Eur J Appl Physiol
DOI 10.1007/s00421-010-1534-3

REVIEW ARTICLE

# Cardiovascular function and the veteran athlete

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Accepted: 31 May 2010


**Abstract** The cardiovascular benefits of exercise are well known. In contrast, the impact of lifelong endurance exercise is less well understood. Long-term high-intensity endurance exercise is associated with changes in cardiac morphology together with electrocardiographic alterations that are believed to be physiologic in nature. Recent data however has suggested a number of deleterious adaptive changes in cardiac structure, function and electrical activity, together with peripheral and cerebral vascular structure and function. This review serves to detail knowledge in relation to; (1) Cardiac structure and function in veteran endurance athletes focusing on the differentiation of physiological and pathological changes in cardiac remodelling; (2) Cardiac electrical activity and the veteran endurance athlete with attention to arrhythmias, the substrate for arrhythmia generation and the clinical significance of such arrhythmias; (3) Peripheral and cerebral vascular structure and function in ageing and endurance-trained individuals; and (4) directions for future research.

**Keywords** Veteran athlete · Endurance · Cardiac remodelling · Arrhythmia · Fibrosis

## Introduction

The central and peripheral cardiovascular benefits of regular physical exercise have been well documented (Paffenbarger et al. 1997). Overwhelming evidence from epidemiological and intervention studies, suggest that cardiovascular disease is largely a disease associated with physical inactivity and that exercise plays a beneficial role

Communicated by Nigel Taylor.

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Published online: 17 June 2010

in prevention and treatment (Kokkinos 2008; Leung et al. 2008; Loomba and Arora 2008; Singer 2008). Much of this work has focussed on endurance exercise of moderate intensity, duration and frequency. In contrast, there is a burgeoning debate surrounding the cardiovascular benefits of endurance and ultra-endurance exercise (Whyte 2008). With a growing population of veteran endurance athletes regularly participating in endurance training and competition there is an emerging requirement to establish the impact of such exercise on the cardiovascular system. For the purpose of this review, a veteran athlete is defined as any individual greater than 50 years of age competing in endurance events.

Long-term high-intensity endurance exercise is associated with changes in cardiac morphology together with electrocardiographic (ECG) alterations that are believed to be physiologic in nature (Pluim et al. 2000; Pelliccia et al. 2002a, b; Whyte et al. 2004a, b; Pelliccia et al. 2008). Recent data however has documented an increased prevalence of supraventricular, complex ventricular, and profound bradyarrhythmias in endurance-trained athletes, predominantly occurring in veteran athletes (Jensen-Urstad et al. 1998; Ector et al. 2007; Whyte et al. 2007; Whyte 2008; Mont et al. 2009). Furthermore, several forms of idiopathic ventricular arrhythmia have been identified in athletes, which, by definition, originate in hearts without structural abnormalities (Anselme 2003). The clinical significance of these arrhythmias remains to be fully elucidated. In support of the potential pathological changes in the cardiac electrical activity recent studies have reported an incomplete reversal of left ventricular hypertrophy in retired elite athletes suggesting, in part, a pathological remodelling process (Pelliccia et al. 2002a, b; Naylor et al. 2005; Baldesberger et al. 2008). Debate continues as to whether changes in cardiac morphology and function, together with electrocardiographic changes persist in veteran endurance athletes, even after detraining.

Studies of the vasculature indicate that ageing is associated with a progressive decline in conduit, resistance and microvascular endothelial function, along with remodelling in larger vessels (Green et al. 2004a, b). Endothelial dysfunction is a strong independent prognostic index in patients with established cardiovascular disease and also asymptomatic apparently healthy individuals, so a decline in endothelial health with age may reflect the impact of other risk factors, or alternatively represent a causative link between ageing and cardiovascular risk. The mechanisms associated with endothelial deterioration with age are incompletely understood, but there is some evidence that they may be linked with elevated inflammation or oxidative stress (Green et al. 2004a, b). Exercise training appears to ameliorate the detrimental impacts of ageing on the vasculature and is associated with enhanced endothelial function at all levels of the vasculature (Buijs et al. 1998; Ainslie et al. 2008a, b; Demirkaya et al. 2008a, b). The impact of chronic endurance exercise on vascular structure and function is less well understood.

A gradual decline in global cerebral blood flow (CBF) occurs between 20 and 80 years of age (Fazekas et al. 1952; Pantano et al. 1984; Grolimund and Seiler 1988; Buijs et al. 1998; Krejza et al. 1999; Scheel et al. 2000; Stoquart-Elsankari et al. 2007; Demirkaya et al. 2008a, b). The reason for this age-related decline in CBF is not well understood; however, a reduced cerebral metabolism both at a cellular and global level due to cerebral atrophy, as well as vascular alterations (e.g. atherosclerosis) have been implicated (Kety 1956; Jernigan et al. 2001; Ainslie et al. 2008a, b). Regular physical activity is associated with an elevated CBF, thus individuals with a higher cardiorespiratory fitness have higher cerebral blood flows than age-matched sedentary individuals (Ainslie et al. 2008a, b). A higher CBF, as observed in physically active individuals may be protective against cerebrovascular disease (Hooker et al. 2008).

Accordingly, ageing is associated with deleterious changes in both the structure and function of the cardiovascular system. Using sedentary, age and gender matched controls, previous studies have described a positive effect of exercise in slowing the progressive decline with age. Care is warranted in the interpretation of such results given the multiple genetic and lifestyle factors that could affect the health of the ageing cardiovascular system particularly when employing cross-sectional designs. With this in mind, the present paper aims to provide a systematic review of the cardiac and vascular structure and function of the veteran athlete and examine whether the aetiology of these exercise-induced changes are physiologic or pathologic in nature. The values presented in this review are obtained under resting conditions unless specifically stated. Of note, this review will examine the link between mechanisms relevant to the limited evidence reporting an increased prevalence of supraventricular, complex ventricular and profound bradyarrhythmias in endurance-trained veteran athletes. The review will conclude with potential areas for future investigations to increase our knowledge of the impact of endurance exercise on the aged cardiovascular system.

## Cardiac structure and function in veteran endurance athletes

### Cardiac output ($\dot{Q}$)

The decrease in peak exercise $\dot{Q}$ in older individuals is in part due to a decrease in maximal heart rate (HR). Less well-known is the decline in peak exercise stroke volume (SV) in the older individuals (Kohrt et al. 1991). Ogawa

et al. (1992) demonstrated that the decline in $\dot{V}O_{2max}$ with age in veteran athletes is related primarily to a lower maximal $\dot{Q}$. Although a lower maximal HR accounts for a portion of this effect, a smaller SV is also of importance. It is thought that compromised early LV filling is compensated partially by an increased contribution during late diastole (i.e., a higher A wave and a lower E/A) (Peterson et al. 2003).

Nussbacher et al. (1999) stated that in addition to a reduction in maximal HR with ageing, there is also an increase in LV afterload and preload. There are four main causes for this increase in LV afterload: increased systemic vascular resistance; reduced arterial compliance; increased inertance due to a larger volume of blood requiring acceleration at the onset of ejection associated with aortic dilatation and; increased pulse wave velocity (Lakatta 1993a, b; Fleg et al. 1995).

## Cardiac systolic and diastolic function

Most data would suggest that global resting LV systolic function (normally represented by EF or fractional shortening) is largely unaltered in the "normal" ageing process (Goldspink 2005; Lumens et al. 2006). Conversely, it is well known that there is a "normal" age-related decrease in resting LV diastolic function that may reflect altered active relaxation, chamber compliance as well as changes in left atrial function (Oxenham and Sharpe 2003; Oxenham et al. 2003; Hees et al. 2004). Whether years of endurance training in the veteran athlete may offset an age-related decline in resting LV diastolic function has been the subject of some debate. Furthermore, whether such years of high-level training could augment LV diastolic and/or systolic function during exercise, when the LV faces significant hemodynamic loading, is also of interest. Indeed, the assessment of LV diastolic and systolic function in veteran endurance athletes effectively serves two functions: (1) to help determine if any structural changes in the heart have an impact on function and potentially, therefore, health, and; (2) to help determine if cardiac function in the older athlete is important in explaining the ability to attain an age-related supra-normal cardiorespiratory or endurance capacity (often assessed as $\dot{V}O_{2\,max}$). Whilst $\dot{V}O_{2\,max}$ declines with age in a similar manner regardless of activity status, the higher absolute cardio-respiratory capacities in veteran endurance athletes compared to age-matched controls is well documented (Hawkins et al. 2001).

