

The Athlete's Heart: Friend or Foe?



Benjamin D. Levine, MD, Grand Rounds, University of Texas Southwestern Medical Center, January 27, 2017

(note that a substantial part of this protocol was derived from Levine BD. Can intensive exercise harm the heart? The benefits of competitive endurance training for cardiovascular structure and function. Circulation 2014)¹

This is to acknowledge that Benjamin D. Levine, M.D. has disclosed that he does not have any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Levine will not be discussing off-label uses in his presentation.

Benjamin D. Levine, M.D., F.A.C.C., F.A.H.A., F.A.C.S.M., F.A.P.S.
Director, Institute for Exercise and Environmental Medicine
S. Finley Ewing Jr. Chair for Wellness at Texas Health Presbyterian Dallas
Harry S. Moss Heart Chair for Cardiovascular Research
Professor of Medicine and Cardiology
Distinguished Professorship in Exercise Science
University of Texas Southwestern Medical Center at Dallas

Dr. Levine is the founder and Director of the Institute for Exercise and Environmental Medicine (IEEM) at Texas Health Presbyterian Hospital Dallas where he also holds the S. Finley Ewing Chair for Wellness and the Harry S. Moss Heart Chair for Cardiovascular Research. He is Professor of Internal Medicine/Cardiology and Distinguished Professor of Exercise Sciences at the University of Texas Southwestern Medical Center. Dr. Levine earned his B.A. magna cum laude in human biology from Brown University and his M.D. from Harvard Medical School. He completed his internship and residency in internal medicine at Stanford University Medical Center followed by a cardiology fellowship at UT Southwestern where he trained under the renowned cardiovascular physiologists Gunnar Blomqvist, M.D. and Jere Mitchell, M.D. Dr. Levine founded the IEEM in 1992 which has become one of the premier laboratories in the world for the study of human clinical and integrative physiology. His global research interests center on the adaptive capacity of the circulation in response to exercise training, deconditioning, aging, and environmental stimuli such as spaceflight and high altitude.

Dr. Levine is a well-known sports cardiologist who sees athletes with cardiovascular medical problems from around the world and serves as a consultant to the NCAA, the NHL, the NFL, the USOC, USA Track and Field, and other athletic organizations. He has been a key contributor to the guidelines for the management of athletes with heart disease since 1994. Dr. Levine also has a unique background in space medicine, serving as a co-investigator on 4 Spacelab missions (SLS-1, SLS-2, D-2 and Neurolab), the MIR space station, and recently was the PI of a large cardiovascular experiment on the International Space Station (ISS), called the "ICV". He has a long, sustained track record of funding by the NIH, NASA and the National Space Biomedical Research Institute (NSBRI), for which he became Team Leader of the Cardiovascular Section in 2007 and he currently advises NASA's flight surgeons on cardiovascular medical issues.

Purpose and Overview: The purpose of this presentation is to discuss the physiological and pathophysiological cardiovascular adaptations that occur in endurance athletes, and are known collectively as "the athletes heart". The normal adaptive response to endurance training will be discussed in both younger and older athletes and literature describing adverse consequences of endurance will be examined in detail. The presentation will be framed by a case of a middle aged man with clear cardiovascular disease who presents asking if he can train for a marathon.

Objectives: At the conclusion of this lecture, the listener should be able: a) To describe the normal cardiovascular physiology of the endurance athlete; b) To interpret the epidemiological evidence regarding increase or decrease risk of cardiovascular disease in athletes; c) To determine whether competitive endurance training is adaptive or pathological for an older athlete.

Elite athletes are paragons of physical fitness in our society, and an entire “sports-industrial complex” has developed from playing/watching/marketing sports.² Although the idiosyncratic example of Phidippides has been used by some to highlight the dangers of extreme endurance efforts³, much more ubiquitous is the Greek model of the athlete as physical perfection, allowing vigor through to great age⁴.

