LOOKING AT THE HEART OF ENDURANCE RUNNING

SPECIFIC CARDIOVASCULAR CHALLENGES, BENEFITS, AND RISKS

– Written by Maria-Carmen Adamuz, Qatar, Juliette van Hattum, Netherlands, and Guido Pieles, Qatar

Running 42195 meters close to the two-hour barrier is a marvelous achievement, reserved only for the top elite marathon runners in the world. Combining an optimal VO2max and specific physiological, biomechanical and other individual performance attributes, make success over this distance one of the most celebrated achievements in elite and amateur sports[1].

The number of running enthusiasts aiming to prove themselves over the marathon increases yearly. However, most of them are far from the make-up of the elite runners testing the now not-so-unthinkable-anymore sub-2-hour marathon. For many athletes, the marathon would be their first intense encounter with athletics and running in their life, often unaware that they face one of the biggest challenges in sports—for their hearts!

Training for and running a marathon require a significant cardiovascular performance. During the marathon, cardiac output increases significantly and the volume of blood expelled with each beat (stroke volume) remains persistently at levels of up to 75% of its exercise maximum due to increased diastolic filling and ventricular emptying[2]. Pulmonary artery pressure may rise to 70% over baseline values and remains elevated throughout the race[3]. This volume and pressure overload increases the right ventricle (RV) workload 3.6- to 5.2-fold, whereas the same exercise results in a 2.1- to 2.8-fold increase in left ventricle (LV) workload[3,4]. Repeated exposure to these demands lead to significant structural and functional changes of the heart. While most of the cardiac adaptive changes are also seen in other sports, the duration and persistence of this adaptation is unique to endurance sports.

As a result, the relationship between life-long endurance running and cardiovascular health has been the focus of attention in the Sports Cardiology community. For lifelong participants' hearts, endurance running has a "dark side". This "dark side" includes evidence of increased coronary calcification and coronary atherosclerosis, increased prevalence of atrial fibrillation in the long term as well as higher prevalence of myocardial fibrosis in endurance athletes which may increase the risk for arrhythmic events.

For this paper, we have chosen to focus on two of the most well-documented cardiac abnormalities affecting endurance runners, especially marathon runners: atrial fibrillation and coronary atherosclerosis. This review does not specifically target the elite athlete as most runners are recreational athletes; therefore, most evidence come from this group. More specifically: mostly middle-aged male participants, the group of sports enthusiasts most commonly diagnosed with atrial fibrillation and coronary atherosclerosis.

ATRIAL FIBRILLATION IN ENDURANCE ATHLETES

Atrial fibrillation (AF) is a common dilemma in the over-40 athletic population, in particular males engaging in endurance sports such as running. AF is characterised by irregular atrial electrical activity that replaces normal sinus rhythm. This leads to loss of regular atrial contraction and atrial–

Image: Illustration.

ventricular synchrony during ventricular diastolic filling. This condition increases the risk of thromboembolic events, heart failure, and, subsequently, mortality. In addition to potential adverse health outcomes, and specifically relevant to athletes, AF also impairs cardiac efficiency thus significantly affecting exercise capacity and athletic performance. AF is not uncommon in the athletic population. Although risk factors for this condition are well-established for both the non-athletic and athletic populations, the picture remains complex. While overall regular exercise, including moderate endurance training, protects individuals from AF occurrence[5,6], the relationship between exercise and AF is less clear. Risk factors for the development of AF, such as chronic volume overload and atrial dilation, are common findings of athletic adaptation in endurance athletes. This is also true for the increased parasympathetic (vagal) resting activity combined with sudden and frequent adrenergic activation during exercise; both proven to be risk factors for AF in athletes[7], but also common physiological adaptation in athletes.

These physiological changes are especially prevalent when practising endurance sports. Long-term strenuous endurance exercise—like cycling, marathon running, triathlon and cross-country skiing—has been associated with an increased risk of developing AF in healthy young or middle-aged adults[6,8–11]. This higher risk translates to a 2- to 10-fold increased risk in incidence of AF when compared to the general age matched non-athletic population[11,12]. A recent meta-analysis suggested that mixed sports (including track and field activities such as short distance running, given their repeated bouts of high-intensity exercise) could also pose a higher AF risk. However, compared to endurance sports, the risk for AF is much lower in these disciplines[13].