A reduction in LV diastolic function commonly occurs in normal ageing, regardless of lifelong physical activity (Nottin et al. 2004). Impairment of active and passive diastolic properties of the myocardium involves both muscular and interstitial components. Impaired $Ca^{2+}$ uptake by the sarcoplasmic reticulum of the cardiomyocytes leads to slow and incomplete active ventricular relaxation (Nikitin et al. 2005), while expansion of the interstitium and alterations in collagen metabolism adversely affected the passive elastic properties of the myocardium (Villari et al. 1997). LV early diastolic filling rate progressively slows after the age of 20 years (Benjamin et al. 1992; Schulman et al. 1992; Swinne et al. 1992), so that by 80 years the rate is reduced, on average, up to 50%. Fibrotic changes within the LV myocardium or residual myofilament $Ca^{2+}$ activation from the preceding systole are presumed mechanisms for a reduced early diastolic LV filling rate. More filling occurs in late diastole, ultimately producing an exaggerated A wave (Lakatta and Levy 2003). This is thought to be due to a general increase in LV stiffness with ageing (Aronow 2001). During vigorous exercise, despite a reduction in the LV early diastolic filling rate (Schulman et al. 1992), the LV at end diastole in healthy older persons is not reduced, but rather is greater in older than in younger men. Whether the capacity for further acute dilation of the LV of veteran athletes is compromised is yet to be determined. Bouvier et al. (2001) demonstrated significantly better diastolic function (E/A ratio, isovolumetric relaxation time, and deceleration time) in healthy male veteran athletes (>70 years) at rest, compared with age-matched control sedentary participants.

LV EF, the most commonly used clinical measure of LV systolic performance, is usually preserved during healthy ageing (Lakatta and Levy 2003; Nikitin et al. 2005). The average value of EF is approximately 65%, and very few healthy, sedentary older individuals examined to exclude clinical and occult coronary disease have an EF <50% (Fleg et al. 1995), which is a value indicative of impaired LV systolic function (Vasan and Levy 2000). Nikitin et al. (2005) demonstrated global LV systolic function does not deteriorate at rest with normal ageing in healthy adults between 40 ± 13 and 73 ± 8 years of age. During exercise, EF has been shown to be significantly higher in veteran athletes (>70 years) than age-matched control participants (Bouvier et al. 2001).

Studies of LV function at rest in veteran endurance athletes have been generally limited to cross-sectional comparisons with age-matched sedentary groups and/or younger healthy subjects. An early non-invasive study of LV function in veteran athletes documented normal systolic function (fractional shortening) in 9 male endurance and 13 male sprint veteran athletes (Child et al. 1984). However, the sample sizes were small, of heterogeneous age (mean 54 and 46 years, respectively), no control group was studied and imaging technologies were limited as no Doppler assessment of LV diastolic function was performed. In a later study, Forman et al. (1992) employed flow Doppler assessment of early (E) and late (A) diastolic filling of the LV and reported that veteran endurance

athletes had E filling velocities similar to younger controls but were significantly greater than older sedentary subjects suggesting some preservation of LV diastolic function due to exercise training into older age. As non-invasive echocardiography techniques have developed further insight has questioned such simple interpretation. Nottin et al. (2004) employed both flow Doppler and myocardial tissue Doppler velocity analyses of early and late LV diastolic function. Whilst early flow velocities were increased in older athletes compared to older controls they were still blunted compared to young sedentary controls. Myocardial tissue Doppler velocities, a less load-dependent measure of LV diastolic function, were not different in both older groups and significantly depressed compared to young sedentary controls. Nottin et al. (2004) concluded that long-term training did not reduce the age-related decline in LV relaxation properties and those factors such as lower HR and higher blood volumes may explain the higher E in veteran athletes. In partial support of Nottin et al. Prasad et al. (2007) reported that maintenance of physical fitness with age did not prevent an age-related decrease in the rate of LV relaxation occurring before the opening of the mitral valve or in the propagation of flow into the LV. In contrast diastolic function, reflecting myocardial relaxation after aortic valve closure and during early mitral inflow was higher in trained versus untrained older individuals. This was ascribed, at least in part, to the more compliant ventricles of fit older individuals (Arbab-Zadeh et al. 2004). A more recent study by D'Andrea et al. (2007) also assessed RV function and suggested that early RV diastolic function may be enhanced in veteran athletes and that this may be an independent determinant of cardiac performance during physical effort.

The study of Arbab-Zadeh et al. (2004) was notable because it adopted invasive assessments of LV diastolic and systolic function in a protocol that included assessment during multiple changes in hemodynamic load on the LV. Loading was altered by rapid saline infusion and lower-body negative pressure which altered LV filling pressure and was correlated to simultaneous changes in stroke volume (SV). The increase in LV filling pressure with rapid saline infusion is partially akin to hemodynamic changes on the LV during exercise. In old endurance-trained individuals the filling pressure-SV curve was shifted upwards and to the left, relative to age-matched controls. In short, for the same filling pressure veteran athletes had greater SV and it was concluded that endurance training improved ventricular compliance.

Taken together, these studies suggest that exercise training may be associated with enhanced LV diastolic function that is most obvious when the LV is placed under some load. Veteran endurance athletes have normal intrinsic global LV systolic function. Exercise training into old age may maintain ventricular compliance that, during exercise, could explain an augmented SV and thus elevated $\dot{V}O_{2\,max}$ compared to age-matched sedentary subjects. Data gleaned from cross-sectional analysis of LV function at rest are more conflicting but suffer from self-selection biases and other confounders. For example, resting heart rate is inversely proportional to the E/A ratio (Galderisi et al. 1993), as a slower heart rate may reduce the atrial component of LV filling by lengthening the diastole filling period (Johannessen et al. 1991). Whether an intrinsic increase in relaxation or LV compliance occurs at rest is, therefore, difficult to interpret from cross-sectional athlete-control comparisons. Longitudinal studies may remove some of these technical issues but of course are highly problematic given a design that requires virtually lifelong exercise training. In shorter aerobic training studies (6–12 months) in older individuals, it is interesting to note that EF at rest was unaltered (Ehsani et al. 1991; Stratton et al. 1994; Spina et al. 1996; Jungblut et al. 2000). Endurance training may offset some of the biochemical consequences of ageing that increase stiffness and reduce compliance (Lakatta and Yin 1982). Another possible mechanism may reflect a training induced improvement in calcium re-uptake by the sarcoplasmic reticulum that has been reported to decrease with healthy ageing (Capasso et al. 1983).

In summary, veteran athletes demonstrate maintenance in LV systolic function and may be able to partially offset the reduction in diastolic filling with regular and intensive endurance exercise. This is most obvious when the LV is placed under some physical load. Whilst some interesting data exist comparing LV function between veteran endurance athletes and age-matched controls further research is required. Studies with larger cohorts including women, e.g. (Hagmar et al. 2005) or a resistance-training stimulus, e.g. (Haykowsky et al. 2000a, b) should be combined with newer imaging techniques (e.g. strain analysis) and different cardiac chamber assessment (e.g. RV, left atria). An extension of work with veteran endurance athletes could further our understanding of age and exercise interactions on major artery structure and function (e.g. stiffness, compliance) as well as cardiac autonomic control.

## Cardiac remodelling with age

Cross-sectional studies of participants without hypertension or clinically apparent cardiovascular disease indicate that LV wall thickness increases progressively with age in both sexes (Lakatta and Levy 2003). At the sub-cellular level, ageing is associated with changes in excitation–contraction coupling mechanisms and diminished $\beta$-adrenergic contractile response (Lakatta 1993a, b). At the cellular level, cardiac ageing is characterised by a significant reduction of cardiomyocyte number with hypertrophy of remaining cells

and an increase in interstitial tissue (Olivetti et al. 1991). Olivetti et al. (1995) reported cardiac myocyte enlargement, together with a decrease in the estimated myocyte number that was greater in males than in females.

