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Does the Human Heart Fatigue Subsequent to Prolonged Exercise?

Ellen Dawson,[1] *Keith George*,[2] *Rob Shave*,[3] *Greg Whyte*[3] and *Derek Ball*[4]

1 Department of Exercise and Sport Science, Manchester Metropolitan University, Alsager, Cheshire, England
2 Research Institute for Sport and Exercise Science, Liverpool John Moores University, Liverpool, England
3 British Olympic Medical Centre, Northwick Park Hospital, Harrow, Middlesex, England
4 Department of Biomedical Sciences, University Medical School, Aberdeen University, Foresterhill, Aberdeen, Scotland

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Abstract

A reduction in left ventricular systolic and diastolic function subsequent to prolonged exercise in healthy humans, often called exercise-induced cardiac fatigue (EICF), has recently been reported in the literature. However, our current understanding of the exact nature and magnitude of EICF is limited. To date, there is no consensus as to the clinical relevance of such findings and whether such alterations in function are likely to impact upon performance. Much of the existing literature has employed field-based competitions. Whilst ecologically valid, this approach has made it difficult to control many factors such as the duration and intensity of effort, fitness and training status of subjects and environmental conditions. The impact of such variables on EICF has not been fully evaluated and is worthy of further research. To date, most EICF studies have been descriptive, with limited success in elucidating mechanisms. To this end, the

assessment of humoral markers of cardiac myocyte or membrane disruption has produced contradictory findings partially due to controversy over the validity of specific assays. It is, therefore, important that future research utilises reliable and valid biochemical techniques to address these aetiological factors as well as develop work on other potential contributors to EICF such as elevated free fatty acid concentrations, free radicals and β-adrenoceptor down-regulation. In summary, whilst some descriptive evidence of EICF is available, there are large gaps in our knowledge of what specific factors related to exercise might facilitate functional changes. These topics present interesting but complex challenges to future research in this field.

Prolonged exercise has been reported to result in skeletal muscle fatigue and damage as well as reduced performance.[1] The effect of prolonged exercise on cardiac muscle integrity and function is less well known. Starnes and Bowles[2] noted that this was surprising when you consider that cardiac muscle, unlike skeletal muscle, cannot 'take a break' after exercise. Current evidence suggests that short-term exercise has little detrimental impact upon left ventricular function.[3] The effects of prolonged exercise are more controversial and are, therefore, the subject of this review. The authors have attempted to review all pertinent full peer-reviewed journal papers on this topic that were sourced through database searches (e.g. Medline, SportsDiscus) or identification from similar articles.

The rationale for interest in this topic is essentially 2-fold. Firstly, what are the clinical consequences, if any, of exercise-induced cardiac fatigue (EICF)? Secondly, does EICF impact performance? Regarding the second point, it is interesting that the most commonly reported cardiovascular consequence of prolonged exercise has been a progressive rise in heart rate with exercise duration, termed cardiovascular drift.[4] Cardiovascular drift has been classically attributed to compensatory thermoregulatory mechanisms as exercise progresses; however, a direct effect of increased core temperature and/or sympathetic nervous activity has been implicated recently.[4] A reduction in intrinsic pump function or contractility has not been considered as a factor in the propagation of classic cardiovascular drift despite a suggestion from Saltin and Stenberg[5] in the 1960s that prolonged exercise may reduce left ventricular pumping performance. Interestingly, recent reports have suggested that a gradual decrease in heart rate is observed towards the end of an ultra-endurance activity.[6] The aetiology of this process has not been fully determined but is likely related to alterations in exercise intensity and substrate utilisation[6] rather than alterations in intrinsic pump function. However, a slow reduction in heart rate as a consequence of EICF, possibly mediated through a reduced chronotropic drive, has not been investigated. Thus, part of the driving rationale for investigating cardiac fatigue may lie in its role in the understanding of cardiovascular drift.