Importantly, recent evidence points to a dose related AF risk association. Endurance exercise of low-to-moderate intensity not only prevents the onset of AF[5,6,8–10] but might also reduce symptoms linked to AF, and decrease both mortality and morbidity in affected individuals. However these beneficial effects depend on the exercise dose. High training volume and intensity increase the AF risk with a typical U-shaped correlation between the incidence of AF and extensive or prolonged exercise[14]. This is likely due to the repetitive and sustained increase in volume and pressure loading while exercising. Combined with atrial wall stretching, induced by long-term engagement in rigorous endurance exercise, this may trigger microtrauma. Microtrauma causes inflammation and fibrosis, both of which have arrhythmogenic potential[15]. Marathon runners, for example, showed a markedly higher annual isolated AF incidence rate of 0.43/100, when compared to sedentary men 0.11/100[10]. Yet, in this study, there was no quantitative relationship between the exact amount of exercise and AF making it difficult to give practical advice on the optimal training volume and intensity to marathon athletes.

Other studies, however, did find a relationship between the amount of exercise and risk to developing AF in endurance athletes. Compared to individuals who exercised less than once a week, endurance athletes (at the age of 30, who were physically more active than five times a week) had a higher risk of AF (RR=1.19)[8]. Another study found a higher risk of developing AF in athletes who engaged in lifetime endurance exercise >1.500 hours (OR=2.87)[16]. A third study found a higher risk of AF in joggers who exercised five to seven times a week (RR=1.53)[6]. Lastly, female athletes who performed prolonged (>40 years) intensive endurance exercise, had

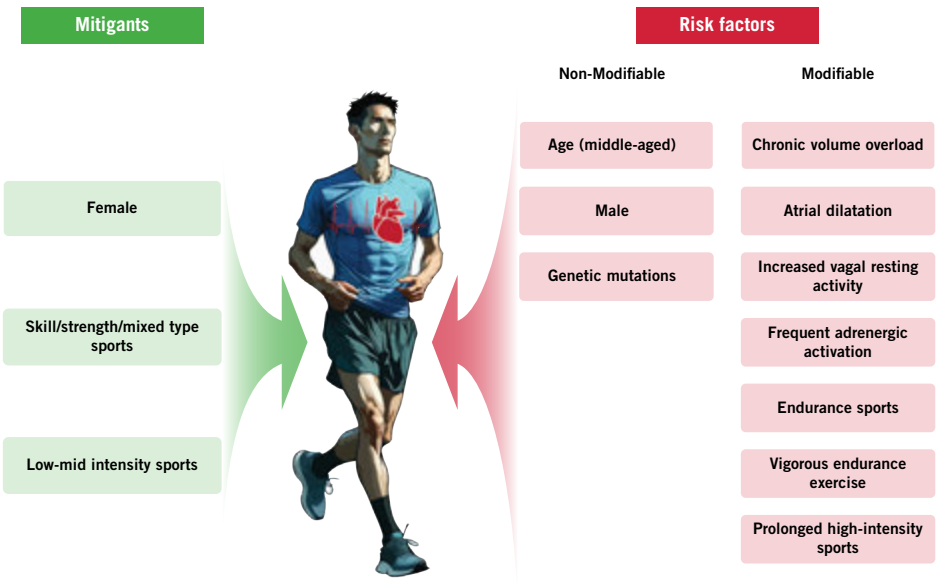

Figure 1: Mitigants and risk factors for the development of atrial fibrillation in athletes.

a higher risk of AF[17,18]. However, as you will read below, the incidence of AF in female athletes is significantly lower compared to their male counterparts.

In sum, prolonged intensive exercise might increase the risk of developing AF. However, the exact optimum dose of exercise is yet to be determined especially taking volume, intensity, and frequency of the sport into account. In addition, important factors such as gender, age and genetic predisposition should form part of the equation. A simple prescription of 'how much exercise is optimal' certainly requires a tailored and individualized approach; at present, challenging and probably not possible yet. Much is known however about the modulating factors when it comes to the risk for AF in athletes.

Gender and AF in athletes

In general, the risk of AF in female athletes appears to be markedly lower than in male athletes. Reasons for this discrepancy include a lower level of atrial remodelling and dilation, and sex hormone differences resulting in higher vagal tone at rest and during exercise in women[17]. Interestingly, the relationship between endurance sports and the onset of AF, has also been demonstrated in female athletes[18]. Importantly, to date, most studies investigated AF in male athletes.