The term “athlete’s heart” was originally coined to reflect its similarities to patients with enlarged hearts from disease⁵, though it is now recognized to reflect the unique physiological adaptation of the endurance athlete^{6,7}: a heart that is big⁸, muscular^{9,10}, compliant¹¹, and can pump a lot of blood very fast, to support high rates of aerobic metabolism¹². For example, cross sectional studies from Jere Mitchell’s team here at UT Southwestern in the late 80s showed that left ventricular mass, measured by cMRI was markedly greater in young competitive endurance athletes (runners, cyclists, cross-country skiers) compared to sedentary controls.⁹ Female athletes had smaller hearts than male athletes (though this difference was reduced when scaled to lean body mass) though still markedly larger than sedentary women.⁸ Subsequent work from our group showed that such endurance athletes have much steeper Starling curves leading to a large increase in stroke volume for any given increase in filling pressure;¹¹ this adaptation is due to a compliant, distensible LV chamber which is much larger for any distending pressure, and fills to a greater degree during volume expansion or exercise.¹¹

Recent longitudinal studies by our group^{13,14} and others¹⁵ have demonstrated that most, but not all of the cardiovascular adaptation to endurance training is a direct response to the load placed on the heart during training.¹⁶ It is worth a short digression to emphasize that although there has been some increased attention placed on basketball players because of their apparent high rates of sudden cardiac death during sports¹⁷, there is absolutely nothing unique about either the cardiovascular stress, or the cardiac adaptation to basketball training or competition that would place such athletes at excessive risk.^{18,19}

It is quite clear that prolonged, high intensity sports training required to compete at an Olympic level is sustainable without adverse effects in young individuals, and does not lead to impairment in cardiovascular structure or function^{20,21}. It is also clear that there is no epidemiological signal that high level

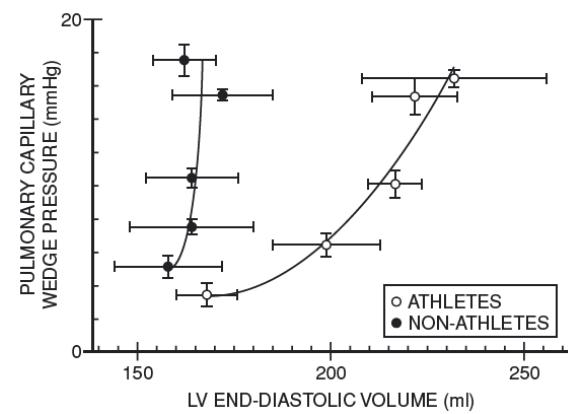


Figure 1: Directly measured cardiac pressure-volume curves for athletes and non-athletic controls. From Levine et al, Circulation 1991¹¹

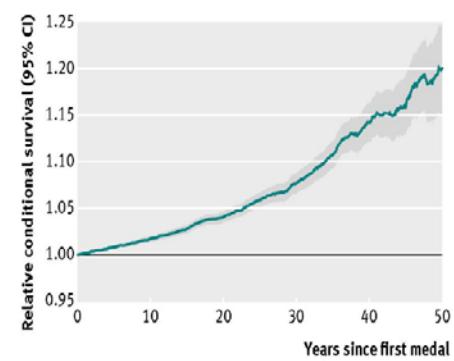


Figure 2: Data from ref 22, showing increase in survival of Olympic medalists compared to controls, which increases with the time since their first medal.

athletics leads to premature death; indeed quite the opposite. For example, when more than 15,000 Olympic medalists from 9 different country groups were examined over decades following their first medal, there was a progressive *increase* in conditional survival (compared to age and sex matched controls from the general population in those countries; fig 2)²² for the Olympic medalists which was greatest in the participants in endurance sports²³. Although there are many possible explanations for such a finding (such as socioeconomic status, or healthier lifestyles), the concept of increased rather than decreased survival in elite endurance athletes has been demonstrated repeatedly²⁴⁻²⁶, and was most recently buttressed by a study of nearly 800 French Tour de France competitors who experienced a substantial reduction in mortality (40%) compared to the French male non-cyclist population²⁷. Therefore although there is growing evidence that the heart may show some signs of fatigue^{28, 29}, especially of the right ventricle³⁰ after single bouts of extraordinary endurance effort³¹, which may be accompanied by the release of biomarkers of cell permeability³² there is little evidence that such physiological signals are pathological³³, and no rash of deaths in participants of long distance events such as marathons³⁴⁻³⁶.

