THE VETERAN ATHLETE'S HEART

IS LIFE-LONG PROLONGED AND INTENSIVE EXERCISE DAMAGING TO THE HEART?

– Written by Mathew Wilson, Qatar

The cardiovascular benefits of regular physical exercise have been well-documented, with overwhelming evidence from epidemiological and intervention studies, suggesting that cardiovascular disease is largely a disease associated with physical inactivity. Exercise plays a beneficial role in the prevention and treatment of cardiovascular disease, with an inverse and robust relationship between physical activity and mortality risk. With such overwhelming evidence to support the promotion of physical activity within the community, the competitive retirement or even death of an athletic individual due to a cardiac pathological mechanism is a tragic and highly publicised event. For the past decade, our research team has been examining the causes of young sudden cardiac death and, more recently, the causes of death and rhythm disturbances within the veteran athlete population.

A DECADE OF EXTREMELY COMPETITIVE OLDER ATHLETES

Over the past few decades, prolonged endurance events such as marathon running have become more popular. In 2001, nearly 480,000 runners completed a marathon in the United States alone, with a shift toward older participants. With the sudden rapid rise in the number of veteran athletes taking part in ultra-endurance exercise, it is apparent that a growing number of athletes are turning in impressive competitive results. The winner of the 2011 Virgin London Marathon male 60 to 64 year age group clocked 3 hours 03 minutes 25 seconds, while the 2010 New York Marathon male 70 to 74 year group winner ran 3 hours 18 minutes 45 seconds! In support of the endurance obsession, we recently published a case study of a 68-year-old male runner who had accurately recorded a total distance of 148,561 miles throughout 43 years of daily running[1]. While we are assured that moderate intensity, duration and frequency exercise is positive for cardiovascular health, can we be sure that running 7 minutes 30 seconds miles repeatedly over 3 hours at 70 years of age, or 150,000 miles throughout a 70-year lifetime, is not damaging to the heart? In essence, can one have too much of a good thing?

ATHLETES HEART OR ACQUIRED CARDIAC PATHOLOGY?

While the cardiac adaptations to intensive physical activity were first described over a century ago[2], the question of whether the pronounced cardiac morphological and functional changes observed in athletes represent a benign physiological adaptation or belong along a continuum of pathology, remains extremely controversial. The physiological cardiac adaptation to chronic increases in preload and afterload on the

Below: Andorran long distance runner Antoni "Toni" Bernadó Planas (born 1966) the first and so far only athlete to have finished five Olympic Marathons.

heart lead to a form of 'apparent' reversible cardiac remodelling comprising of left and/or right ventricular hypertrophy, increases in cardiac chamber size and enhanced diastolic ventricular filling, which permits an increase in stroke volume. These cardiac manifestations have thus been termed the 'athletes heart'. Ageing is associated with changes to the cardiovascular system that reduce functional capacity. Regular endurance exercise training appears to slow this progressive decline, however, do such benefits apply to intensive lifelong endurance activity in veteran athletes (>50 years)?

Recent data has documented an increased prevalence of supraventricular, complex ventricular and profound bradyarrhythmias in endurance-trained athletes, predominantly occurring in veteran athletes[3,4]. Several forms of idiopathic ventricular arrhythmia have been identified in athletes which, by definition, originate in hearts without structural abnormalities. The clinical significance of these arrhythmias remains to be fully elucidated. Yet, in support of the potential pathological changes in the cardiac electrical activity, several studies have reported an incomplete reversal of left ventricular hypertrophy in retired elite athletes suggesting, in part, a pathological remodelling process[5,6]. Accordingly, the debate focuses upon whether changes in cardiac morphology and function together with electrocardiographic changes commonly observed in young high-level athletes persist in the veteran athletic population, even after detraining.

An important distinction in exercise-related sudden death is made on the basis of age. Most sudden cardiac deaths in young athletes (<35 years of age) are associated with inherited cardiac pathologies, with cardiomyopathies presenting as the most common cause. In contrast, sudden cardiac deaths in older athletes (>35 years) are caused predominately by atherosclerotic coronary artery disease. Compared to age-matched sedentary controls, a higher prevalence of sub-clinical cardiac disease has been reported in veteran athletes that may increase the risk of an exercise-associated cardiac event[7]. Strenuous endurance activities, such as marathon running, may even lead to an increased risk of acute cardiac events, although the occurrence of coronary events during marathons is rare[8].