Atrial fibrillation and age in athletes

As we get older, our hearts' atria become more stiff and dilated resulting in a higher risk of AF (>10% when older than 80 years) in the general population[5]. Age also plays a role in modulating AF risk among athletes. The prevalence of AF varies from 0.3% in younger elite athletes (24 years) to up to 12.8% in older athletes (60-89 years)[19,20]. Above the age of 60, AF is more likely to be caused by acquired structural heart disease irrespective of other factors. As such, it is the middle-aged healthy athlete who is most prone to developing AF associated to endurance training. And although AF among younger athletes is rare, it has been described even in 24-year-old male athletes[21]. At present, the aetiology in the younger healthy athlete population is thought to be individual genetic susceptibility, atrial dilatation, and an increased adrenergic surge during exercise resulting in a high vagal resting tone. In contrast, AF in healthy older athletes is often triggered by an enhanced vagal response after exercise, a consequence of standard secondary autonomic dysfunction[7].

Genetics and AF in athletes?

Genetics might indeed play an important role in the development of AF in endurance athletes. However, we still lack conclusive studies investigating the interplay between genetics, AF and exercise in humans. Studies of relatives with AF suggest a genetic basis for the condition, especially in younger subjects. While the relationship between AF and athletes seems to be multifactorial, the role of genetics should be acknowledged. High-quality studies to better understand the interplay between genetics, AF and exercise could inform better and individually-tailored risk guidelines for athletes—genetic susceptibility to AF is likely to be multigenetic with genetic and epigenetic modifiers making the picture too complex to confidently risk stratify at the moment.

In summary, atrial fibrillation is one of the most common arrhythmias of an aging population, and its incidence is highest in older, sedentary individuals with co-morbidities. It is important to appreciate that causal factors for AF (Figure 1) such as chamber dilatation, altered vagal and sympathetic autonomous activity, cardiac micro-injury and inflammation, and genetic susceptibility are all part of an adaptive and possibly maladaptive cardiac response in endurance athletes. A documented age-specific increased incidence of AF in athletes compared to the sedentary population—with a clear dose-response relationship—reflects this. So, when it comes to endurance exercise while your heart keeps beating in rhythm, the classic Greek mantra of "nothing in excess" certainly applies!

CORONARY ATHEROSCLEROSIS IN MARATHON RUNNERS

In 1977, Thomas Bassler[22] published an article in the Annals of the New York Academy of Sciences with the hypothesis that marathon running confers immunity against coronary atherosclerosis. At the time, the American Medical Joggers Association (AMJA) considered marathon runners the ideal population to study the effects of their specific active lifestyle in the prevention of atherosclerosis[22]. Also in 1977, James Fuller Fixx published his best-selling book "The Complete Book of Running". This book contributed significantly to popularizing the sport of running and spreading the undisputed health benefits of regular jogging. Tragically and somewhat ironically, Fixx died of a heart attack while jogging in 1984, at 52 years of age; the autopsy, revealed the presence of severe coronary atherosclerosis with severe

obstructions of the three main coronary arteries.

Coronary artery disease (CAD) is the most common cause of death in athletes over 35 years of age[23–25], and the most common cause of cardiac arrest and sudden cardiac death (SCD) in marathon runners[26,27]. While the cardiovascular benefits of regular physical activity are well established, the potential detrimental long-term effects of marathon and ultra-endurance running on the cardiovascular system—and particularly on the coronary arteries—have been a matter of controversy in recent years.

Using computed tomography (CT) imaging, Mohlenkamp[28] found that male marathon runners have a similar rate of coronary artery calcification as an age-matched sedentary population, despite the fact that the marathon runners had a better cardiovascular risk profile with lower percentage of hyperlipemia, smoking, hypertension, and obesity. Even more surprising was the finding that male marathon runners had more coronary artery calcification than the control population (with a similar cardiovascular risk profile), highlighting for first time the possibility that marathon training and running might after all not be the cardiovascular protective exercise it was once believed to be. Exploring this phenomenon, a more precise evaluation of the characteristics of atherosclerotic coronary artery plaques in marathon runners was performed using coronary CT angiography[29]. This study confirmed that male marathon runners had indeed a higher volume of atherosclerotic calcified and non-calcified plaques in their coronary arteries.