*Long-term consequences of cardiac remodelling*

Henschen et al. (1889) first described the athlete's heart over a century ago using young cross-country skiers. Heschen noted that "skiing causes an enlargement of the heart, and that this enlarged heart can perform more work than the normal heart. There is therefore, a physiologic enlargement of the heart, due to athletic activity" (Rost 1997). In the mid-1930s, Kirch (1935, 1936) presented data on 35 athletes who had died suddenly, reporting that cardiac hypertrophy was the result of 'physical exercise'. Further work by notable Scandinavian scientists, such as Kjellberg et al. (1949) and Reindell et al. (1957) on the athlete's heart using radiological techniques developed the understanding between heart size and performance. However, it was the development of echocardiography and computed tomography scanning in the 1970s, which accelerated our understanding of the athlete's heart.

Establishment of upper normal limits of physiological hypertrophy in response to physical training is important in the differentiation of physiological and pathological LV hypertrophy. Whyte et al. (2004a, b) examined the hearts of 306 young, international British male athletes identifying 11 (2.5%, mean age: 24.4 ± 5.9 years) with a wall thickness >13 mm, commensurate with a diagnosis of hypertrophic cardiomyopathy. Furthermore, 18 (5.8%) presented with a LV internal diameter during diastole >60 mm, with an upper limit of 65 mm. This British experience is in line with previous Italian data (Pelliccia et al. 1999; Pelliccia et al. 1999, 2002a, b) promoting concern for individuals with extreme LV remodelling. It is worth noting that the majority of evidence for cardiac remodelling with prolonged and intensive exercise comes from endurance-based populations. However, the 11 athletes identified in Whyte et al. paper with a wall thickness >13 mm, competed in a range of sports including judo, skiing, cycling, triathlon, rugby and tennis. Thus, different long-term training methods, such as resistance exercise (either strength and/or explosive power) may have different remodelling effects, both structurally and functionally, and on components such as arterial stiffness (Scharhag et al. 2009).

Incomplete reversal of extreme LV cavity dilatation with deconditioning has been documented with longitudinal echocardiographic examinations. Pelliccia et al. (2002a, b) reported that substantial chamber enlargement persisted in 20% of retired and deconditioned former elite athletes after 5 years. Miki et al. (1994) echocardiographic examination of nine veteran cyclists 2 years post retirement demonstrated a significant reduction in LV dimension ($p < 0.001$) but with no change in LV wall thickness or fractional shortening. The authors also noted a significant increase in E:A ratio ($p < 0.05$), postulating that the abnormal increase in E:A ratio observed within retired veteran cyclists, may by induced by lifelong high-intensity exercise, resulting in LV diastolic dysfunction. Although observed in young athletes (mean 20 years), Naylor et al. (2005) documented that following a 6-week detraining period, athletes exhibited a significantly higher LV mass with a significant reduction in diastolic function compared to controls. Noteworthy was the normalisation of diastolic function following return to training raising the possibility that diastolic function may be normal in athletes who exhibit LV hypertrophy in the presence of a training stimulus, whereas the absence of an ongoing training stimulus may be associated with decreased diastolic function in subjects who exhibit LV hypertrophy.

Conclusions in this area are difficult to draw however; Pelliccia et al. (2010) recently provided new insights into the risk/benefit relationship of long-term exercise by reporting the results of a longitudinal cardiovascular evaluation in 114 Olympic endurance athletes (mean age 22 ± 4 years) over a 4–17-year period. Global LV systolic function was unchanged whilst wall motion abnormalities were absent. In addition, LV volumes and LV mass index were unchanged, and LV filling patterns remained within normal limits, although left atrial dimension showed a mild increase. The authors concluded that intensive endurance conditioning over many years in Olympic athletes was not associated with inappropriate LV remodelling or dysfunction or with adverse clinical events, onset of symptoms, or new diagnosis of cardiomyopathies. Importantly, Bhella and Levine (2010) point out, that 2 of these 114 athletes did have significant ventricular arrhythmias that required medical intervention. Whilst the Pelliccia et al. (2010) paper significantly contributes to our understanding of the long-term consequences of cardiac remodelling in trained athletes in the short-term (<17 years), the impact of lifelong endurance exercise noted in veteran athlete's (>50 years) remains unclear. The application of modern imaging techniques, such as strain and cardiac magnetic resonance (to be discussed), longitudinally in both young and veteran athletes, may help resolve this debate.

## Ultra-endurance exercise and cardiac structure and function

Our group, and others, have demonstrated that acute bouts of ultra-endurance exercise result in a depression in indices of global LV diastolic function and the unrelated appearance of elevations in humoral markers of cardiac myocyte

damage above acute myocardial infarction cut-off levels, most notably reflected by an elevation in cardiac troponin I or T (George et al. 2005; Neilan et al. 2006; Shave et al. 2007, 2008; Middleton et al. 2008). Although the presence of cardiac troponins is pathognomonic of cardiac damage, the rapid return of cardiac troponins to baseline (<24 h) has led to the suggestion that this phenomenon is physiological and not pathological in nature.

The impact of multiple episodes of prolonged exercise, as experienced by highly trained veteran endurance athlete however is not fully understood. Whyte et al. (2007) proposed that in the absence of any other cause, lifelong, repetitive bouts of arduous endurance exercise may result in fibrous replacement of the myocardium, resulting in a pathological substrate for the propagation of arrhythmias. This proposed mechanism is supported by studies in non-ischaemic cardiomyopathy where myocardial damage leading to fibrosis has been implicated in myocardial re-entry leading to ventricular arrhythmias (Hsia and Marchlinski 2002). Furthermore, previous studies have supported the view that conduction system abnormalities and arrhythmias in athletes may be associated with myocardial damage (Bjornstad et al. 1993).

Evidence for Whyte et al. (2007) proposed theory that, lifelong repetitive endurance exercise results in fibrous replacement of the myocardium, comes from the same research group who recently observed idiopathic interstitial myocardial fibrosis at post-mortem in the heart of an athlete that died suddenly during marathon running (Whyte et al. 2008). The deceased had been running for 20 years, having completed multiple marathons, with a personal best time of 2 h 30 min. 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 LV hypertrophy of indeterminate causation (also known as "idiopathic left ventricular hypertrophy") in the presence of idiopathic interstitial fibrosis (Whyte 2008).

The presence of idiopathic interstitial fibrosis could act as a pathological substrate in the development of fatal arrhythmias. Limited evidence reporting idiopathic fibrosis exists in the literature, likely due to the absent histological examination of the hearts of veteran athletes at post-mortem. Focal fibrosis of the papillary muscle in a highly trained endurance athlete has been reported previously (Rowe 1993) and lends support to this observation. Furthermore, idiopathic left ventricular hypertrophy has been previously documented in athletes at post-mortem and is associated with sudden cardiac death (Sharma et al. 1997; Seto 2003).

Changes to the myocardium with ageing are difficult to separate with diseases associated with ageing, namely, hypertension (Lakhan and Harle 2008). An autopsy study of 230 non-cardiac patients demonstrated increased fibrosis and fat within the cardiac conduction system of elderly patients (Song et al. 1999), together with an age-related increase in right atrial fibrosis and a decrease in nerve plexus population (Burkauskiene et al. 2006). The causes of interstitial fibrosis are not well understood, however variable and dense interstitial fibrosis are observed in dilated cardiomyopathy (Marijianowski et al. 1995), non-infarcted myocardium from hearts with ischaemic scars (Volders et al. 1993), dilated non-ischaemic myocardium (Brooks et al. 2003) and systemic hypertension (Pardo Mindan and Panizo 1993). An increased collagen content following sirius red FB3 staining of the myocardium is also observed in the presence of inflammatory and amyloid cells, and as a result of myocarditis. Wilson et al. (2002) 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, LV dysfunction and atrial and ventricular arrhythmias. However, from a biochemical-mechanical standpoint, Lakhan and Harle (2008) noted that myocardial fibrosis that occurs with normal ageing should 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 loose compliance with age, resulting in some degree of pressure overload with normal ageing. Whether this age-related pressure overload is severe enough to cause cardiac ischaemia and fibrosis is unknown.

