocardial injury and ventricular dysfunction related to training levels among nonelite participants in the Boston marathon. Circulation 2006;114:2325-33.
18. Douglas PS, O'Toole ML, Hiller WD, Reichek N. Different effects of prolonged exercise on the right and left ventricles. J Am Coll Cardiol 1990;15:64-9.
19. Trivax JE, Franklin BA, Goldstein JA, et al. Acute cardiac effects of marathon running. J Appl Physiol 2010;108:1148-53.
20. 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 2008;94:860-6.
21. Mousavi N, Czarnecki A, Kumar K, et al. Relation of biomarkers and cardiac magnetic resonance imaging after marathon running. Am J Cardiol 2009;103:1467-72.
22. Neilan TG, Yoerger DM, Douglas PS, et al. Persistent and reversible cardiac dysfunction among amateur marathon runners. Eur Heart J 2006;27:1079-84.
23. Ector J, Ganame J, van der Merwe N, et al. Reduced right ventricular ejection fraction in endurance athletes presenting with ventricular arrhythmias: a quantitative angiographic assessment. Eur Heart J 2007;28:345-53.
24. Heidbuchel H, Hoogsteen J, Fagard R, et al. High prevalence of right

ventricular involvement in endurance athletes with ventricular arrhythmias. Role of an electrophysiologic study in risk stratification. Eur Heart J 2003;24:1473-80.

25.   La Gerche A, Robberecht C, Kuiperi C, et al. Lower than expected desmosomal gene mutation prevalence in endurance athletes with complex ventricular arrhythmias of right ventricular origin. Heart 2010;96:1268-74.

26.   Schwartz J, Merkel-Kraus S, Duval S. Does elite athleticism enhance or inhibit coronary artery plaque formation. Paper presented at: American College of Cardiology 2010 Scientific Sessions March 16, 2010; Atlanta, GA.

27.   Bearak B. Caballo Blanco's Last Run: The Micah True Story. The New York Times. May 20, 2012. http://www.nytimes.com/2012/05/21/sports/caballo-blancos-last-run-the-micah-true-story.html?_r=3&pagewanted=all.

28.   Trivax JE, McCullough PA. Phidippides cardiomyopathy: a review and case illustration. Clin Cardiol 2012;35:69-73.

29.   Staff Mc. USA Marathoning: 2007 Overview. MarathonGuide.com. New York: Web Marketing Associates, 2008.

30.   Redelmeier DA, Greenwald JA. Competing risks of mortality with marathons: retrospective analysis. Bmj 2007;335:1275-7.

30a-Take the marathon ref from NEJM

31.   Kim JH, Malhotra R, Chiampas G, et al. Cardiac arrest during long-distance running races. N Engl J Med 2012;366:130-40.

32.   Harris K, Henry J, Rohman E, et al. Sudden death risk during the triathlon. Journal of the American Medical Association 2009.

33.   Harmon KG, Asif IM, Klossner D, Drezner JA. Incidence of sudden cardiac death in national collegiate athletic association athletes. Circulation 2011;123:1594-600.

34.   Maron BJ, Pelliccia A, Spirito P. Cardiac disease in young trained athletes. Insights into methods for distinguishing athlete's heart from structural heart disease, with particular emphasis on hypertrophic cardiomyopathy. Circulation 1995;91:1596-601.

35.   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 2000;101:336-44.

36.   Maron BJ, Pelliccia A. The heart of trained athletes: cardiac remodeling and the risks of sports, including sudden death. Circulation 2006;114:1633-44.

37.   Spirito P, Pelliccia A, Proschan MA, et al. Morphology of the "athlete's heart" assessed by echocardiography in 947 elite athletes representing 27 sports. Am J Cardiol 1994;74:802-6.

38.   Pelliccia A, Culasso F, Di Paolo FM, Maron BJ. Physiologic left ventricular cavity dilatation in elite athletes. Ann Intern Med 1999;130:23-31.

39.   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 1991;324:295-301.

40.   Pelliccia A, Maron BJ, Di Paolo FM, et al. Prevalence and clinical significance of left atrial remodeling in competitive athletes. J Am Coll Cardiol 2005;46:690-6.

41.   Benito B, Gay-Jordi G, Serrano-Mollar A, et al. Cardiac arrhythmogenic remodeling in a rat model of long-term intensive exercise training. Circulation 2011;123:13-22.

42.   Scherr J, Braun S, Schuster T, et al. 72-h kinetics of high-sensitive troponin T and inflammatory markers after marathon. Med Sci Sports Exerc 2011;43:1819-27.