Were women marathon runners also affected by a higher burden of coronary plaques than sedentary women? A more comprehensive study of male and female runners answered this question in 2017[30]: compared to female runners, male runners at low cardiovascular risk had a higher volume of coronary plaques than sedentary controls (44.3% vs 22%), and higher prevalence of coronary stenosis > 50% of the artery lumen (7.5% vs 0%). Interestingly, plaque composition was different between runners and controls: runners had a higher prevalence of calcified plaques (70% in runners) while the sedentary population had a higher volume of mix and soft plaques (these plaques are known to be more unstable and susceptible to rupture causing acute coronary events). Interestingly, this increased prevalence of coronary plaques was observed only in male runners; compared with sedentary female population, female runners did not show differences in atherosclerotic burden or plaque composition. Furthermore, weekly training load was not associated with a higher prevalence of coronary calcification. However, the number of years of training was independently associated with the presence of coronary plaques. Similarly to these findings, Aengevaeren VL[31] demonstrated that athletes—and not specifically runners—engaged in more than 2000 MET/min/ week (metabolic equivalent of task = energy expenditure) of exercise had more coronary plaques than those engaged in less than 1000 MET/min/ week. Coronary plaques of those in the high range of exercise were more frequently calcified and therefore less prone to acute rupture-acute cardiac events.

In sum, so far, it seemed that marathon running was associated with a higher volume of coronary plaques in male runners, even in those with low cardiovascular risk profile. The observation that coronary plaques were mostly calcified (and therefore more stable and less susceptible to rupture than the plaques observed in sedentary population) was interpreted as a benign feature and non-alarming. Similarly, participants in three different physical activity trajectories across a 25-year span (about three times the physical activity recommendations) had a higher risk of coronary artery calcium progression than those in the low physical activity trajectory[32]. – However, in this study, the more physically active participants did not have an increased incidence of cardiovascular disease.

Importantly, this hypothesis has been questioned by the findings of the Master@ Heart study[33], to date the largest and most comprehensive multicenter prospective cohort observational study assessing the dose-response relationship between intensive endurance exercise and coronary atherosclerosis in endurance athletes (cyclists, runners, triathletes). The study included 191 lifelong master athletes and 191 late-onset athletes (training onset

Longstanding participation in marathon running is associated with the development of higher volume of atherosclerotic coronary plaques in male runners.

after the age of 30 years) and a control group of 176 healthy active non-athletes. All participants were males (45-70 years of age) with low CV risk profile. Lifelong endurance athletes were more likely to demonstrate elevated coronary artery calcification and greater plaque burden and were more likely to demonstrate luminal stenosis ≥50%, including proximal luminal stenosis, compared with late-onset athletes, suggesting a dose–response effect of endurance training.

Although observational, this study seemed to indicate that lifelong endurance sports did not show additional protection against coronary atherosclerosis compared with an active, healthy lifestyle that excludes endurance sports. On the contrary, in this study, lifelong endurance sports was related to a higher number of coronary plaques including higher number of unstable non-calcified plaques in proximal segments of the coronary arteries (both, non-calcified plaques and proximal plaques are risk factors for acute events). Finally, the Master@Heart study[33] also found a dose-response relationship between lifelong endurance exercise and development of coronary atherosclerosis with those late-onset endurance athletes fitting between the lifelong athletes and the non-athletes when it comes to the plaque volume and composition.

These studies raise several questions. First, does the higher prevalence of coronary plaques indeed translate into an increased risk of acute coronary events during participation in endurance events? To date, no scientific evidence supports this possible increased risk of acute coronary events[32]. One plausible explanation is that, despite the increased coronary plaque burden in lifelong athletes, the overall plaque burden remains low in athletes compared to individuals at high risk for coronary events[33]. Furthermore, while lifelong athletes are more likely to demonstrate luminal coronary artery stenosis >50%, it is known that overall event rates in those with stenosis <70% are low[34]. Finally, it is also important to consider the role of coronary artery remodelling in athletes. The higher diameter of arteries, and greater vasodilator response during exercise increases threshold for myocardial ischemia during exercise. Nevertheless, to lower the potential risk during endurance events, the International Marathon Medical Directors Association proposed to administer pre-race oral aspirin to those marathon runners likely to be at higher risk of myocardial infarction[35]. However, this secondary prevention measure has shown inconclusive benefits, remains controversial and has not entered common practice yet.