In contrast, the evidence that high performing, Masters endurance athletes have healthy, youthful cardiovascular structure and function is quite robust. For example, in studies by our group, we recruited highly trained and very competitive endurance athletes who had been training for at least 25 years, competing successfully in multiple marathons, triathlons, or other endurance events and performed high resolution studies of cardiovascular structure and performance. Using invasive methods, we created cardiac pressure-volume curves in these athletes (Fig 3) and compared them to a group of highly screened, extremely healthy but sedentary seniors of the same age and sex distribution (mean 70±3 yrs, half women) and young (29±5 yrs) sedentary controls. Despite being very healthy, the sedentary seniors had hearts that were smaller and stiffer than the Masters athletes; most impressively, the athletes had cardiac compliance that was indistinguishable from healthy young controls³⁷.

The large blood vessels were similarly youthful in these athletes. For example, we developed a technique that can quantify the biological age of the aorta and applied it to this same group of Masters athletes and controls³⁸. As expected, both the healthy, sedentary seniors and young controls had biological aortic ages that were virtually identical with their chronological ages. However the biological aortic age of the Masters athletes was approximately 30 years “younger” than their chronological age (Fig

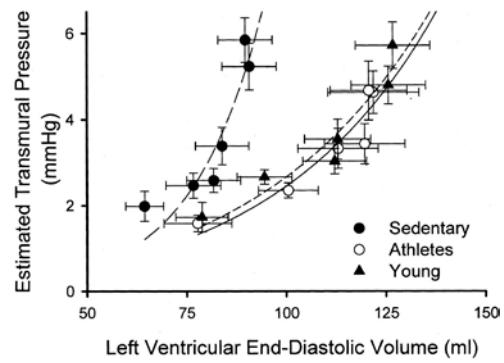


Figure 3: Data from ref 37; Diastolic limb of the pressure-volume curves for Masters athletes, sedentary but healthy seniors, and young controls; estimated transmural pressure derived from the difference betw

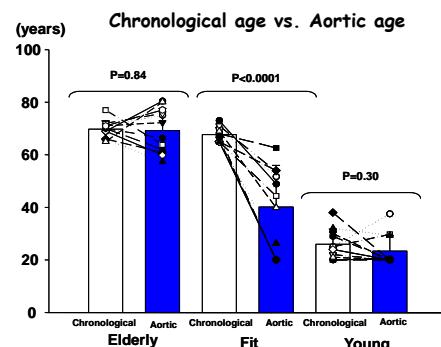


Figure 4: Data from ref 38; note that the biologic aortic age of both healthy, sedentary seniors and young controls matched their chronologic age exactly. However the fit Masters athletes had biologic aortic age that was 30 years younger.

4). The functional outcome of this improved myocardial and vascular compliance was that their ventricular-arterial coupling was substantially better (more than twice the increase in stroke volume for any given increase in LV filling pressure) than their healthy but unfit counterparts³⁹; enhanced ventricular-arterial coupling is also a hallmark of highly trained young endurance athletes.⁴⁰

This discussion is particularly important because some investigators have suggested that intense, marathon training leads to cardiac fibrosis⁴¹. However in this high profile study of 102 middle aged marathon runners, there was no statistically significant difference between the prevalence of positive delayed enhancement by cMRI in the athletes compared to a group of controls from the Heinz Nixdorf Recall Study. Multiple other studies have failed to confirm the development of delayed enhancement in marathon runners⁴²⁻⁴⁴, though it is clear that intense training in the setting of pre-existing coronary artery disease can lead to the development of ischemic type subendocardial scar⁴⁵. Indeed, training in the face of ischemia has been shown to result in prolonged, and cumulative myocardial stunning and LV dysfunction⁴⁶, and could be a mechanism of myocardial injury in athletes who train hard with undetected coronary artery disease. In our own studies of > 100 individuals performing varying doses of life-long exercise, including 21 elite Masters athletes, none showed delayed enhancement, except for one casual exerciser who had a non-coronary pattern of delayed enhancement⁴⁷.

Some animal studies examining structural changes with exercise training have been done, but are hard to interpret. Some do show fibrosis⁴⁸, though the training involved intense tail shock (perhaps a stress response, rather than an exercise response) to get the animals to train. Most importantly, there was no hint of fibrosis in the left ventricle – the

fibrosis was only in the RV free wall; and there was no evidence of *progressive* increases in fibrosis – the magnitude of the fibrosis was the same in rats sacrificed at 4, 8, and 16 weeks of training. This time independence suggests that the fibrosis likely was not a response to prolonged training (otherwise the fibrosis would have gotten progressively worse), but supports the idea that it might have been a response to the tail shock.