Despite Saltin and Stenberg's[5] suggestion that prolonged exercise may reduce left ventricular function, independent of haemodynamic loading (preload or afterload), relatively few studies have investigated the myocardial consequences of prolonged exercise in humans. Where data exist, they are primarily descriptive, utilising a broad range of assessment techniques with subjects in competitive, field-based environments. This has not allowed specific control of many confounding factors that might influence left ventricular function such as exercise intensity, duration, subject training status and environmental conditions. As a consequence, available data are contradictory. It is pertinent to note that the terminology used to describe the phenomenon of depressed left ventricular function subsequent to prolonged exercise is inconsistent in the growing literature base. Many authors[3] use the term cardiac fatigue or EICF whereas others[7] prefer left ventricular or cardiac dysfunction associated with exercise. Whilst the semantics of this debate may be impor-

Table I. Left ventricular function assessed during prolonged exercise

Author	Training status	Mode of exercise	Findings
Saltin and Stenberg[5]	T (n = 1) and U (n = 3)	180 min (75% $\dot{V}O_{2max}$) supine and upright exercise	SV decreased in upright and supine exercise with maintained BV
Upton et al.[9]	T (n = 9)	120 min (60–70% maximal workload) upright cycle exercise	Unchanged EDV and EF at 60 and 120 min
Palatini et al.[10]	T (n = 16)	Semi-supine cycle exercise to exhaustion at AT (50–80 min)	SV, EF, SBP/ESV ratio maintained throughout exercise
Goodman et al.[7]	T (n = 15)	150 min (60% $\dot{V}O_{2max}$) upright cycle	Unchanged EF and pressure : volume ratio throughout exercise

AT = anaerobic threshold; **BV** = blood volume; **EDV** = end-diastolic volume; **EF** = ejection fraction; **ESV** = end-systolic volume; **SBP** = systolic blood pressure; **SV** = stroke volume; **T** = trained; **U** = untrained; **$\dot{V}O_{2max}$** = maximum oxygen consumption.

tant, this review will use these terms interchangeably and in most instances as they appear in specific original research.

There is an increasing number of recent publications despite these problems, especially those relating to potential evidence of myocardial damage, that have prompted this review to build on earlier publications of Rowe[8] and Starnes and Bowles.[2] Therefore, it is the intention of this review; to document and evaluate current evidence for a reduction in left ventricular performance consequent to prolonged exercise in humans, to postulate potential mechanisms for such functional changes, to assess the clinical significance of such data and to highlight the necessity for further research to clarify specific practical and theoretical questions.

1. Evidence of Cardiac Fatigue

In an effort to obtain data in circumstances where the greatest possible exercise-related haemodynamic stress is placed upon the left ventricle, most studies have tended to concentrate on competitive athlete performances in the 'field'. Consequently, most investigations have been limited to the assessment of left ventricular function pre- and post-exercise. This has implications for assessment method choice as well as data interpretation. The few studies to have assessed ventricular function during exercise are reviewed in the following section.

1.1 During Prolonged Exercise

The investigation of left ventricular function during prolonged dynamic exercise is rare mainly because of logistical difficulties and cost (table I). The study by Saltin and Stenberg[5] provided the first potential link between prolonged exercise and cardiac fatigue. With stroke volume (SV) decreased after 3 hours of exercise despite the maintenance of blood volume, the authors suggested that in the face of unaltered preload it was likely that intrinsic pump function was reduced. This was supported when SV was not affected by exercise in the supine position when it is likely that preload increases.

More recently, studies have assessed left ventricular function during exercise using radionuclide angiography[7,9] which allows the determination of ejection fraction (EF) as a surrogate of left ventricular contractility, and echocardiography.[10] The studies by Palatini et al.[10] and Goodman et al.[7] are also notable as they reported functional data both during exercise and post-exercise. Upton et al.,[9] reported only small changes in SV and EF after 2 hours of upright cycling. However, maximal SV and cardiac output (brief maximal exercise bout) were reduced after prolonged exercise compared with a similar bout with no prior exercise. While this may be suggestive of some form of cardiac fatigue it is clear from the data that significant dehydration occurred that may have altered preload and limited maximal exercise performance. Similarly, Goodman et al.,[7] reported no change in SV and EF after 150 minutes of upright cycling at 60% of maximum oxygen consumption. Palatini et al.[10] reported that all aspects of left ventricular function were well maintained over the final half of an exercise test to exhaustion at the anaerobic threshold. It is interesting that all three studies found little evidence of

cardiac fatigue during the specific exercise regimen adopted. However, given that they utilised relatively shorter exercise sessions as well as controlled and quite low exercise intensities it is entirely possible that these studies simply did not place the necessary volume of haemodynamic and metabolic stress on the heart that may elicit signs of cardiac fatigue. However, the three studies should be applauded as rare examples where a controlled and structured approach to cardiac fatigue research has been utilised.

