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.

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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 Phidipiddes has been used by some to highlight the dangers of extreme endurance efforts [3], much more ubiquitous is the Greek model of the athlete as physical perfection, allowing vigor through to great age [4].

The term "athlete's heart" was originally coined to reflect its similarities to patients with enlarged hearts from disease [5], though it is now recognized to reflect the unique physiological adaptation of the endurance athlete [6, 7]: a heart that is big[8], muscular[9, 10], compliant[11], and can pump a lot of blood very fast, to support high rates of aerobic metabolism[12]. 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]

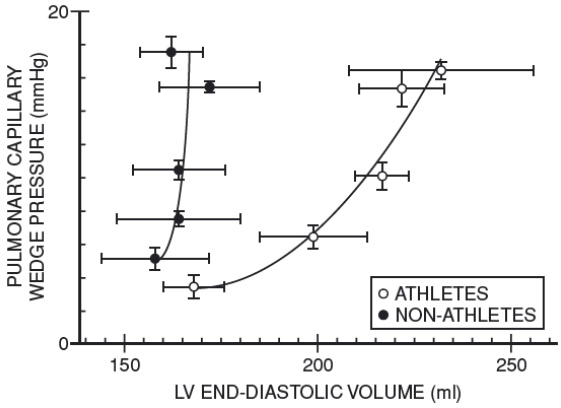

Figure 1: Directly measured cardiac pressure-volume curves for athletes and non-athletic controls. From Levine et al, Circulation 1991[11]

Recent longitudinal studies by our group[13, 14] and others [15]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 sports[17], 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]

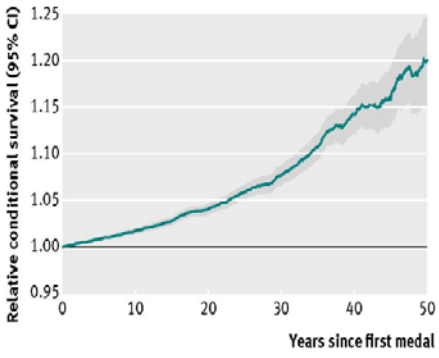

Figure 2: Data from ref 22, showing increase in survival of Olympic medalists compared to controls, which increases with the time since their first medal.

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

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 sports[23]. 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 repeatedly[24-26], 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 population[27]. Therefore although there is growing evidence that the heart may show some signs of fatigue[28, 29], especially of the right ventricle[30] after single bouts of extraordinary endurance effort[31], which may be accompanied by the release of biomarkers of cell permeability[32] there is little evidence that such physiological signals are pathological[33], and no rash of deaths in participants of long distance events such as marathons[34-36].

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 controls[37].

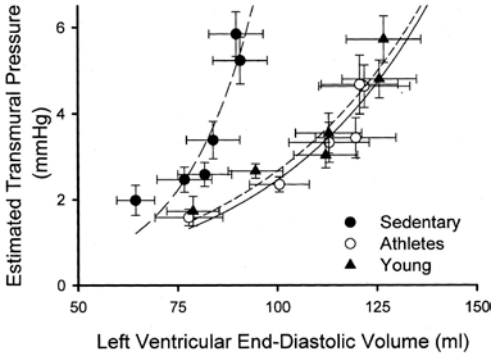

Figure 3: Data from ref 37; Diastolic limb of the pressure-volume curves for Masters athletes, sedentary but healthy seniors, and young controls; estimated transmural pressure derived from the difference betw

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 controls[38]. 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

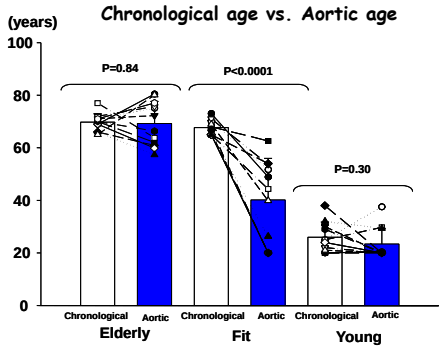

Figure 4: Data from ref 38; note that the biologic aortic age of both healthy, sedentary seniors and young controls matched their chronologic age exactly. However the fit Masters athletes had biologic aortic age that was 30 years younger.

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 counterparts[39]; 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 fibrosis[41]. 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 runners [42-44], 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 scar[45]. Indeed, training in the face of ischemia has been shown to result in prolonged, and cumulative myocardial stunning and LV dysfunction[46], 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 enhancement[47].

Some animal studies examining structural changes with exercise training have been done, but are hard to interpret. Some do show fibrosis[48], 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.