Gadolinium-enhanced CMR provides a sensitive tool for detection of myocardial fibrosis, which is distinguished by bright late-enhancement regions where the contrast lingers in the extracellular spaces of scarred myocardium (McCrohon et al. 2003). This technique relies on the difference in wash-in and wash-out kinetics and volume of distribution of gadolinium in oedematous/fibrotic myocardium, and with increasing image resolution shows promise in other causes of myocardial fibrosis including sarcoid, systemic sclerosis, hypertrophic cardiomyopathy and dilated cardiomyopathy (McCrohon et al. 2003; Moon et al. 2004). Recently, several research groups have employed CMR to address the cardiac structure and function of the veteran endurance athlete (Breuckmann et al. 2009; Yared and Wood 2009). Breuckmann et al. (2009) examined 102 healthy asymptomatic veteran male marathon runners and reported an unexpectedly high prevalence of late

gadolinium enhancement (12%), although not significantly different from control participants (4%, $p = 0.07$). However, Breuckmann et al. (2009) differentiated sub-endocardial regions of late gadolinium enhancement, typical of myocardial infarction (CAD) pattern ($n = 5$) from regions of a predominately, mid-myocardial patchy pattern of late gadolinium enhancement (non-CAD) pattern ($n = 7$). A limitation of these investigations was firstly, the use of veteran participants, who whilst endurance trained, were not truly lifelong ultra-endurance athletes and secondly, their ultra-endurance history was too weak to draw significant conclusions from.

In conclusion, the cause(s) and consequence(s) of the myocardial fibrosis are currently unknown. Whether myocardial fibrosis reflects ageing, lifelong intense endurance training, subclinical cardiovascular disease or the interaction of these factors in some individuals cannot be determined from available data. The case for a direct effect of exercise in promoting myocardial fibrosis is limited but has (re)gained some popularity in recent years. Case studies such as the report of focal fibrosis in the papillary muscle of a highly trained endurance athlete (Rowe 1993) have been widely reported. However, experimental data is still limited and does not reflect cause and effect. Many studies lack an age-matched sedentary control population, whilst lifelong female veteran athletes (both endurance and resistance); are often neglected. Future studies employing large cohorts of lifelong veteran male and female athletes are warranted to enhance our understanding of the impact of long-term endurance exercise on cardiac structure and function; particularly in those veteran athletes currently experiencing cardiac arrhythmia.

## Electrocardiography and the veteran endurance athlete

### Cardiac autonomic function

Physical exercise has a beneficial effect upon cardiac autonomic activity. Regardless of age, endurance athletes demonstrate a higher parasympathetic modulation and have a particularly high global heart rate variability compared with sedentary individuals, indicating that endurance activity may have a favourable effect on the cardiac autonomic profile (Sztajzel et al. 2008). Veteran athletes demonstrate a decreased heart rate (HR) variability in both time and frequency domains suggesting an increased parasympathetic withdrawal during the autonomic control of post-exercise tachycardia (Brown and Brown 2007).

Pollock et al. (1997) conducted a 20-year review of veteran athletes documenting a linear decrease in maximal HR of 5–7 beat $min^{-1}$ $decade^{-1}$ that was independent of continued high-intensity training. Early data suggested the decrease in maximal exercise HR with age was mainly due to the withdrawal of cardiac parasympathetic modulation and diminished $\beta$-adrenergic responsiveness. This weakened $\beta$-adrenergic responsiveness in older sedentary individuals appeared to contribute to an attenuated LV contractile response to exercise, regardless of a larger $\beta$-adrenergic stimulation (Schulman et al. 1992; Seals et al. 1994a, b). Although, recent experiments with atropine administration demonstrate that there is no change in peak HR, suggesting that the reduction in peak HR was not due to parasympathetic withdrawal (Uusitalo et al. 1998; Stein et al. 2002). At present, the degree to which $\beta$-adrenergic responsiveness diminishes in veteran athletes has yet to be documented. However, the reduction in HR response to exercise is the reason why the maximum acute cardiac output reserve in healthy individuals decreases, on average, by about 30% between ages 20 and 85 years (Lakatta and Levy 2003).

### Electrocardiographic changes

ECG changes are common in elite athletes with up to 40% demonstrating minor changes (Pelliccia et al. 2000) including, most commonly, repolarisation abnormalities and increased R- or S-wave voltage suggestive of LV hypertrophy (Bjornstad et al. 1991; Pelliccia et al. 2002a, b; Pelliccia et al. 2008). In the majority of cases, these ECG alterations are considered an innocent and benign consequence of athletic training (Sharma et al. 1999). However, data from the Italian National pre-participation screening programme (Pelliccia et al. 2000), identified a small but important number of athletes (5% of 1,005 athletes) demonstrating a particularly abnormal or bizarre ECG pattern, but with no evidence of structural cardiovascular abnormalities or an increase in cardiac dimensions. The long-term clinical outcome of this cohort as they progress through the ageing process, to veteran athletes, remains largely unknown.

Recently, from a database of 12,550 athletes, Pelliccia et al. (2008) reported on 81 athletes with diffusely distributed and deeply inverted T waves ($\geq$2 mm in at least three leads) who had no apparent cardiac disease and who had undergone serial clinical, ECG, and echocardiographic studies for a mean (SD) of 9 $\pm$ 7 years (range 1–27). From the 81 athletes, 63 with an abnormal repolarisation pattern (78%) were still engaged in regular competition and training. During serial follow-up, ECG alterations remained essentially unchanged (or showed deeper T-wave inversion) in 54 athletes (67%). In the remaining 27 athletes, ECG patterns either normalised completely (in 12) or became less abnormal (in 15) by showing reduced T-wave inversion. No changes in LV dimensions were observed in the 81 athletes during the follow-up period regardless of

change in ECG patterns. Importantly, a diagnosis of cardiomyopathy was made in 5 (6%) of the 81 athletes who had no previous evidence of cardiac disease. Pelliccia et al., suggest that these abnormal ECG's may represent the initial expression of genetic cardiac disease, preceding by many years phenotypic expression and adverse clinical outcomes (Corrado et al. 2006).

### Supraventricular, complex ventricular and profound bradyarrhythmias

Together with a high vagal tone, lifelong endurance athletes are also known to incur 'apparent' innocent arrhythmias and conduction alterations, such as sinus bradyarrhythmia, junctional rhythm, and first degree AV block. Recent data has documented an increased prevalence of substantial ectopy with frequent premature beats and complex ventricular tachyarrhythmias (including couplets and bursts of non-sustained ventricular tachycardia), predominantly occurring within endurance-trained veteran athletes (Jensen-Urstad et al. 1998; Biffi et al. 2002, 2004; Ector et al. 2007; Whyte et al. 2007; Whyte 2008; Mont et al. 2009). Biffi et al. (2008) reported that intensive endurance training may shift cardiovascular autonomic modulation from parasympathetic toward sympathetic dominance, thereby enhancing cardiovascular performance at peak training (Iellamo et al. 2002). However, the increased ventricular irritability, caused by predominance of sympathetic modulation, might explain the clinical occurrence of ventricular arrhythmias in some veteran athletes (Chen et al. 2007).

### Paroxysmal and lone atrial fibrillation

Atrial fibrillation (AF) is characterised by rapid and chaotic electrical impulses (300–600 per min) circulating within the atria and resulting in dysfunctional atrial activity and an irregular heart rate. AF is the most common sustained cardiac arrhythmia, which affects approximately 1.0–1.5% of the general population, and has a projected incidence that is markedly increasing (Miyasaka et al. 2006). Although many comorbidities and risk factors are known (prevalence of AF doubles approximately every 10 years after age 50) (Kannel et al. 1998), the ultimate underlying cause(s) remain unknown. Obel and Davidson (2005) reported that studies using prolonged rapid atrial pacing as a method of inducing sustained AF in animal models, long periods of intense physical activity may result in a propensity to atrial tachyarrhythmia. Studies examining the effects of prolonged rapid atrial pacing on the electroanatomic remodelling of the atria have shown that sympathetic hyperactivity occurs, which has a powerful influence on the maintenance of AF under such conditions. Interestingly, the authors provide evidence of a 53-year-old male endurance runner with symptomatic cardiac arrhythmias, including atrial ectopy and AF, but otherwise healthy. After 3 months of detraining, the patient's symptoms were ameliorated, atrial ectopy all but vanished, as did AF—these changes were sustained at a 6-month follow-up.