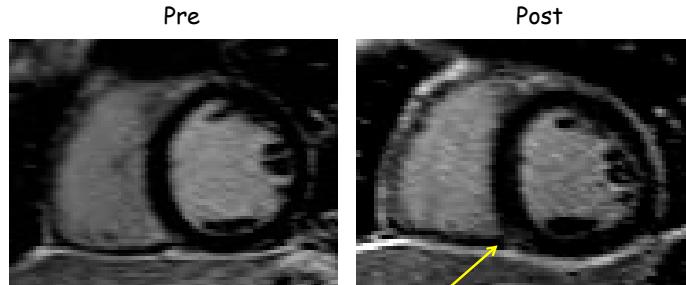


Figure 5: Images from ref 50. Note no evidence of gadolinium uptake in one of the world's most extreme endurance athletes prior to his race across America (Pre). However after running 1500 km and cycling 1500 km in 30 days, including substantial time at high altitude, there was delayed enhancement present at the ventricular insertion point (yellow arrow).

The RV has been shown to be susceptible to excessive strain during exercise⁴⁹, and in extraordinary, ultra-endurance athletes, a small fraction has been shown to have late gadolinium enhancement (LGE) at the RV/LV junction³¹. However this LGE may not necessarily represent fibrosis; for example there was no LGE present in one of the world's greatest ultra-endurance athletes despite many extreme events. However a small amount of LGE was identified at the ventricular insertion point immediately after a race across America⁵⁰ (Fig 5). Therefore this type of LGE may represent edema from acute, prolonged strain, rather than actual scar⁵¹ since it has been demonstrated to be reversible in other circumstances, such as repair of an ASD⁵². However caution should be taken for those individuals who

carry a desmosomal mutation for RV cardiomyopathy; training in such individuals can cause deterioration of RV function and accelerate the phenotype of RVC⁵³.

There has also been some concern articulated that older marathon runners have an excessive amount of coronary atherosclerosis⁵⁴. However in this study involving the same athletes reporting delayed enhancement in marathoners⁴¹, there actually was no difference in CAC between marathoners and age matched controls, and more of the marathoners had a CAC of zero. Most importantly, all of the marathoners in this study started training later in life, and 50% of them were smokers, raising the possibility that these individuals started training in an attempt to reverse the effects of adverse cardiovascular risk factors. Other evidence suggests that physiologically, the coronaries of elite ultra-endurance athletes are actually quite healthy^{55, 56}. For example, invasive measurement of coronary vasodilatory capacity (Fig 6) showed a markedly increased coronary diameter in response to nitroglycerin in ultra-endurance runners compared to sedentary controls⁵⁶. In addition, for individuals with subclinical CAD, as determined by a CAC>100, a high degree of fitness reduced the risk for CV events by a remarkable 75%⁵⁷ (Fig 7). Therefore although it is plausible that some marathoners might have higher levels of CAC based on an increase in PTH levels during running⁵⁸, any increase in marathoners as a group is modest, and functionally, their coronaries have superior vasomotor reserve, and reduced risk of plaque rupture.

Perhaps the most compelling data about the risks of prolonged, high intensity endurance exercise involve the risk for atrial fibrillation. Not only are the ventricles of endurance athletes larger than controls, but the atria are as well.⁵⁹ This adaptation likely arises because of the high flows achieved during exercise (from high cardiac output). Since the atrio-ventricular valves are closed during systole, and the HR increase during exercise occurs primarily because of a reduction in diastolic filling period, the a-v valves stay closed for an increasing proportion of the cardiac cycle, even as flow into the atria increase many fold (fig 8). This process leads to a dam like effect in the atria and contributes to atrial distension during exercise.⁶⁰ This

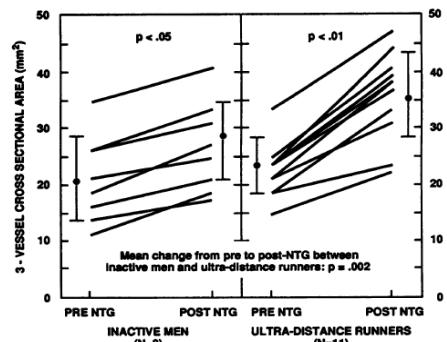


Figure 6: Data from ref 56. Note that the total cross-sectional area of the coronary circulation increased substantially more after intracoronary nitroglycerin in ultra-distance runners than inactive men.