A second key question: is the undisputed presence of high levels of coronary artery calcification in the setting of the endurance sports practiced by master marathon runners associated with increased mortality? Current observational studies show the following[36,37]: There was no evidence to suggest an increased mortality risk in individuals with high levels of physical activity, even in the presence of clinically significant coronary artery calcification. Cardiovascular disease and all-cause mortality among individuals with low coronary artery calcification who were very active, seemed significantly reduced. Notedly, all-cause mortality among very active individual with high coronary artery calcification were also lower[37]. Further to these results it is important to know that, overall, athletes (including endurance athletes) have an increased life expectancy compared to the general population[38–40]. In addition to the cardiovascular reasons, many other factors (e.g. biological, genetics, and lifestyle) contribute to this increased life expectancy in athletes.

A third intriguing question is what the exact mechanism of increased coronary atherosclerosis in marathon runners might

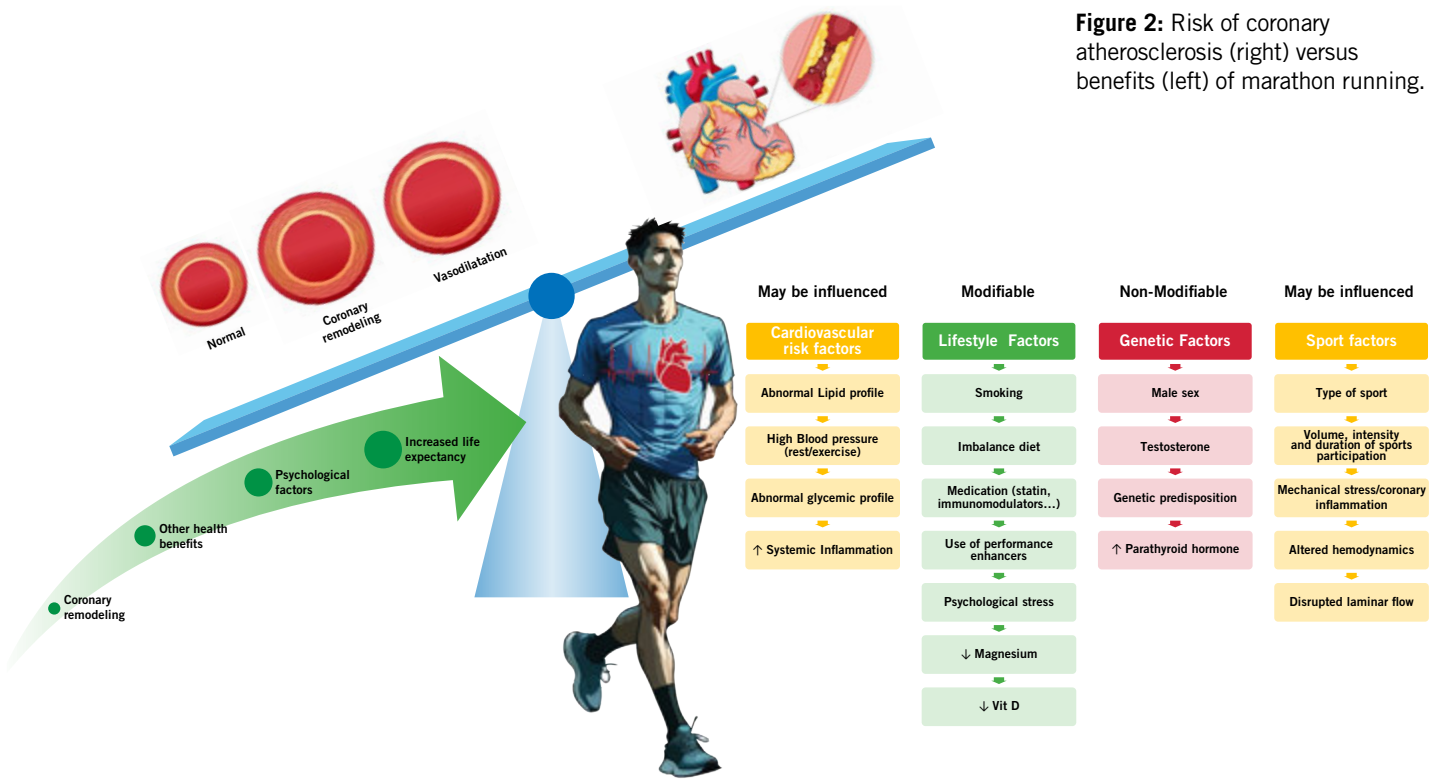

Figure 2: Risk of coronary atherosclerosis (right) versus benefits (left) of marathon running.