WHAT EVIDENCE SUPPORTS THE DAMAGING EFFECTS OF LIFE-LONG INTENSIVE AND PROLONGED EXERCISE?

In 2008, we postulated that, in the absence of any other cause, life-long repetitive bouts of arduous endurance exercise may result in fibrotic replacement of the myocardium

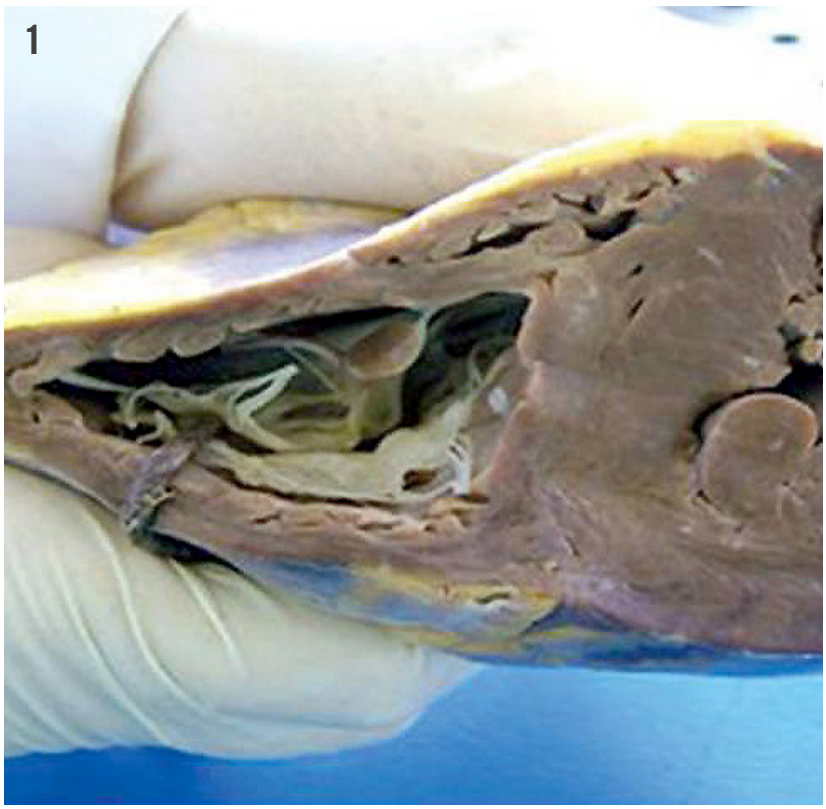


Figure 1: Gross morphology of the heart demonstrating circumferential left ventricular hypertrophy.

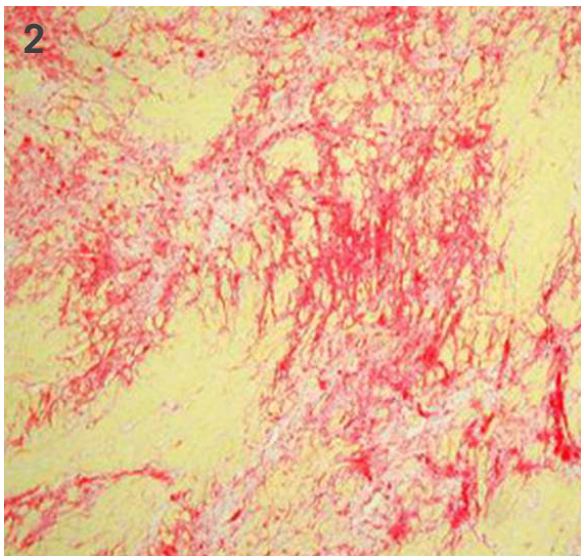


Figure 2: Histology slide of the left ventricular myocardium following sirius red FB3 staining, showing idiopathic interstitial myocardial fibrosis in the deceased marathon runner.

in susceptible individuals resulting in a pathological substrate for the development of arrhythmias. This proposed mechanism is supported in studies in non-ischaemic cardiomyopathy where myocardial damage leading to fibrosis has been implicated in myocardial re-entry leading to ventricular arrhythmia. Furthermore, previous studies have supported the view that conduction system abnormalities and arrhythmias in athletes may be associated with myocardial damage[9].