Despite the theoretical benefit of cardiovascular assessment during exercise it is pertinent to note the potential limitations of assessment during exercise. Despite being semi-invasive both dye dilution and radionuclide angiography can provide consistent estimates of cardiac function during submaximal steady-state exercise. Warburton et al.,[11,12] suggested that radionuclide angiography consistently underestimated cardiac output from rest through submaximal exercise intensities. Despite these issues, the use of echocardiography during exercise has proven to be even more limiting with technical problems associated with adequate image acquisition.[13] The utilisation of supra-sternal Doppler analysis of aortic flow potentially holds an accurate method of assessment of left ventricular function during exercise.[14]

1.2 Post-Prolonged Exercise

The majority of studies investigating EICF have assessed post-exercise left ventricular performance and compared the results with pre-exercise measurements (table II). It is clear from this data that contradictory outcomes are reported and that a broad range of exercise settings makes the direct comparison of studies difficult. We have made a simple delineation of studies related to trained and untrained subjects in table II. This is partially arbitrary as it relies on the individual authors definitions. Whilst duration of exercise is noted, information on exercise intensity is not always available due to the competitive nature of events and no details are included on ambient conditions because these are often not clearly reported or they are subject to significant change. Not surprisingly, given the technical difficulties of assessment, most studies presented in table II have ivuetilovoni@actrix.co.nz investigated the left ventricle with only scant attention paid to the right ventricle.[15-17]

1.2.1 Alterations in Systolic Function

Left ventricular systolic function has been assessed primarily with echocardiographic parameters that commonly include EF, fractional shortening (FS) and velocity of circumferential fibre shortening (V_{cfc}). These are indices of global left ventricular contractility. Whilst common and simple to perform it must be remembered that these variables make specific assumptions about the geometry of the left ventricle that may introduce error into the data.[35]

Following prolonged exercise, a decrease in contractility indices has been reported in several studies (table II), leading some authors to suggest that EICF is, in part, due to a depression in the inotropic state of the heart. This finding is not, however, universal as some studies have reported unaltered systolic dysfunction post-exercise.[7,9,10,14,24] Care must be taken in the interpretation of significantly reduced ejection phase indices as these are also dependent on changes in preload and afterload. Therefore it is important to interpret data in light of concomitant changes in the loading of the left ventricle especially when considering the likely effect of prolonged exercise on dehydration, hypovolemia and body mass.

Some studies have not reported data related to loading. It is therefore difficult to clearly underpin decrements in contractile function. Few, if any, studies assessed blood volume or central venous pressure as a surrogate of preload. In several studies, in which no direct measure of preload was reported, a lack of change in body mass, haemoglobin, haematocrit and serum electrolytes would suggest that there was only a limited change in preload.[18,26,30,33] However, using a decrease in body mass as an indicator of preload is open to question as preload may be maintained by internal fluid shifts from the extravascular to intravascular space.[33] Most studies relied on the interpretation of end-diastolic volume/diameter (EDV/D) data as an indicator of preload, although the technical limitations

Table II. Summary of research that has examined ventricular function after prolonged exercise in trained and untrained subjects (data are from left ventricle unless otherwise stated)

