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Editorial Commentary: Relationship between strenuous exercise and cardiac "morbimortality": Benefits outweigh the potential risks

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Although it is well known that regular exercise promotes health and longevity, there is growing concern about the potential association between long-term strenuous endurance exercise [hereinafter strenuous exercise (SE)] and higher risk of some acute or chronic cardiac conditions [1,2]. In the current issue of the *Trends in Cardiovascular Medicine*, a timely article by Merghani et al. from the research group led by Sanjay Sharma, nicely reviews the scientific evidence available on the impact of SE on the healthy human heart [3]. Based on a thorough literature search, the authors raise doubts about the potential cause–effect relationship between SE and increased risk of cardiac conditions, particularly coronary heart disease (CAD), myocardial fibrosis or right ventricular (RV) dysfunction (as shown in Figure 1 of their paper) [3]. We do agree with Merghani et al. for the reasons that are explained below.

First, cardiac adaptations to SE are usually healthy ones and, even those at the outer normal limits are generally reversible. The term "athletes' heart" is characterized by enlargement of the heart together with a slowed heart rate induced by years of SE [4]. Such prolonged and usually intense training provokes an increase in both LV internal size (LV dilation) and muscle mass (LV hypertrophy, LVH), with normal or supra-normal LV systolic/diastolic function [5–8]. Endurance athletes also have greater ventricular diastolic chamber compliance and distensibility compared with non-athletes and thus operate on the steep portion of the Starling curve [9]. The aforementioned training-induced changes are physiological adaptations; that is, they tend to disappear with training cessation. In contrast with pathological LVH, the septal wall thickness of healthy athletes decreases after only 3 months of detraining [10]. The LV cavity dimension returns to baseline levels after 1–13 years of training cessation [11]. Although LV end-diastolic diameter can remain elevated up to 5 years of detraining, this dilation is not accompanied by impaired LV function nor does it lead to adverse cardiac events [12]. Likewise, LV mass increases in athletes are virtually always associated with normal ejection fraction at rest, whereas systolic volume is normal or augmented [6,13–16]. Importantly, and contrary to conventional thinking, regular SE does not seem to represent a primary cardiac "volume overload" stimulus [17]. Thus, in sedentary people trained intensively for 12 months such as to finish a marathon, the LV showed concentric remodeling during the first 6–9 months but returned to normal mass-to-volume ratio thereafter whereas the RV showed a balanced remodeling, i.e., eccentric hypertrophy with normal mass-to-volume-ratio, throughout the entire program [17].

The potential negative effects of SE on RV remodeling, biomarkers of myocardial damage or accelerated heart failure are also receiving growing attention [18,19]. However, RV dysfunction or perhaps more appropriately termed "fatigue" typically reverses within 24–48 h of recovery [20], and does not seem to stimulate pathological biological pathways [8]. In

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fact, no case of RV dysfunction has been reported in cohorts of middle-aged ultra-marathon runners [21] or former top athletes [22]. Except for the recent provocative work by La Gerche and Heidbuche [19]and La Gerche et al. [23,24], who reported right heart dysfunction after SE, the vast majority of the echocardiographic data published in the last 4 decades show no pathological changes in LV/RV function or cardiac dimensions in top athletes [25].

Similarly, epidemiological evidence does not support the hypothesis that long-term SE affects cardiovascular disease (CVD)-related mortality in elite endurance athletes. On the contrary, the CVD-related mortality of former top-level athletes [n = 42,807 (707 women) including Olympic-class marathoners or Tour de France finishers] was considerably lower compared with the general population [i.e., standard mortality rate of 0.73 (95% CI: 0.65–0.82; $P < 0.001$)] [26]. In a Finnish study, the hazard ratio (HR) for CVD was lower in endurance athletes compared with controls (HR = 0.68; 95% CI: 0.54–0.86). Another Finnish male population-based cohort study reported lower probability of initiating medication for CVD (HR = 0.72; 95% CI: 0.58–0.89) in former elite endurance athletes [27]. These findings are in agreement with previous epidemiological data in more than 50,000 Scandinavians participating in ultra-endurance cross-country ski events who showed 57% lower CVD-mortality compared to non-athletic controls [28]. Recent findings by Marijon et al. [29] are also eloquent, showing 33% lower CVD-mortality among 786 French cyclists who competed in 1 or more editions of the Tour de France during 1947–2012 compared with the reference population.