Whilst there are over 16,000 AF articles indexed on Medline (Swanson 2006), few articles exist documenting the impact of lifelong endurance exercise upon prevalence rates of AF in veteran athletes (Zeppilli et al. 1994). Although not considered veteran athletes for this review, Mont et al. (2002) reported 32 men out of 51 (63%) with lone AF (mean age 44) had been engaged in long-term physical activity (av. 22 years) at least 3 h per week. Athletes started their episodes of AF at a younger age, they had a lower incidence of mild hypertension and their episodes of AF were predominantly vagal in contrast to the sedentary patients. When compared to healthy controls, and not sedentary participants, the athletes had greater atrial and ventricular dimensions and a higher ventricular mass. Karjalainen et al. (1998) postulated that enhanced vagal modulation, atrial enlargement and LV hypertrophy, all characteristic of many endurance veteran athletes, may predispose normal hearts to AF.

Baldesberger et al. (2008) examined 62 former Swiss professional cyclists (66 $\pm$ 7 years), who completed the Tour de Suisse at least once during the years 1955–1975, in comparison with 62 male golfers who had never engaged with high-intensity endurance activity and were age, weight, hypertension, and cardiac medication matched. Former cyclists demonstrated a lower HR and a higher incidence of AF or atrial flutter (10 vs. 0%, $p < 0.028$) and non-sustained ventricular tachycardia. Mont et al. (2009) noted that the higher proportion of AF and flutter when compared with the study by Karjalainen et al. (1998) is probably explained because the former cyclists were older, suggesting that incidence of AF and flutter further increases with ageing in veteran athletes, as with any kind of AF.

Elosua et al. (2006) assessed former and current sport practice and the number of lifetime hours of sport practice in 51 men with lone AF (20 with vagal characteristics) in comparison to 109 general population control participants. Two important, yet cautious findings were reported: (1) the proportion of patients with lone AF who reported current sport practice was higher than in controls (31 vs. 14%), and (2) current practice of sport was associated with a higher prevalence of lone AF, with the practice of more than 1,500 lifetime hours of sport appearing to be the threshold for the observed association. Baldesberger et al. (2008) examination 62 former Swiss professional cyclists (noted above) corroborated these observations by reporting that former athletes with a very high number of previous bicycle years had a higher LV mass, larger atria, and a significant higher

occurrence of AF or flutter, indicating that there might be a threshold (volume) above which irreversible cardiac changes occur as another cause for AF or flutter.

*Potential arrhythmic substrate(s) for AF*

In patients with hypertension or structural heart disease, AF may be the consequence of structural changes in the atria, dilatation and/or fibrosis, secondary to chronic volume and pressure overload (Mont et al. 2009). It would seem logical, that lifelong endurance exercise may induce structural changes in the atrium (enlargement and/or fibrosis) that may create a favourable substrate for AF. Interestingly, Frustaci et al. (1997) found structural changes in a series of 12 patients with paroxysmal, recurrent, drug refractory lone AF. Inflammatory lymphonomonuclear infiltrates, compatible with myocarditis, were documented in 66% of patients; a non-inflammatory cardiomyopathic process in 17%; and patchy fibrosis in the remaining 17%. Whilst numerous authors have examined myocarditis and its role within sudden cardiac death, few have examined the link between myocarditis, fibrotic infiltrate and lifelong endurance exercise in veteran athletes (Andersson et al. 2001; Durakovic et al. 2005; Chimenti et al. 2006; Basso et al. 2007; Durakovic et al. 2008).

Recently, our group investigated a 68-year-old male veteran runner who had accurately recorded running a total distance of 148,561 miles over a 42 year period, but was recently experiencing symptoms of sustained tachycardia, chest discomfort, dyspnoea and loss of competitive running performance (Wilson et al. 2009). On questioning, the patient reported several periods of sustained intensive exercise whilst suffering with flu-like symptoms to maintain his World Record attempt. On examination, resting 12-lead electrocardiography, maximal cardiopulmonary exercise stress testing and echocardiography were all entirely normal. Cardiovascular magnetic resonance imaging demonstrated no regional wall motion abnormality together with normal RV and LV wall thickness. However, a pattern of late gadolinium enhancement which indicated myocardial scarring in the basal, lateral wall as a result of previous myocarditis was observed (Fig. 1).

Acute myocarditis is typically a viral or post-viral process, which may result in the acute onset of LV systolic dysfunction. It can range from mild and clinically undetectable to fulfilment and fatal over a short time course. Clinically, patients with acute viral myocarditis present with tachycardia, hypotension and shortness of breath. The clinical course of myocarditis is highly variable with complete or near complete resolution occurring in a few weeks. The majority will experience some degree of recovery of function but are often left with a degree of left ventricular dysfunction. Myocarditis should be suspected in athletes with unexplained cardiac arrhythmias and dysfunction, especially if preceded by a flu-like syndrome. An early diagnosis is desirable in order to avoid the risk of fatal consequences, since physical activity can enhance the inflammatory process (Chimenti et al. 2006). In patients with acute or chronic myocarditis, arrhythmia may be the only clinical symptom in the natural course of the disease. The potentially malignant tachyarrhythmias and bradyarrhythmias caused by myocarditis are of particular concern. Acutely, inflammatory processes in the cardiac myocytes and interstitium can lead directly to fluctuations in membrane potential, hence arrythmogenesis (Babu-Narayan et al. 2007).

Sustained lifelong endurance activity, provides ample opportunity for viral or post-viral infection to occur. Treatment is often difficult for highly competitive athletes to comprehend, as initial treatment for athletes with myocarditis should be complete absence from all physical activity for at least 6 months. Athletes should only resume training when ventricular function and cardiac dimensions return to normal and the clinically relevant arrhythmias disappear. Adherence to such guidelines should be strongly advocated to reduce the potential of life-threatening arrhythmias or rapidly progressive cardiac dysfunction and the introduction of antiviral or an immunosuppressive treatment (Chimenti et al. 2006).

In summary, veteran athletes are at increased risk of developing supraventricular arrhythmias. Likely reasons include changes in autonomic drive including increased parasympathetic modulation at rest and increased sympathetic modulation during exercise, increased atrial size and increased inflammation (Sorokin et al. 2009).

## Ventricular arrhythmias

Recent data has documented an increase in complex ventricular arrhythmias (VA), including couplets and bursts of non-sustained ventricular tachycardia, predominantly occurring within veteran athletes (Jensen-Urstad et al. 1998; Biffi et al. 2002; Biffi et al. 2004; Ector et al. 2007; Baldesberger et al. 2008; Mont et al. 2009). Debate continues to the clinical nature of VA and the specific outcome of high-level endurance athletes with frequent and complex ventricular arrhythmias (Heidbuchel et al. 2003). Indeed, VA's are sensitive to deconditioning in athletes with and without structural heart disease. Biffi et al. (2004) reported an 80% decrease in frequency and complexity of ventricular arrhythmias (from $10{,}611 \pm 10{,}078$ to $2{,}165 \pm 4{,}877$), as well as a 90% decrease in the occurrence of non-sustained ventricular tachycardia's with deconditioning. Using longitudinal data, the authors conclude that frequent and complex ventricular tachyarrhythmias are not ominous in trained athletes without cardiovascular abnormalities,