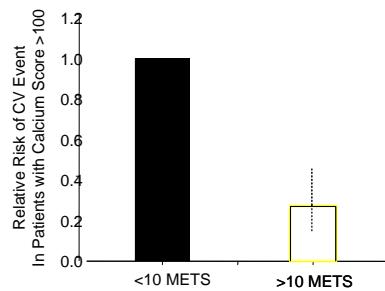


Figure 7: Data from ref 57. In a large number of patients from the Cooper Clinic Longitudinal Study with subclinical CAD as determined by a CAC score >100, high fit individuals had a dramatically reduced risk (75%) of suffering a cardiovascular event.

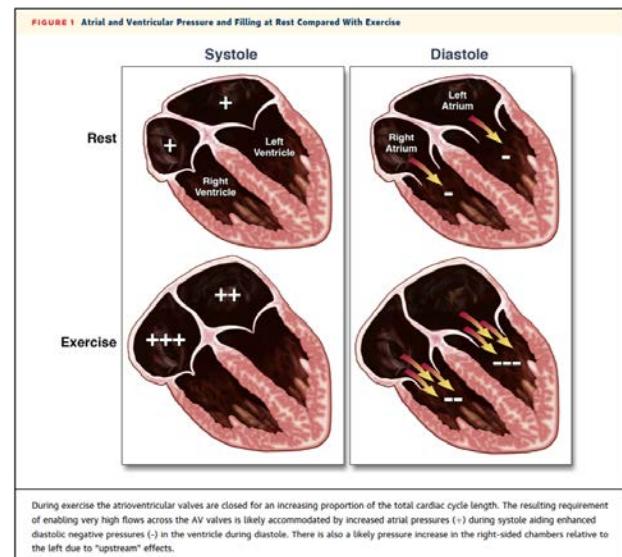


Figure 8 from reference 60. A-v valves "dam" during increases in HR (shortening of diastole) with exercise, leading to dilation/remodeling.

mechanical adaptation is compounded by a number of other adaptations including increased vagal tone, increased triggered activity, and perhaps atrial inflammatory responses to increase the risk of atrial fibrillation in competitive endurance athletes (fig 9).⁶¹ One meta-analysis has estimated the relative risk of developing atrial fibrillation in endurance athletes to be ~ 5 fold greater than the general population.⁶²

However it is important to emphasize that non-competitive endurance training does not increase the risk of afib⁶³, and may actually decrease it, especially compared to sedentary⁶⁴ or unfit⁶⁵ individuals.

Ongoing work from our group has shown that 2 years of endurance training in healthy middle aged individuals results in prominent increases in LV and LA size (though still well below that observed in life-long endurance athletes), but no increase in atrial ectopy or changes in atrial electrophysiology that might increase the risk of afib.

In summary, table 1 highlights the take home messages from this presentation. Although it would be foolish to argue that extraordinary endurance

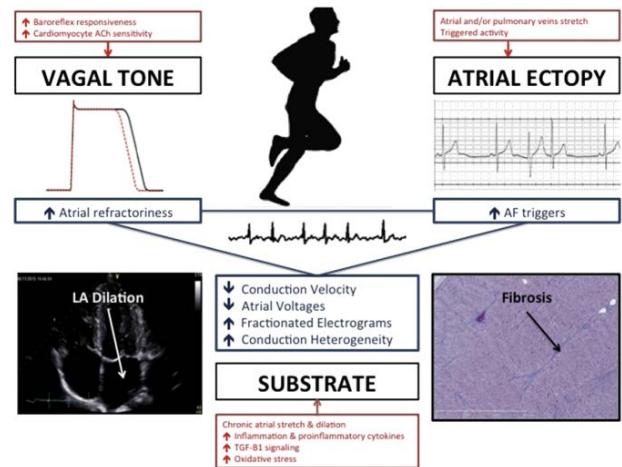


Figure 9 from ref 61. This summary depicts the electrical, neural, structural, and ultrastructural changes in endurance athletes which may increase the risk for atrial fibrillation.