be. In many recreational athletes, traditional cardiovascular risk factors undoubtedly play a major part (e.g. abnormal lipid profile, hypertension, abnormal glycemic profile, chronic inflammation, proatherogenic dietary patterns, smoking, psychological stress, the use of certain medication such as anti-inflammatories, deficiency of magnesium or Vit D, gender, or genetic predispositions.) In addition, other proposed factors include: (i) suboptimal endothelial repair from repetitive macroscopic shear stress of coronary arteries; (ii)inflammation secondary to shearing forces within coronary arteries during exercise[41–43]; (iii) altered hemodynamics in arteries with increased turbulent flow and disrupted laminar flow in relation with exercise; and (iv) protracted increase in cardiac afterload[44]. Exercise also results in specific hormonal responses, e.g., increased parathyroid hormone level which may favor coronary artery calcification[45]. All these responses are certainly influenced by the type, volume, intensity, and duration of sports participation (Figure 2). At present, we cannot be certain which of these physiological mechanisms might initiate coronary atherosclerosis and which are drivers of progression. For example, in the MARC-1 study[31] exercise volume was associated with an increased prevalence of coronary plaques. However, the MARC-2 study did not indicate an association with the progression of coronary atherosclerosis after 6.3 years of follow up[46]. What we know for certain is that exercise volume is directly associated with the presence of coronary artery calcification.

What about exercise intensity? Interestingly, both cross sectional[31] and longitudinal studies mentioned above[46], have found that vigorous exercise was associated with a lower coronary artery calcification, and lower progression, while very vigorous exercise was also associated with a higher plaque burden, accelerated coronary artery calcification, and plaque progression. Therefore, very vigorous exercise is related to calcified plaque formation. Although uncertain, mechanisms for this could include: (i) the production of higher catecholamine levels during higher intensity exercise which increases blood pressure and heart rate more (both of which increase coronary mechanical stress); (ii) catecholamines producing long-lasting detrimental proinflammatory changes in monocytes. Consequently, increases in blood pressure, heart rate, mechanical stress, disrupted laminar flow and inflammation become potential mechanisms of increased coronary atherosclerosis in athletes[46].

Lastly, what about different endurance sports? There is a suggestion that marathon runners have more coronary atherosclerosis than cyclists, while the plaques in cyclists are mostly calcified; in runners, coronary plaques are mixed. We don't know why, but differences in exercise intensity or differences in skeletal stress, bone turnover and calcification scores between the two activities could all play a role[47].

SUMMARY

Longstanding participation in marathon running is associated with the development of higher volume of atherosclerotic coronary plaques in male runners. Plaque progression seems to be associated with exercise volume and the highest exercise intensity levels. Longstanding participation in marathon running is also associated with cardiovascular adaptations and other health benefits. These benefits might eventually balance the increased risk of coronary artery disease or acute events especially in runners with a healthy lifestyle at low cardiovascular risk.

While the evidence indicating a higher volume of atherosclerotic coronary plaques in male runners is irrefutable more high-quality prospective studies are needed on coronary atherosclerosis in athletes. Specifically, studies to: (i) further explore risk factors (causal and prognostic); (ii) implement effective prevention; and (iii) inform early detection (screening, perhaps) and appropriate management. Finally, 'screening' or periodic health evaluations in marathon runners should be considered especially in those with traditional cardiovascular risk factors as per current ESC Guidelines recommendations[48]. These periodic health evaluations should include appropriate cardiovascular assessment and risk stratification performed by experienced health care professionals, ideally sports cardiologists whenever available. Another important strategy, is the education of all stakeholders, including athletes (cardiovascular risk factors control, red flag symptoms recognition etc), coaching teams, and their medical teams.

After all this science, what should we advise endurance runners to start doing tomorrow? "Keep running!", if it makes you happy, and - particularly if you are an over 35-years-old male- , work hard to lower all other risk factors for heart disease, seek medical advice if you have cardiovascular risk factors or experience any cardiac symptoms or unexplained reduction in your performance before your next big endurance event.

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Maria-Carmen Adamuz Ph.D. M.D.
Sports Cardiologist
Aspetar Orthopaedic and Sports Medicine Hospital
Doha, Qatar

Juliette van Hattum M.D.
Sports Cardiologist
Amsterdam UMC
University of Amsterdam
Amsterdam, the Netherlands

Guido Pieles M.D., Ph.D.
Head of Sports Cardiology & Screening
Aspetar Orthopaedic and Sports Medicine Hospital
Doha, Qatar

Contact:
mariadelcarmen.adamuz@aspetar.com