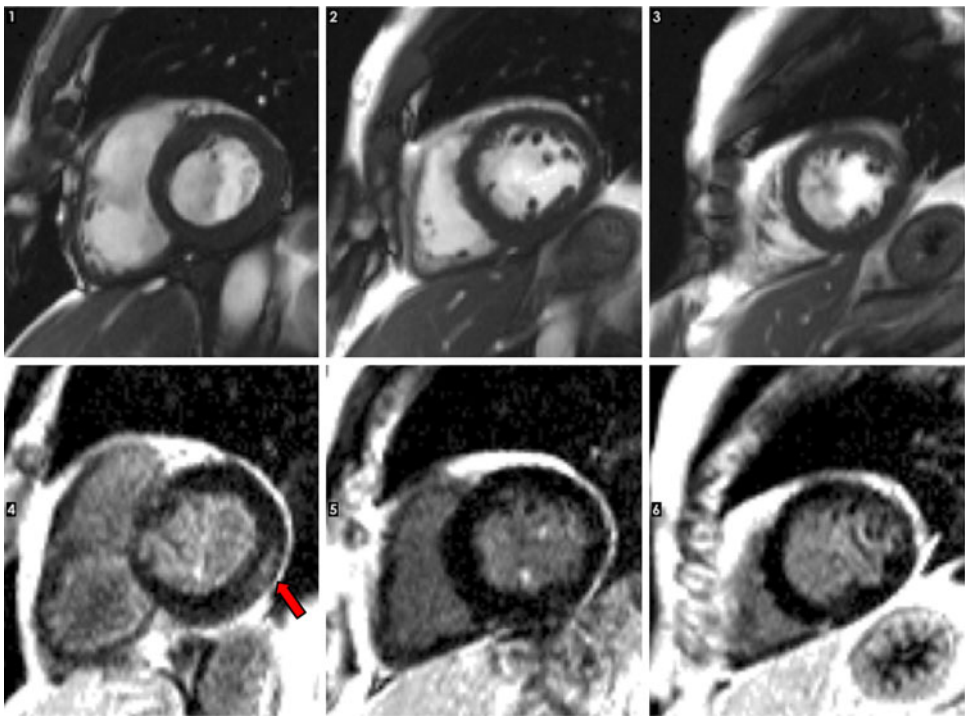


**Fig. 1** SA cine stack on the *top*. LGE images on the *bottom row* (*arrow* indicates mid wall enhancement indicative of myocarditic scarring) (Wilson et al. 2009)

and that these rhythm disturbances are another expression of the athlete's heart.

However, the specific outcome of high-level endurance athletes with frequent and complex ventricular arrhythmias remains unclear. Although examining younger athletes, Heidbuchel et al. (2003) reported on 46 high-level endurance athletes with ventricular arrhythmias (45 male; median age 31 years) followed up for a median of 4.7 years. Right ventricular (RV) arrhythmogenic involvement was manifested in 59% of the athletes, and suggestive in another 30%. Thirty-seven athletes (80%) had ventricular arrhythmias with left bundle branch morphology, indicating an origin in the RV or the interventricular septum. The worst arrhythmia documented non-invasively at initial evaluation (12-lead ECG, Holter, exercise test) was sustained ventricular tachycardia in 17 athletes (37%), non-sustained ventricular tachycardia in 24 (52%), and only ventricular extrasystoles or couplets in five (11%). An invasive EP study induced sustained monomorphic ventricular tachycardia in 15 out of 40 athletes, of whom 13 (87%) in the baseline state.

Eighteen developed a major arrhythmic event, with nine sudden deaths. They were significantly younger than those without event (median 23 years vs. 38 years; $p = 0.01$). Importantly, the outcome could not be predicted by presenting symptoms, non-invasive arrhythmia evaluation or morphological findings at baseline. Only the induction of sustained ventricular tachycardia or ventricular fibrillation during invasive electrophysiological testing was significantly related to outcome (RR 3.4; $p = 0.02$). The authors oppose longitudinal observations by Biffi et al. (2004) concluding that complex VA do not necessarily represent a benign finding in endurance athletes. Endurance athletes with arrhythmias have a high prevalence of RV structural and/or arrhythmic involvement, thus providing further evidence for the development and/or progression of the underlying arrhythmogenic substrate with high-intensity lifelong endurance activity.

Recently, Biffi et al. (2008), examining young athletes, documented no significant relationship between LV mass (or mass index) and the grade or frequency of ventricular tachyarrhythmias. Athletes with more frequent ventricular arrhythmias did not show parallel increases in LV mass, and athletes with the greatest LV mass did not demonstrate more frequent ventricular arrhythmias than athletes with lesser or normal mass. Of particular interest, whilst not biologically significant, athletes with the most frequent and complex ventricular ectopy (those with >1,000 premature ventricular contractions) showed the smallest calculated LV masses and mass indexes. Biffi et al. observations demonstrate that ventricular tachyarrhythmias in trained athletes (without cardiovascular abnormalities) arise largely independent of training- related LV remodelling, meaning that the underlying determinants of ventricular tachyarrhythmias remain unresolved. However, whilst examining younger athletes, Ector et al. (2007) noted that VA's in high-level endurance athletes frequently originate from a mildly dysfunctional right ventricle (RV). Studying 22 athletes with VA against 15 athletes without VA, the authors reported a RV ejection fraction of 64 ± 6% in

athletes without VA and a reduced RV ejection fraction (49 ± 10%) in athletes with VA. Since both groups of athletes were engaged in the same intensity and frequency of exercise, this finding cannot be attributed to the presence of athlete's heart per se. The authors suggest that endurance exercise and volume overload subject the thin-walled RV to a greater increase in workload than the thick-walled LV with subsequent different remodelling. Indeed, animal models have demonstrated that chronic volume overload causes a greater mass increase in the RV than in the LV, resulting in an increased collagen deposition and selective growth factor activation restricted to the RV (Modesti et al. 2004).

In summary, the relationship between ventricular arrhythmias and sudden cardiac death in athletes without evident heart disease is controversial. Furthermore, the origins and clinical significance of complex ventricular arrhythmias within veteran athletes remain to be fully elucidated and requires a robust methodological and longitudinal examination of a large number of lifelong veteran athletes, especially those currently experiencing arrhythmia.

## Vascular structure and function in veteran endurance athletes

The ageing process leads to various changes in the artery wall which impact upon function and structure. For example, a progressive decrease occurs in the compliance of large elastic arteries and peripheral arterial compliance (Avolio et al. 1983; Tanaka et al. 2000; Miyachi et al. 2003; Moreau et al. 2003). In women, this effect may be predominant in central rather than peripheral arteries (Tanaka et al. 1998). This suggests that sex and site-specific changes in arterial compliance occur with ageing in the large, elastic vessels. In larger conduit arteries, ageing is associated with impaired endothelial function (Celermajer et al. 1994; Eskurza et al. 2004; Eskurza et al. 2005; Eskurza et al. 2006; Black et al. 2009), which begins to decline at the age of 40 in men. A steeper decline occurs in women around the time of the menopause (Celermajer et al. 1994). Resistance artery endothelial function is also impaired in healthy older humans (Taddei et al. 1995; DeSouza et al. 2000a, b). In parallel to conduit and resistance vessels, physiological ageing is associated with impairment in the skin microvascular function (Minson et al. 2002; Holowatz et al. 2007). Indeed, microvascular responses to both physiological (local heating) and pharmacological stimuli are impaired with age (Black et al. 2008).

### Impact of ageing on vascular structure

Ageing leads to a gradual thickening of the artery wall, predominantly demonstrated by the age-dependent increases in carotid and femoral artery wall thickness (Dinenno et al. 2000; Moreau et al. 2002; Galetta et al. 2006). Most studies have observed no difference in baseline arterial diameter between young and middle-aged or older individuals (i.e. 50-60 years) (Parker et al. 2006; Nishiyama et al. 2008; Thijssen et al. 2008). However, the oldest cohort of men (>70 years), but not women, show an increase in baseline diameter (Parker et al. 2008; Gonzales et al. 2009). Nonetheless, the wall (thickness)-to-lumen ratio demonstrates an age-dependent increase in men as well as women. It has been suggested that the increase in wall thickness with ageing is related to elevation in sympathetic outflow in the older individuals (Dinenno et al. 2000). Peak reactive hyperemic blood flow, an index of remodelling in resistance vessels in humans, is typically smaller in older individuals and independent of gender (Takeshita and Mark 1980; Sinoway et al. 1986; Silber and Sinoway 1990; Silber et al. 1991; Sarabi et al. 1999). This suggests an age-dependent decrease in collective cross-sectional area of peripheral resistance artery vascular bed and may infer the existence of some concentric arterial remodelling at this level of the vasculature.