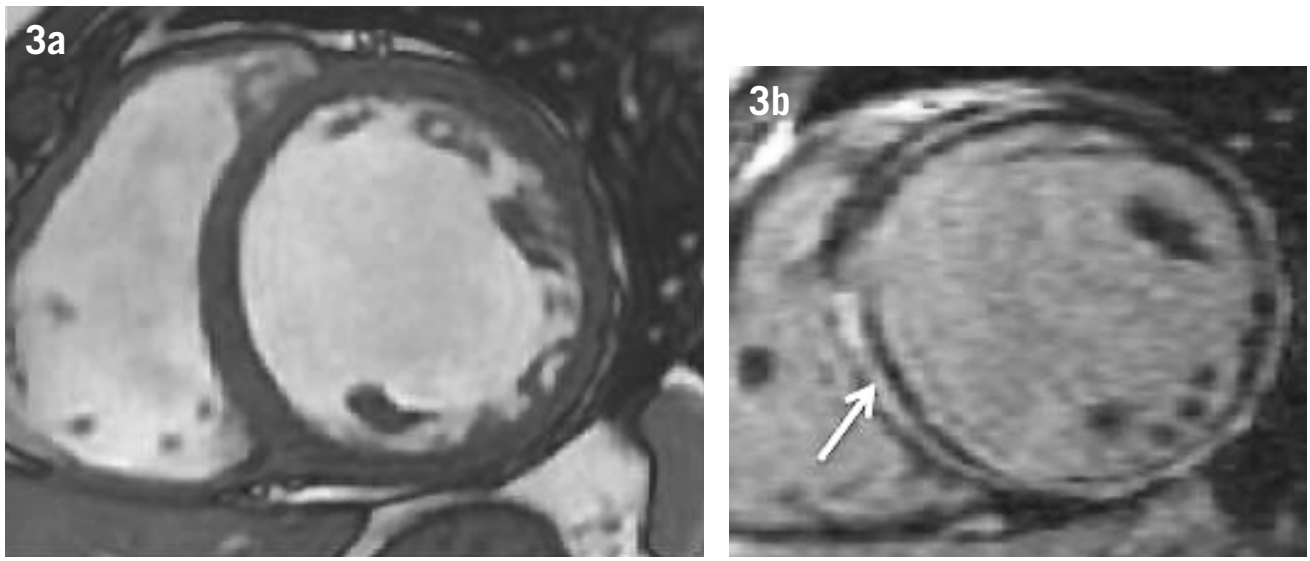
CASE REPORT: SUDDEN CARDIAC DEATH IN A VETERAN ATHLETE

We recently observed idiopathic interstitial myocardial fibrosis at post-mortem in the heart of an athlete who died suddenly during marathon running[10]. The deceased had been running for 20 years, having completed multiple marathons with a personal best time of 2 hours 30 minutes. At autopsy, the weight of the heart was 480 g (above that expected for a 75 kg male - upper limit of 431 g) with widespread replacement fibrosis particularly in the lateral and posterior ventricular walls as well as interstitial fibrosis in the inner layer of the myocardium.

Pre-mortem, the athlete was healthy and free from cardiovascular disease, and there was no documented evidence of diseases associated with widespread myocardial fibrosis. The cardiac pathologic findings were consistent with a left ventricular hypertrophy of indeterminate causation (also known as idiopathic left ventricular hypertrophy) in the presence of idiopathic interstitial fibrosis[11].