Although the existence of a possible dose–response benefit of SE remains more uncertain compared with less intense exercise, the current body of knowledge does not support a dose-related harm, that is, the existence of a J- or U-shaped relationship between SE loads and mortality remains to be convincingly demonstrated. In the bulk of original studies and meta-analyses [30–35], the mortality/exercise curve shows a steep decrease in mortality from sedentary behavior to moderate exercise, a more attenuated decrease from moderate to vigorous exercise activity, and finally a plateau (yet not really an increase) with heavy exercise (i.e., SE) with NO evidence of a worsening of survival compared directly to lower doses of training. In a 15-year follow-up of 55,137 adult men/women, runners had lower CVD-mortality (−45%) compared with non-runners, although no dose–benefit was found [36]. A study of 1878 joggers reported lower mortality among joggers than non-joggers irrespective of training loads, yet the greatest benefits have been shown for lower loads (≤150 min/week at a slow/average speed) [37]. A study with 416,175 adults found no additional mortality benefits for >50 min/day of SE [38]. A 21-year follow-up showed that endurance runners aged ≥50 years and performing ~270 min/week of SE had 39% lower mortality than those engaging in lower loads (~70 min/week) [39]. An 8-year longitudinal analysis of 35,402 male runners showed that running >9 km/day decreased angina (−65%), nonfatal cardiac heart disease (−29%), and both fatal/nonfatal cardiac heart disease risk (−26%) compared to running less than 3 km/day [40]. A prospective study of 44,551 men reported that SE (e.g., running) was slightly (+4%) more protective than moderate exercise in decreasing CVD risk [41]. Although the relative risk of sudden cardiac death (SCD) increases 16.9-fold during or up to 30 min after SE, the absolute risk is very low (1/1.51M episodes of exertion), and in fact decreases with habitual exercise [42]. Notably, the incidence of SCD in US was only 0.39 [43], 0.75/100,000 runners for half-marathons/marathons [44], and 1.5/100,000 participants for triathlons [45].

Concerns about the potential association between SE and higher risk of arrhythmias, in particular atrial fibrillation (AF) also exist. More research is needed, but potential causative factors in previously healthy long-term exercisers include left-atrial (LA) enlargement or fibrosis, increased parasympathetic tone and inflammation [46–49]. Light-moderate exercise (e.g., walking) is associated with lower risk of AF in older adults [8,50] and a recent pooled analysis of 4 studies showed no association between increasing amount of time spent on physical activity and AF [51]. In contrast, long-term practice of SE raises the risk of AF, particularly lone AF [52–56]. Although there is no widespread agreement [57,58], the association seems stronger in highly competitive athletes.

Finally, Masters athletes represent a population of special interest. The heart of the senior athlete is youthfully compliant (equivalent to healthy 30-year old) [8]. Masters athletes (65–73 years), show a much younger biological aortic age compared with their chronological age [59]. In addition, during healthy aging, a sedentary lifestyle is associated with decreased left ventricular (LV) compliance and diastolic performance, whilst endurance training preserves ventricular compliance, thereby preventing heart failure in later life [60]. Likewise, “committed” (4–5 training sessions/week) or “competitive” Masters level athletes (6–7 sessions/week) show greater LV distensibility and compliance as well as lower LV stiffness constants compared with their sedentary peers [61]. Further, the ventricular-arterial coupling is impaired with human ageing possibly due to ventricular-arterial stiffening whereas life-long daily exercise training may minimize this impairment [62].

In summary, it seems that, overall, a cause–effect relationship between SE and cardiac alterations other than AF cannot be clearly established in humans. Convincing evidence is lacking that athlete's heart remodeling leads to long-term cardiac disease; on the contrary, it represents a physiological adaptation leading to improved cardiac compliance and performance. Nonetheless, the possible association with cardiac diseases cannot be excluded in some high-level athletes and certainly deserves further research.

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