Table 1: Summary and Take Home Messages

- 1). Athletes have large compliant hearts that generate a large stroke volume during exercise, as well as compliant arteries with large vasodilatory capacity;
- 2). The heart of the senior athlete, with a life-long pattern of intensive training, is youthfully compliant, equivalent to healthy 30 year olds, and their large blood vessels have a biological age ~ 30 years younger than their chronological age;
- 3). Acutely, extraordinary endurance exercise may cause fatigue of cardiac muscle, which seems to be more prominent in the right than the left ventricle. But this recovers quickly following even very long events and does not appear to stimulate pathological biological programs;
- 4). The older athlete is probably at increased risk for atrial fibrillation, though lower doses of physical activity do not appear to increase this risk;
- 5). The evidence that years of, intense training accelerates atherosclerosis or causes cardiac fibrosis is weak, and given the known and clear benefits of competitive training on both cardiac and vascular structure and function, not likely to be clinically important;
- 6). High intensity training in the presence of advanced atherosclerosis however, likely does increase the risk, especially if ischemia is present, and exercise training does not prevent the atherosclerotic process.

training can never be harmful, it is equally inappropriate to frighten individuals who wish to undertake competitive endurance training, including marathons, triathlons, or even ultra-endurance events based on fears of accelerating coronary artery disease or initiating a cardiomyopathic process.

References

1. Levine BD. Can intensive exercise harm the heart? The benefits of competitive endurance training for cardiovascular structure and function. *Circulation*. 2014;130:987-991
2. Eitzen DS. *Fair and foul: Beyond the myths and paradoxes of sport*. Plymouth, UK: Rowman and Littlefield; 2012.
3. Trivax JE, McCullough PA. Phidippides cardiomyopathy: A review and case illustration. *Clinical cardiology*. 2012;35:69-73
4. Golden M. *Sport and society in ancient greece*. Cambridge, UK: Cambridge University Press; 1998, 2000, 20003.
5. Thompson PD. D. Bruce dill historical lecture. Historical concepts of the athlete's heart. *Medicine and science in sports and exercise*. 2004;36:363-370
6. Baggish AL, Wood MJ. Athlete's heart and cardiovascular care of the athlete: Scientific and clinical update. *Circulation*. 2011;123:2723-2735
7. Prior DL, La Gerche A. The athlete's heart. *Heart*. 2012;98:947-955
8. 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. *Journal of the American College of Cardiology*. 2002;40:1856-1863
9. Riley-Hagan M, Peshock RM, Stray-Gundersen J, Katz J, Ryschon TW, Mitchell JH. Left ventricular dimensions and mass using magnetic resonance imaging in female endurance athletes. *The American journal of cardiology*. 1992;69:1067-1074
10. Milliken MC, Stray-Gundersen J, Peshock RM, Katz J, Mitchell JH. Left ventricular mass as determined by magnetic resonance imaging in male endurance athletes. *The American journal of cardiology*. 1988;62:301-305
11. 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*. 1991;84:1016-1023
12. Levine BD. Vo₂max: What do we know, and what do we still need to know? *The Journal of physiology*. 2008;586:25-34
13. Arbab-Zadeh A, Perhonen M, Howden E, Peshock RM, Zhang R, Adams-Huet B, Haykowsky MJ, Levine BD. Cardiac remodeling in response to 1 year of intensive endurance training. *Circulation*. 2014;9:2152-2161
14. Howden EJ, Perhonen M, Peshock RM, Zhang R, Arbab-Zadeh A, Adams-Huet B, Levine BD. Females have a blunted cardiovascular response to one year of intensive supervised endurance training. *Journal of applied physiology*. 2015;119:37-46
15. Weiner RB, DeLuca JR, Wang F, Lin J, Wasfy MM, Berkstresser B, Stohr E, Shave R, Lewis GD, Hutter AM, Jr., Picard MH, Baggish AL. Exercise-induced left ventricular remodeling among competitive athletes: A phasic phenomenon. *Circulation. Cardiovascular imaging*. 2015;8
16. Levine BD, Baggish AL, Kovacs RJ, Link MS, Maron MS, Mitchell JH, American Heart Association E, Arrhythmias Committee of Council on Clinical Cardiology CoCDiYCoC, Stroke Nursing CoFG, Translational B, American College of C. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: Task force 1: Classification of sports: Dynamic, static, and impact: A scientific statement from the american heart association and american college of cardiology. *Circulation*. 2015;132:e262-266
17. Harmon KG, Asif IM, Maleszewski JJ, Owens DS, Prutkin JM, Salerno JC, Zigman ML, Ellenbogen R, Rao AL, Ackerman MJ, Drezner JA. Incidence, cause, and comparative frequency of sudden