### Impact of ageing on the vasculature: mechanisms

Evidence supports an important role for the NO-pathway in age-related impairment in endothelial function (Taddei et al. 1995). Animal studies have observed lower eNOS gene and protein expression and activation in older rats (Spier et al. 2004) (Durrant et al. 2009). Elevated levels of oxidative stress may contribute to age-related endothelial dysfunction (Taddei et al. 2000; Eskurza et al. 2004). This is supported by the finding that vitamin C supplementation, a strong anti-oxidant, can restore the impaired NO-mediated endothelial function in sedentary older men (Galetta et al. 2006). Another mechanism linked with the NO-pathway relates to tetrahydrobiopterin ($BH_4$), an essential co-factor for eNOS-regulated production of NO, which decreases with age in animals (Delp et al. 2008), while $BH_4$-supplementation improves endothelial function in sedentary older men (Eskurza et al. 2005). Recent studies also found elevated endothelin(ET)-mediated vascular tone in older men, predominantly through $ET_A$-receptors (Thijssen et al. 2007a, b; Van Guilder et al. 2007). These findings suggest that vasodilator (NO) as well as constrictor (ET) pathways may contribute to the age-related endothelial dysfunction.

## Impact of exercise training on vascular function

Exercise training reduces cardiovascular events. However, the effects of exercise on traditional risk factors do not fully account for the magnitude of risk reduction (Mora et al. 2007). The direct effects of exercise on the vasculature provide a plausible explanation for the reduction in cardiac events associated with exercise training, independent of change in traditional risk factors (Green et al. 2008). Regular aerobic exercise is associated with enhanced arterial compliance in ageing larger arteries, whilst short-term exercise training in previously sedentary older men can also improve arterial compliance (Tanaka et al. 2000). Older endurance-trained men demonstrate enhanced arterial compliance compared to their sedentary peers, but compliance is nonetheless lower than that in young men (Monahan et al. 2001). In contrast, postmenopausal athletic women demonstrate a similar carotid artery compliance compared with their younger peers (Tanaka et al. 1998). These cross-sectional data suggest a sex-specific effect of exercise training on the age-related decrease in arterial compliance. However, exercise training studies in sedentary older men and women indicate that exercise training in previously sedentary subjects improves vascular compliance (Moreau et al. 2003; Thijssen et al. 2007a, b).

Regular endurance exercise in middle-aged and veteran athletes prevents the attenuation of the age-related endothelial dysfunction in conduit and resistance arteries (Rywik et al. 1999; DeSouza et al. 2000a, b; Rinder et al. 2000; Taddei et al. 2000; Hagmar et al. 2006; Black et al. 2009). The beneficial impact of exercise training is reinforced by various studies which have observed improved endothelial function in previously sedentary older humans after exercise training. Black et al. (2009) recently identified a gender-specific effect of exercise training on conduit artery endothelial function. Improvement in brachial artery endothelial function was observed after exercise training in women, but not men (who had a smaller age-related decline in endothelial function). This suggests that exercise training is an effective method to improve conduit artery endothelial function, especially in those with a larger age-related attenuation in vascular function.

Microvascular functional impairment in older humans can be prevented by maintaining a high level of physical fitness, whilst exercise training in previously sedentary older men partly reverses the age-related impairment in microvascular function (Black et al. 2008). This indicates that maintaining fitness and taking up exercise prevents the age-related decline in microvascular NO-mediated vasodilator function.

## Impact of exercise training on vascular structure

Exercise training represents a potent stimulus to structural remodelling in conduit arteries. Endurance-trained older male and female athletes demonstrate a smaller wall thickness in the carotid and femoral arteries compared with their inactive peers (Moreau et al. 2002; Galetta et al. 2006), while a larger femoral diameter is found in older athletes (Dinenno et al. 2001). Also, 3–6 months exercise training in older men induces remodelling of conduit arteries, leading to decreased wall thickness and outward remodelling of conduit arteries, with consequent decrease in the wall-to-lumen ratio (Green et al. 2010).

The effects of exercise training on wall thickness may be time-specific, since 8 weeks of training is insufficient to induce significant changes in conduit artery wall thickness (Thijssen et al. 2007a, b). Exercise-induced effects on intima-media thickness may also be site-specific. It has been suggested that endurance exercise training has a larger effect on wall thickness in 'muscular' arteries (e.g. femoral) than in more 'elastic' arteries (e.g. carotid) (Moreau et al. 2002), possibly due to the larger number of smooth muscle cells and plasticity of muscular arteries. Indeed, exercise-induced improvements in wall thickness have also been reported in the brachial and popliteal artery, supporting the idea that exercise has a systemic effect on muscular artery wall thickness in older humans.

In resistance arteries, exercise partly prevents the age-related decline in the peak blood flow response; i.e. the surrogate marker of resistance artery structural remodelling. Several studies have demonstrated that a period of exercise training, varying from 8 weeks up to 6 months, in previously sedentary older men increases the peak blood flow (Martin et al. 1987; Martin et al. 1990; Thijssen et al. 2007a, b). Evidence from healthy individuals indicates that the improvement in peak blood flow may be a systemic response in resistance arteries, rather than a localised response limited to the exercised limbs only (Silber et al. 1991). Accordingly, these changes in resistance arteries may contribute to a decrease in arterial blood pressure and cardiac afterload, typically observed after training.

Regarding the mechanisms of vascular adaptation to exercise training, a number of animal studies have demonstrated a key role for shear rate in inducing endothelium-dependent changes in vascular size and wall thickness (Langille and O'Donnell 1986; Tuttle et al. 2001; Brown 2003). Indeed, a recent series of experiments in humans examined the role for shear rate in exercise-induced changes in both vascular function and remodelling (Tinken et al. 2009; Tinken et al. 2010). Eight weeks handgrip exercise induced a time-dependent change in vascular

function and structure. However, when shear rate was experimentally normalised during exercise, no vascular adaptations were observed. These experiments support previous experiments which indicate that shear rate plays a key role in mediating vascular adaptations to exercise training in humans (Hambrecht et al. 2003).

In summary, the data above indicate that ageing impairs vascular function and distensibility and is associated with detrimental and pro-atherogenic changes in arterial wall thickness. Such effects are evident at all major functional levels of the arterial tree. Recent evidence indicates that exercise training and physical fitness can retard or even reverse these effects. Exercise training, in this context, represents a direct and particularly efficacious form of vascular medicine.

## Cerebral vascular blood flow and syncope

As previously stated, global CBF undergoes a gradual continuous decline of 25–30% between 20 and 80 years of age, or 5% per decade (Fazekas et al. 1952; Kety 1956; Buijs et al. 1998; Krejza et al. 1999; Scheel et al. 2000; Stoquart-Elsankari et al. 2007; Demirkaya et al. 2008a, b). The reason for this age-related decline in CBF is not well understood; however a reduced cerebral metabolism both at a cellular and global level due to cerebral atrophy, as well as vascular alterations (e.g. atherosclerosis) have been postulated to cause this decline in CBF with increasing age. Regular physical activity is associated with an elevated CBF, that is, individuals with a higher cardiorespiratory fitness have 17% higher cerebral blood flows than those who are sedentary of the same age (Fig. 2) (Ainslie et al. 2008a, b). This fitness difference equates approximately to a 10 year reduction in middle cerebral artery blood velocity equivalent age, i.e. a 60-year-old trained male has a middle cerebral artery blood velocity similar to that of a sedentary male aged 50. Many factors may contribute to this elevated middle cerebral artery blood velocity with fitness. Regular aerobic exercise is associated with an enhanced systemic arterial endothelial function, reduced large artery stiffness and a reduced risk of atherosclerosis (Clarkson et al. 1999; DeSouza et al. 2000a, b; Green et al. 2004a, b). Furthermore, longitudinal exercise training studies indicate that an increased fitness can also offset declines in cerebral tissue density, and can even increase brain volume in older adults. Animal studies have also identified that exercise can improve long-term stroke outcome by stimulating angiogenesis and elevating CBF (Endres et al. 2003; Gertz et al. 2006). Although a relationship between fitness and stroke incidence has been observed (Hooker et al. 2008), whether an elevated CBF is protective against stroke has not been clearly established.