The presence of idiopathic interstitial fibrosis could act as a pathological substrate in the development of fatal arrhythmias resulting in sudden cardiac death. Limited evidence reporting idiopathic fibrosis exists in the literature, likely due to the absent histological examination of the hearts of veteran athletes' post-mortem. Focal fibrosis of the papillary muscle in a highly trained endurance athlete has been reported previously[12] and lends support to this observation. Idiopathic left ventricular hypertrophy has been previously documented in athletes at post-mortem and is associated with sudden cardiac death[13].

Changes to the myocardium with ageing are difficult to separate from diseases associated with ageing, namely hypertension. An autopsy study of 230 non-cardiac patients demonstrated increased fibrosis and fat within the cardiac conduction system of elderly patients[14]. The causes of interstitial fibrosis are not well understood, however variable and dense interstitial fibrosis is observed in dilated cardiomyopathy, non-infarcted myocardium from hearts with ischaemic scars, dilated non-ischaemic myocardium and systemic hypertension. Wilson et al[15] suggested that myocardial ischaemia secondary to intramyocardial small-vessel coronary artery disease and the increased oxygen requirements of a hypertrophied myocardium may contribute to the development of myocardial fibrosis, left ventricular dysfunction and atrial and ventricular arrhythmias. However, from a biochemical-mechanical standpoint, Lakhan and Harle[16] noted that myocardial fibrosis that occurs with normal ageing may not be dependent upon the renin-angiotensin-aldosterone system or inflammatory mediators as neither of these systems are activated in the healthy elderly patient. Even in the absence of overt hypertension, arterial vascular walls lose compliance with age, resulting in some degree of pressure overload with normal ageing. Whether this age-related pressure overload is severe enough to result in cardiac fibrosis is unknown.



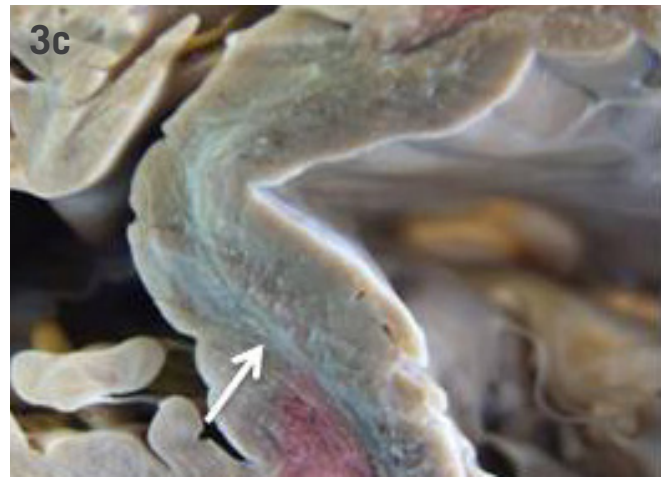


Figure 3: Dilated cardiomyopathy. Cine image (A) showing dilated left ventricle with wall thinning and mild increase in lateral wall trabeculation. Late gadolinium images (B) show typical mid wall enhancement (white arrows), confirmed macroscopically (C) as myocardial fibrosis.

Recently, Trivax et al[17] suggested that prolonged periods (>4 hours) of endurance exercise with sustained and elevated cardiac outputs lead to increases in right atrial and ventricular wall tension and, in susceptible individuals, dilation of those chambers secondary to myocyte changes possibly due to slippage of myocytes within cardiac tissue. The loss of intercellular junction integrity may lead to chronic changes in activity of pericytes and myofibroblasts, participating in cardiac fibrosis. It is particularly concerning for those individuals participating in intensive and prolonged endurance sports such as professional tour cycling and ultra-marathon running.

BIOMARKER OF CARDIAC DAMAGE AND ENDURANCE EXERCISE

The lack of association between the rise in biomarkers of cardiac damage, namely troponin I and T, with prolonged and intensive endurance exercise and cardiac symptoms, electrocardiogram abnormalities or sustained deterioration in cardiac function in the short term have led some investigators to conclude that this phenomenon may reflect a regulatory physiological adaptive process facilitating compensatory cardiac hypertrophy to cope with the haemodynamic burden of prolonged intensive exercise. However, care is warranted for the interpretation of short-term acute impact studies upon a career of lifelong physical endurance activity. Consequently, the impact of multiple episodes of prolonged exercise, as experienced by highly trained veteran endurance athletes, is not fully understood.