- cardiac death in national collegiate athletic association athletes: A decade in review. *Circulation*. 2015;132:10-19
18. Venckunas T, Lionikas A, Marcinkeviciene JE, Raugaliene R, Alekrinskis A, Stasiulis A. Echocardiographic parameters in athletes of different sports. *Journal of sports science & medicine*. 2008;7:151-156
 19. D'Ascenzi F, Pelliccia A, Alvino F, Solari M, Loffreno A, Cameli M, Focardi M, Bonifazi M, Mondillo S. Effects of training on lv strain in competitive athletes. *Heart*. 2015;101:1834-1839
 20. Pelliccia A, Kinoshita N, Pisicchio C, Quattrini F, Dipaolo FM, Ciardo R, Di Giacinto B, Guerra E, De Blasis E, Casasco M, Culasso F, Maron BJ. Long-term clinical consequences of intense, uninterrupted endurance training in olympic athletes. *Journal of the American College of Cardiology*. 2010;55:1619-1625
 21. Bhella PS, Levine BD. The heart of a champion. *Journal of the American College of Cardiology*. 2010;55:1626-1628
 22. 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*. 2012;345:e8308
 23. 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. *British journal of sports medicine*. 2015;49:898-902
 24. Sarna S, Sahi T, Koskenvuo M, Kaprio J. Increased life expectancy of world class male athletes. *Medicine and science in sports and exercise*. 1993;25:237-244
 25. Chakravarty EF, Hubert HB, Lingala VB, Fries JF. Reduced disability and mortality among aging runners: A 21-year longitudinal study. *Archives of internal medicine*. 2008;168:1638-1646
 26. 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. *Journal of internal medicine*. 2003;253:276-283
 27. 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). *European heart journal*. 2013;34:3145-3150
 28. Douglas PS, O'Toole ML, Hiller WD, Hackney K, Reichek N. Cardiac fatigue after prolonged exercise. *Circulation*. 1987;76:1206-1213
 29. Oxborough D, Birch K, Shave R, George K. "Exercise-induced cardiac fatigue"--a review of the echocardiographic literature. *Echocardiography*. 2010;27:1130-1140
 30. 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. Cardiovascular imaging*. 2011;4:253-263
 31. 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. *European heart journal*. 2012;33:998-1006
 32. Shave R, Baggish A, George K, Wood M, Scharhag J, Whyte G, Gaze D, Thompson PD. Exercise-induced cardiac troponin elevation: Evidence, mechanisms, and implications. *Journal of the American College of Cardiology*. 2010;56:169-176
 33. Hill JA, Olson EN. Cardiac plasticity. *The New England journal of medicine*. 2008;358:1370-1380
 34. Roberts WO. A 12-yr profile of medical injury and illness for the twin cities marathon. *Medicine and science in sports and exercise*. 2000;32:1549-1555
 35. Roberts WO, Maron BJ. Evidence for decreasing occurrence of sudden cardiac death associated with the marathon. *Journal of the American College of Cardiology*. 2005;46:1373-1374

36. 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 G. Cardiac arrest during long-distance running races. *The New England journal of medicine*. 2012;366:130-140
37. Arbab-Zadeh A, Dijk E, Prasad A, Fu Q, Torres P, Zhang R, Thomas JD, Palmer D, Levine BD. Effect of aging and physical activity on left ventricular compliance. *Circulation*. 2004;110:1799-1805
38. Shibata S, BD L. Biologic aortic age derived from the arterial pressure waveform. *J Appl Physiol*. 2011;110:981-987
39. Shibata S, Hastings JL, Prasad A, Fu Q, Okazaki K, Palmer MD, Zhang R, Levine BD. 'Dynamic' starling mechanism: Effects of ageing and physical fitness on ventricular-arterial coupling. *The Journal of physiology*. 2008;586:1951-1962
40. Florescu M, Stoicescu C, Magda S, Petcu I, Radu M, Palombo C, Cintea M, Lichiardopol R, Vinereanu D. "Supranormal" cardiac function in athletes related to better arterial and endothelial function. *Echocardiography*. 2010;27:659-667
41. 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*. 2009;251:50-57
42. Trivax JE, Franklin BA, Goldstein JA, Chinnaiyan KM, Gallagher MJ, deJong AT, Colar JM, Haines DE, McCullough PA. Acute cardiac effects of marathon running. *Journal of applied physiology*. 2010;108:1148-1153
43. 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. *The American journal of cardiology*. 2009;103:1467-1472
44. 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. *Clinical science*. 2011;120:143-152
45. 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. *Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance*. 2012;14:58
46. Homans DC, Laxson DD, Sublett E, Lindstrom P, Bache RJ. Cumulative deterioration of myocardial function after repeated episodes of exercise-induced ischemia. *The American journal of physiology*. 1989;256:H1462-1471
47. Abdullah SM, Barkley KW, Bhella PS, Hastings JL, Matulevicius S, Fujimoto N, Shibata S, Carrick-Ranson G, Palmer MD, Gandhi N, DeFina LF, Levine BD. Lifelong physical activity regardless of dose is not associated with myocardial fibrosis. *Circulation. Cardiovascular imaging*. 2016;9
48. 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*. 2011;123:13-22
49. 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. *Medicine and science in sports and exercise*. 2011;43:974-981
50. Bhella PS, Kelly JP, Peshock R, Levine BD. Delayed enhancement of the intraventricular septum following an extraordinary endurance exercise. *BMJ case reports*. 2010;2010