43.   McCullough PA, Chinnaiyan KM, Gallagher MJ, et al. Changes in renal markers and acute kidney injury after marathon running. Nephrology (Carlton) 2011;16:194-9.

44.   Middleton N, Shave R, George K, et al. Altered left ventricular diastolic filling following a marathon is a reproducible phenomenon. Int J Cardiol 2007;122:87-9.

45.   Breuckmann F, Mohlenkamp S, Nassenstein K, et al. Myocardial late gadolinium enhancement: prevalence, pattern, and prognostic relevance in marathon runners. Radiology 2009;251:50-7.

46.   Vlachopoulos C, Kardara D, Anastasakis A, et al. Arterial stiffness and wave reflections in marathon runners. Am J Hypertens 2010;23:974-9.

47.   Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol 2010;55:1318-27.

48.   Mohlenkamp S, Lehmann N, Breuckmann F, et al. Running: the risk of coronary events : Prevalence and prognostic relevance of coronary atherosclerosis in marathon runners. Eur Heart J 2008;29:1903-10.

49.   Goel R, Majeed F, Vogel R, et al. Exercise-induced hypertension, endothelial dysfunction, and coronary artery disease in a marathon runner. Am J Cardiol 2007;99:743-4.

50.   Maron BJ. Hypertrophic cardiomyopathy and other causes of sudden cardiac death in young competitive athletes, with considerations for preparticipation screening and criteria for disqualification. Cardiol Clin 2007;25:399-414, vi.

51.   Nassenstein K, Breuckmann F, Lehmann N, et al. Left ventricular volumes and mass in marathon runners and their association with cardiovascular risk factors. Int J Cardiovasc Imaging 2009;25:71-9.

52.   Douglas PS, O'Toole ML, Hiller WD, Hackney K, Reichek N. Cardiac fatigue after prolonged exercise. Circulation 1987;76:1206-13.

53.   Magalski A, Maron BJ, Main ML, et al. Relation of race to electrocardiographic patterns in elite American football players. J Am Coll Cardiol 2008;51:2250-5.

54.   Westrol MS, Kapitanyan R, Marques-Baptista A, Merlin MA. Causes of sudden cardiac arrest in young athletes. Postgrad Med 2010;122:144-57.

55.   Rector RS, Rogers R, Ruebel M, Hinton PS. Participation in road cycling vs running is associated with lower bone mineral density in men. Metabolism 2008;57:226-32.

56.   Mont L, Sambola A, Brugada J, et al. Long-lasting sport practice and lone atrial fibrillation. Eur Heart J 2002;23:477-82.

57.   Elosua R, Arquer A, Mont L, et al. Sport practice and the risk of lone atrial fibrillation: a case-control study. Int J Cardiol 2006;108:332-7.

58.   Molina L, Mont L, Marrugat J, et al. Long-term endurance sport practice increases the incidence of lone atrial fibrillation in men: a follow-up study. Europace 2008;10:618-23.

59.   Mont L, Tamborero D, Elosua R, et al. Physical activity, height, and left atrial size are independent risk factors for lone atrial fibrillation in middle-aged healthy individuals. Europace 2008;10:15-20.

60.   Aizer A, Gaziano JM, Cook NR, Manson JE, Buring JE, Albert CM. Relation of vigorous exercise to risk of atrial fibrillation. Am J Cardiol 2009;103:1572-7.

61.   Biffi A, Pelliccia A, Verdile L, et al. Long-term clinical significance of frequent and complex ventricular tachyarrhythmias in trained athletes. J Am Coll Cardiol 2002;40:446-52.

62.   Burstein B, Nattel S. Atrial fibrosis: mechanisms and clinical relevance in atrial fibrillation. J Am Coll Cardiol 2008;51:802-9.

63.   Thompson PD, Venero CV. A history of medical reports on the Boston Marathon: 112 years and still running. Med Sci Sports Exerc 2009;41:1341-8.

64.   Oxborough D, Birch K, Shave R, George K. "Exercise-induced cardiac fatigue"--a review of the echocardiographic literature. Echocardiography 2010;27:1130-40.

65.   Nybo L, Sundstrup E, Jakobsen MD, et al. High-intensity training versus traditional exercise interventions for promoting health. Med Sci Sports Exerc 2010;42:1951-8.

66.   Wisloff U, Stoylen A, Loennechen JP, et al. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. Circulation 2007;115:3086-94.

67.   Farrar MW, Bogart DB, Chapman SS, Rigden LB. Atrial Fibrillation in Athletes. Missouri Medicine 2006;103:183-187

Disclosure

None reported.

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