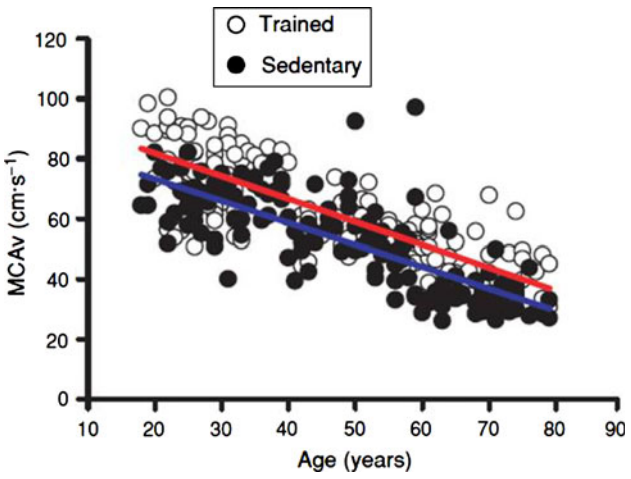


**Fig. 2** Relationship between age, cerebral blood flow velocity and physical fitness. The *red line* represents linear regression for the endurance-trained group. The *blue line* represents linear regression for the sedentary group. MCAv was consistently elevated by 9.1 ± 3.3 cm $s^{-1}$ [CI 2.7–15.6, $P = 0.006$ (~17%)] in endurance-trained men throughout ageing (Ainslie et al. 2008a, b)

Syncope occurs as a result of inadequate cerebral perfusion. In a 'normal' population, the incidence of syncope is increased with age (Tan and Parry 2008). The effect of fitness on orthostatic tolerance and syncope remains controversial. A lowered resting orthostatic tolerance has been observed in young highly trained athletes (Levine et al. 1991; Raven and Pawelczyk 1993; Ogoh et al. 2003), as outlined by the statement "trained men can run but they cannot stand" (Greenleaf et al. 1981). Others have found orthostatic tolerance to be unchanged (Hernandez et al. 2005) or even improved in young highly trained individuals (Convertino 1993; Winker et al. 2005). Similar work comparing young and older trained and untrained individuals found no differences in orthostatic tolerance between groups (Hernandez and Franke 2004; Franke et al. 2006). One situation where a reduced orthostatic tolerance and syncope is more common is following prolonged exercise (such as a marathon) (Gratze et al. 2005; Murrell et al. 2007; Lucas et al. 2008). Peripheral vasodilatation in active muscle beds combined with post-exercise hypotension and an impaired sympathetic responsiveness to postural change all may contribute to the development of orthostatic intolerance and syncope post-exercise. Due to an increased incidence of syncope, a reduced basal CBF and reduced baroreflex sensitivity, it would seem likely that older athletes may be at an increased risk of syncope following prolonged exercise; however, recent data from our group (Fig. 3) indicates that, although the mechanisms differ, there are no age-related difference in the occurrence of syncope following prolonged exercise (Murrell et al. 2009).

In summary, although reductions in CBF with ageing may contribute to the higher incidence of syncope, it does

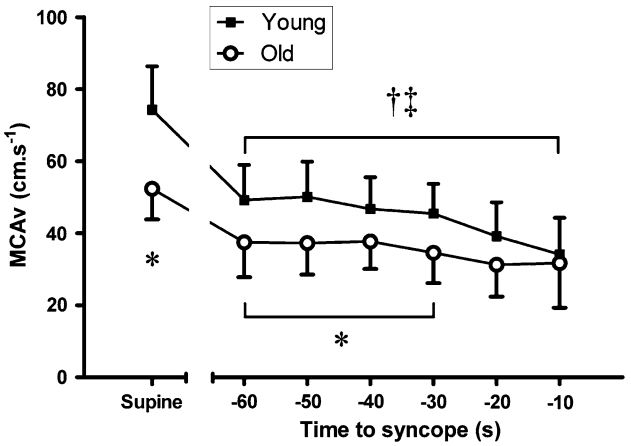


**Fig. 3** Middle cerebral artery blood flow velocity (MCAv) response in the final 60 s prior to syncope during head-up tilt in young and older athletes following 4 h of running at 70–80% maximal heart rate. *Different from young; †Different from supine (young); ‡different from supine (older; all $p < 0.05$) (Murrell et al. 2009)

not further augment the likelihood of syncope following exercise in healthy older individuals.

## Conclusions and directions for future studies

Cardiovascular disease is largely a disease associated with physical inactivity and that regular physical activity plays a beneficial role in prevention and treatment. However, ever since Henschen et al. (1889) first described the cardiac adaptations to intensive physical activity over a century ago, the question of whether the pronounced cardiac morphology and functional changes observed in athletes represent a benign physiological adaptation or crosses into the category of pathology remains controversial. In summary, whilst $\dot{V}O_{2\,max}$ declines with age regardless of activity status, the higher absolute cardiorespiratory capacities in veteran endurance athletes compared to age-matched controls are well documented. Exercise training may be associated with enhanced LV diastolic function and also have normal intrinsic global LV systolic function. Exercise training into old age may maintain ventricular compliance that, during exercise, could explain an augmented SV and thus elevate $\dot{V}O_{2\,max}$ in veteran athletes when compared to age-matched sedentary individuals. Regular aerobic exercise is associated with enhanced arterial compliance in ageing larger arteries; it also helps prevents the attenuation of the age-related endothelial dysfunction in conduit and resistance arteries. Furthermore, physical activity is also associated with an elevated cerebral blood flow, meaning that individuals with a higher cardiorespiratory fitness have a 17% higher cerebral blood flow than those who are sedentary of the same age. Veteran athletes may also have an enhanced systemic arterial endothelial function, reduced large artery stiffness and a reduced risk of atherosclerosis.

Structurally, evidence is a little more controversial. Recently, Pelliccia et al. (2010) concluded that intensive endurance conditioning over many years in Olympic athletes was not associated with inappropriate LV remodelling or dysfunction or with adverse clinical events, onset of symptoms, or new diagnosis of cardiomyopathies. However, Naylor et al. (2005) 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 ongoing 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 LV enlargement and that the E/A ratio was lower after athletic retirement, transforming a physiological entity into a pathological phenomena.

ECG changes are common in athletes with up to 40% demonstrating minor changes. However, in veteran athletes there has been an increase in the prevalence of supraventricular, complex ventricular and profound bradyarrhythmias in endurance-trained veteran athletes. Idiopathic ventricular arrhythmias have also been identified in athletes, which, by definition, originate in hearts without structural abnormalities. Some authors have noted that ventricular arrhythmias are sensitive to deconditioning in athletes with and without structural heart disease, and are thus a benign extension of the athlete's heart entity. Whilst others have noted that endurance athletes with arrhythmias have a high prevalence of right ventricular structural and/or arrhythmic involvement, providing further evidence for the development and/or progression of the underlying arrhythmogenic substrate with high-intensity lifelong endurance activity.

Recently, using cardiac magnetic resonance, Breuckmann et al. (2009) examined 102 healthy asymptomatic veteran male marathon runners and reported an ominously high prevalence of late gadolinium enhancement (12%, indicative of myocardial fibrosis), although not significantly different from control participants. The presence of idiopathic interstitial fibrosis could act as a pathological substrate in the development of fatal arrhythmias resulting in sudden cardiac death, with the cause(s) and consequence(s) of the myocardial fibrosis in veteran athletes unknown. Whether myocardial fibrosis reflects ageing, lifelong intense endurance training, subclinical cardiovascular disease or the interaction of these factors in some individuals cannot be determined from available data.

In conclusion, the veteran athlete may not be as healthy as believed with many established areas lacking conclusive evidence to support the benefits of a lifelong career in high intensive endurance exercise. Future studies employing large cohorts of veteran athletes, employing modern techniques such are cardiac magnetic resonance, are warranted to enhance our understanding of the impact of long-term endurance exercise on cardiac, peripheral vascular and cerebrovascular structure and function. Importantly, the systematic and longitudinal follow-up of veteran athletes (both male and female) who are currently experiencing arrhythmia is paramount. These studies will add to the relatively small body of knowledge providing important information regarding the differentiation of physiologic and pathologic cardiovascular remodelling and in the identification and management of cardiovascular pathology in veteran endurance athletes.

**Acknowledgments** DG received funding support from the National Heart Foundation of Australia. GW has received funding from Cardiac Risk in the Young (CRY, UK) and KG and GW have received technical and equipment support from General Electric (UK, South Africa, Australia and New Zealand). PA and CM received funding from Sport and Recreation New Zealand (SPARC).

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