51. Sato T, Tsujino I, Ohira H, Oyama-Manabe N, Ito YM, Noguchi T, Yamada A, Ikeda D, Watanabe T, Nishimura M. Paradoxical interventricular septal motion as a major determinant of late gadolinium enhancement in ventricular insertion points in pulmonary hypertension. *PLoS one*. 2013;8:e66724
52. Sato T, Tsujino I, Ohira H, Oyama-Manabe N, Nishimura M. Paradoxical motion of the interventricular septum as a primary mechanism of late gadolinium enhancement at ventricular insertion points. *International journal of cardiology*. 2012;158:156-157
53. 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. *Journal of the American College of Cardiology*. 2013;62:1290-1297
54. 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, Marathon Study I, Heinz Nixdorf Recall Study I. Running: The risk of coronary events : Prevalence and prognostic relevance of coronary atherosclerosis in marathon runners. *European heart journal*. 2008;29:1903-1910
55. Levine BD, Mitchell JH. 'Ultra' coronary arteries: Bigger and better? [editorial; comment]. *Circulation*. 1993;87:1402-1404
56. Haskell WL, Sims C, Myll J, Bortz WM, St Goar FG, Alderman EL. Coronary artery size and dilating capacity in ultradistance runners. *Circulation*. 1993;87:1076-1082
57. LaMonte MJ, Fitzgerald SJ, Levine BD, Church TS, Kampert JB, Nichaman MZ, Gibbons LW, Blair SN. Coronary artery calcium, exercise tolerance, and chd events in asymptomatic men. *Atherosclerosis*. 2006;189:157-162
58. Scott JP, Sale C, Greeves JP, Casey A, Dutton J, Fraser WD. The effect of training status on the metabolic response of bone to an acute bout of exhaustive treadmill running. *The Journal of clinical endocrinology and metabolism*. 2010;95:3918-3925
59. 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. *Journal of the American College of Cardiology*. 2005;46:690-696
60. La Gerche A, Claessen G. Increased flow, dam walls, and upstream pressure: The physiological challenges and atrial consequences of intense exercise. *JACC. Cardiovascular imaging*. 2016;9:1389-1391
61. Sanchis-Gomar F, Lucia A. Pathophysiology of atrial fibrillation in endurance athletes: An overview of recent findings. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne*. 2016;188:E433-E435
62. 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 : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology*. 2009;11:1156-1159
63. Ofman P, Khawaja O, Rahilly-Tierney CR, Peralta A, Hoffmeister P, Reynolds MR, Gaziano JM, Djousse L. Regular physical activity and risk of atrial fibrillation: A systematic review and meta-analysis. *Circulation. Arrhythmia and electrophysiology*. 2013;6:252-256
64. Morseth B, Graff-Iversen S, Jacobsen BK, Jorgensen L, Nyrnes A, Thelle DS, Vestergaard P, Lochen ML. Physical activity, resting heart rate, and atrial fibrillation: The tromso study. *European heart journal*. 2016;37:2307-2313
65. Faselis C, Kokkinos P, Tsimploulis A, Pittaras A, Myers J, Lavie CJ, Kyritsi F, Lovic D, Karasik P, Moore H. Exercise capacity and atrial fibrillation risk in veterans: A cohort study. *Mayo Clinic proceedings*. 2016;91:558-566