CARDIAC MAGNETIC RESONANCE STUDIES, CARDIAC FIBROSIS AND THE VETERAN ATHLETE

Cardiac imaging technology is improving yearly, with late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging (CMR) currently providing a sensitive tool for the detection of myocardial fibrosis. CMR can also image focal and global myocardial inflammation and oedema, owing to the relaxation properties of water, using T2-weighted techniques. Imaging after intravenous gadolinium can detect regional hyperaemia secondary to inflammation and focal areas of myocardial fibrosis.

A recent case report by Bhella et al[18] documented the appearance of LGE on CMR in the inferior insertion of the right ventricle and interventricular septum, with no evidence of decrement in systolic function and undetectable levels of troponin I and T in a male runner attempting the North American transcontinental. In support of this hypothesis, animal studies have documented myocardial fibrosis following an exercise intervention. Benito et al[19] recently conditioned male Wistar rats to run vigorously for 16 weeks. The authors observed collagen deposition and a significant increase in messenger ribonucleic acid and protein expression of

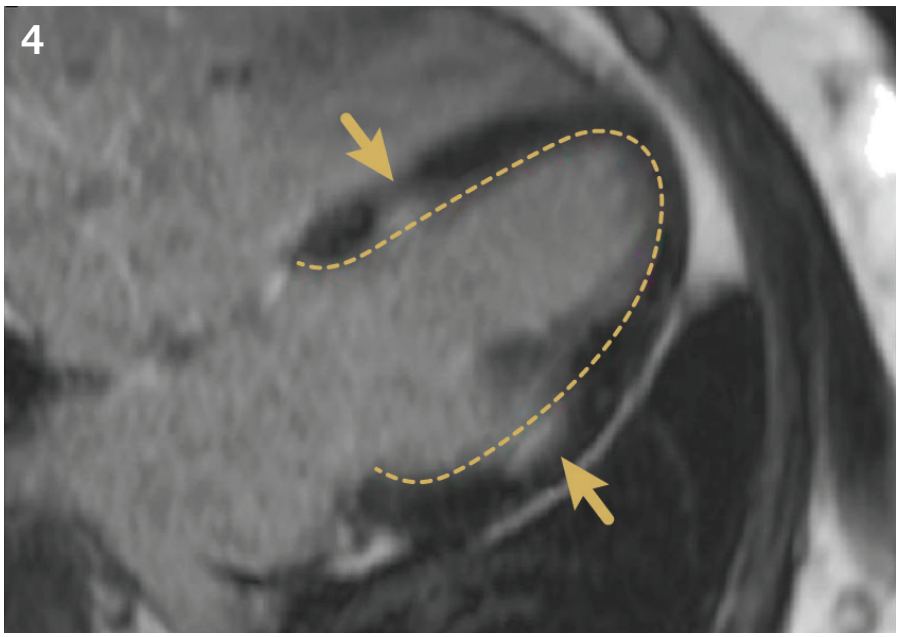


Figure 4: Late enhancement study, following gadolinium-contrast agent, demonstrating localised infarction in both the septal and lateral walls (arrows).

fibrotic markers after long-term intensive exercise training, together with changes in ventricular function and increased arrhythmia inducibility. Positively, the authors documented that the cessation of endurance training was able to arrest and even reverse this pathological process.

Within humans, Breuckmann et al[20] were the first to investigate whether competitive running history was linked to the prevalence of LGE in male marathon runners. Despite a non-significant difference in the prevalence of LGE (12 vs 4%, *P*=0.07) between athletes and age-matched controls, the lack of life-long continuous competitive endurance history and the higher prevalence of former (51.9%) and current smokers (4.6%) in the runners, the higher prevalence of non-coronary artery disease patterns of LGE in runners raised the possibility that it was the distance run and not life-long distance running career that may be key to this acquired pathology.