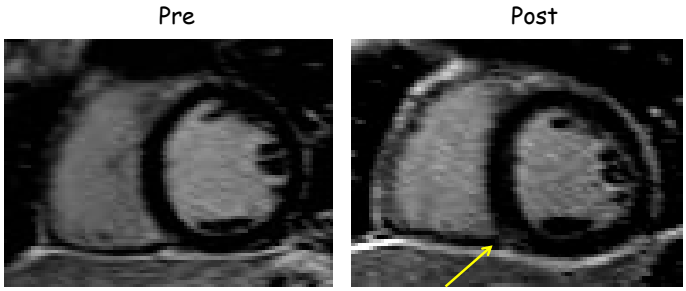

Figure 5: Images from ref 50. Note no evidence of gadolinium uptake in one of the world's most extreme endurance athletes prior to his race across America (Pre). However after running 1500 km and cycling 1500 km in 30 days, including substantial time at high altitude, there was delayed enhancement present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

The RV has been shown to be susceptible to excessive strain during exercise[49], and in extraordinary, ultra-endurance athletes, a small fraction has been shown to have late gadolinium enhancement (LGE) at the RV/LV junction[31]. 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 America[50] (Fig 5). Therefore this type of LGE may represent edema from acute, prolonged strain, rather than actual scar[51] since it has been demonstrated to be reversible in other circumstances, such as repair of an ASD[52]. 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 RVC[53].

There has also been some concern articulated that older marathon runners have an excessive amount of coronary atherosclerosis[54]. However in this study involving the same athletes reporting delayed enhancement in marathoners[41], 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 controls[56]. 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 running[58], any increase in marathoners as a group is modest, and functionally, their coronaries have superior vasomotor reserve, and reduced risk of plaque rupture.

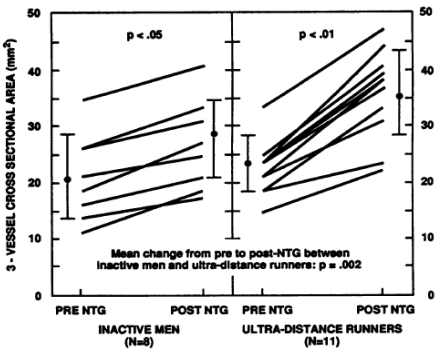

Figure 6: Data from ref 56. Note that the total cross-sectional area of the coronary circulation increased substantially more after intracoronary nitroglycerin in ultra-distance runners than inactive men.

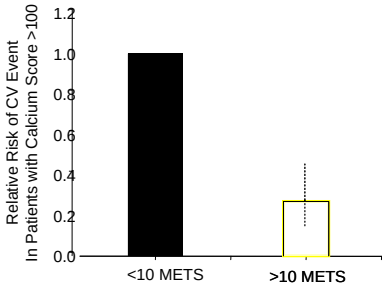

Figure 7: Data from ref 57. In a large number of patients from the Cooper Clinic Longitudinal Study with subclinical CAD as determined by a CAC score >100, high fit individuals had a dramatically reduced risk (75%) of suffering a cardiovascular event.

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 atrial 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

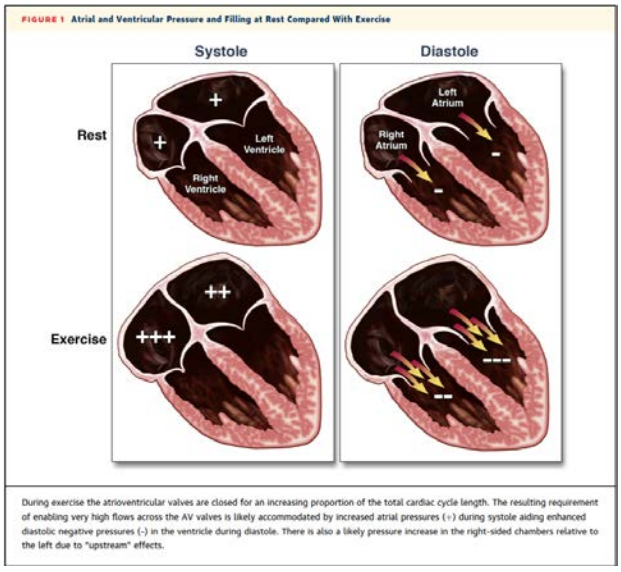

Figure 8 from reference 60. A-v valves "dam" during increases in HR (shortening of diastole) with exercise, leading to dilation/remodeling.

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 afib[63], and may actually decrease it, especially compared to sedentary [64] or unfit[65] 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.

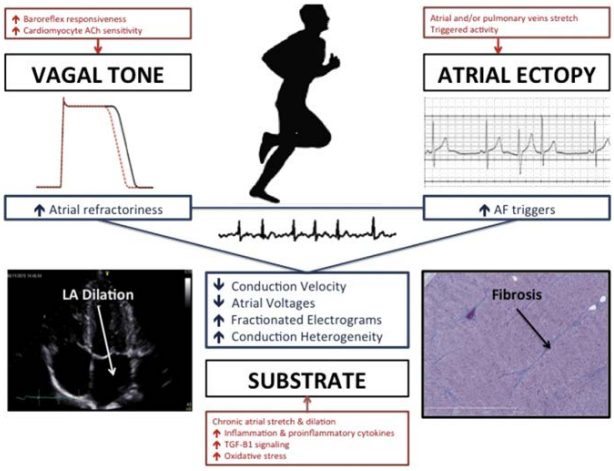

Figure 9 from ref 61. This summary depicts the electrical, neural, structural, and ultrastructural changes in endurance athletes which my increase the risk for atrial fibrillation.

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

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.

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