In order to address the lack of experimental data in high level healthy athletes, we recently examined the cardiac structure and function of a unique cohort of 12 truly life-long competitive veteran endurance athletes vs 20 age-matched veteran controls and 17 younger male endurance athletes using CMR with LGE with a view to identifying potential fibrotic infiltrate[21]. Our veteran athlete group was unique, with a competitive endurance career spanning 43±6 years (range 35 to 52), competing in 178±209 marathons (range 20 to 650) and 65±91 ultra-marathons (range 0 to 257). We observed evidence of myocardial fibrosis in six (50%) athletes (four with LGE of non-specific cause, one with probable previous myocarditis and one probable previous silent myocardial infarction).

Importantly, there was no LGE in the age-matched veteran control group nor in the young athletes, with the prevalence of LGE associated with the number of years spent training (*P* <0.001), number of competitive marathons (*P* <0.001) and ultra-endurance (>50 miles) marathons (*P* <0.007) completed. In support of this data, a recent study of 40 healthy ultra-endurance athletes found that a small number of athletes (n=5; 13%) exhibited LGE in the interventricular septum together with increased RV remodelling. Importantly, this small cohort had been competing in endurance sports for significantly longer (20+16 vs 8+6 years, *P* <0.05) than those athletes similar in age, but without LGE[22].

One of the problems of examining such a small and unique group of life-long athletes is that it is often difficult to understand the potential mechanisms responsible for the increased incidence of myocardial fibrosis. Unlike some inherited cardiac conditions such as hypertrophic cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy (ARVC), it appears that not all adverse cardiac remodelling has a genetic constitution. La Gerche et al[23] examined the prevalence of ARVC causing mutations within genes encoding desmosomal proteins in 47 symptomatic endurance athletes with complex right ventricular arrhythmias. The majority of the athletes studied (n=41; 87%) fulfilled Task Force criteria for definite or suspected ARVC. A total of 10 different heterozygous mutations were identified within five candidate desmosomal genes however, in only six cases (13%) were these considered to be pathogenic. Individuals who were gene positive (n=6) had worse right ventricular ejection fraction but did not differ from gene negative athletes (n=41) in relation to symptomatic presentation, electrocardiographic anomalies, therapeutic intervention or subsequent implantable cardioverter-defibrillator discharge. The study adds to the hypothesis that the ARVC phenotype may be acquired through intensive and sustained cardiovascular exercise and may not be solely attributed to a genetic predisposition relating to 'known' desmosomal proteins.

WHAT DO THE RETIRED OLYMPIC ATHLETES TELL US?

Recently, Pelliccia et al[24] concluded that intensive endurance conditioning over many years in Olympic athletes was not associated with inappropriate left ventricular remodelling or dysfunction or with adverse clinical events, onset of symptoms or new diagnosis of cardiomyopathies. However, Naylor et al[6] reported a reduction in diastolic function following short-term cessation of training in elite athletes that was normalised on return to training, raising the possibility that diastolic function may be normal in athletes who exhibit ventricular hypertrophy in the presence of a training stimulus, whereas the absence of an on-going training stimulus may be associated with decreased diastolic function in subjects who exhibit ventricular hypertrophy. Furthermore, detraining in athletes has been associated with only partial reversal of left ventricular enlargement and that diastolic function was lower after athletic retirement, transforming a physiological entity into a pathological phenomena.

CONCLUSION

In conclusion, given emerging evidence supporting a potential link between life-long intensive endurance competition and acquired cardiac pathology, it is attractive to suggest that excessive life-long exercise may be damaging to the heart. However, in light of the overwhelming evidence promoting the beneficial effects of regular exercise upon long-term cardiovascular health in the general population, care is warranted in the delivery of this message to this small and unique population of life-long veteran athletes. The perception that many athletes have is that the more exercise you do, the healthier you become. As Wallace Stegner wrote in his 1976 novel The Spectator Bird "most things break, including hearts. The lessons of life amount not to wisdom, but to scar tissue and callus."

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Mathew G Wilson B.Sc. (Hon), M.Phil., Ph.D., C.S.C.S.

Cardiovascular Physiologist

Aspetar - Qatar Orthopaedic and Sports Medicine Hospital

Doha, Qatar

Contact: Mathew.wilson@aspetar.com