Study	Mode of exercise	Findings: recovery versus pre-exercise
Trained subjects		
Niemelä et al.[18]	24h run	Decreased EDD, ESD, FS
Perrault et al.[14]	Marathon	Decreased SBP
Douglas et al.[3]	Ironman triathlon	Decreased EDD, FS, E : A
Niemelä et al.[19]	24h run	Decreased FS, EDD, LV filling rate. Duration of LV filling reduced in fastest group
Carrió et al.[15]	6h run	Decreased RV EF. Increased LV EF. Systolic period prolonged
Douglas et al.[16]	Ironman triathlon	Decreased RV-E : A
Douglas et al.[20]	Ironman triathlon	Decreased EF, FS
Manier et al.[21]	Marathon	Decreased EDV, BP, systolic wall stress
Palatini et al.[10]	60 min cycling at AT	Decreased EDV
Siegel et al.[22]	Marathon	Antimyosin myocardical scintigarphy scans were normal
Davila-Roman et al.[17]	163km high altitude run	Increased RV end-diastolic area. Decreased RV fractional area change with hypokinesia and paradoxic septal motion
Douglas et al.[23]	Ironman triathlon	Decreased EF, FS
Lucía et al.[24]	Marathon	Decreased E : A
Rifai et al.[25]	Ironman triathlon	Decreased EF. Increased abnormal echo segments.
Whyte et al.[26]	Half and full Ironman triathlon	Decreased EDD, SV, FS, EF after full Ironman Decreased E : A after full and half Ironman
Warburton et al.[27]	Half-Ironman triathlon	2 of 9 subjects had ECG-derived late potentials
Goodman et al.[7]	150 min cycling	Increased time to peak filling in diastole
Haykowsky et al.[28]	Half-Ironman triathlon	Decreased systolic BP, FS, SBP to end-systolic cavity ratio (measure of LV contractility)
Shave et al.[29]	Lowe Alpine Mountain marathon (2 days: day 1 = 513 ± 121 min; day 2 = 348 ± 59 min)	Decreased EF, FS, SV, E : A after second days competition
Untrained subjects		
Seals et al.[30]	170 ± 10 min run	Decreased FS, mVcf, ESD, EDD
Vanoverschelde et al.[31]	20km run	Increased ESD. Decreased EDD, SBP, FS and EF
Ketelhut et al.[32]	60 min cycle at HR 130–140 beats/min	Decreased Q, EF, diastolic posterior wall velocity. Increase in TPR
Ketelhut et al.[33]	60 min cycle at HR 130–140 beats/min	Decreased Q, EF, fractional fibre shortening and contractility index. Increase in TPR
Eysmann et al.[34]	36–135 min cycle at 5–10% below AT until fatigue	Decreased EDV, SV, EF, E : A. Increased % atrial filling fraction

AT = anaerobic threshold; **BP** = blood pressure; **E : A** = early : artrial diastolic filling velocities; **ECG** = electrocardiogram; **EDD** = end diastolic dimension; **EDV** = end-diastolic volume; **EF** = ejection fraction; **ESD** = end systolic dimension; **FS** = fractional shortening; **HR** = heart rate; **LV** = left ventricle; **mVcf** = mean velocity of circumferential fibre shortening; **Q** = cardiac output; **RV** = right ventricle; **SBP** = systolic blood pressure; **SV** = stroke volume; **TPR** = total peripheral resistance; **Vcf** = velocity of circumferential fibre shortening.

of echocardiography to determine this must be recognised. Despite this, a decrease in EDV/D has been reported by several authors[3,18,19,21,26,31-34] as a likely consequence of reduced preload. However, a lack of significant correlation between the change in the EDV and the change in FS has been reported[3,18,26] suggesting that some other factor, in addition to a change in preload, may have affected contractile performance. Douglas et al.[3] reported a decreased FS and EDV after the Hawaii Ironman Triathlon; however, FS recovered towards baseline 48 hours post-exercise, whilst there was still a re-

duction in cavity size, indicating the decrease in FS was influenced not only by preload but also by additional factors.

Measures of contractility also vary inversely with afterload.[36] Arterial blood pressure or wall stress have been used as indictors of afterload in a number of the studies. A decreased or unaltered ventricular shortening in the presence of decreased systolic blood pressure/wall stress suggests a depression in cardiac contractility and has been reported by several authors.[3,18,19,21,26,31,34] If the stress-shortening relationship is used to measure contractility, the loading conditions of the left ventricle can be taken into account and a 'true' depression in contractility can be inferred with more confidence. This relationship has been reported as being displaced downwards by several authors suggesting a depression in inotropic state.[3,18,31,32]

1.2.2 Alterations in Diastolic Function

The diastolic component of left ventricular function is important but relatively poorly understood. Ventricular relaxation, and the decay in left ventricular pressure during diastole reflects a complex energy-requiring process during which Ca^{2+} is taken up by the sarcoplasmic reticulum within the myofibrils.[37] For complete myocyte relaxation to occur, the cytosol must be cleared of calcium so that calcium dissociates from troponin-C, and all tension-generating actin-myosin bonds are lysed. The diastolic clearance of cytosolic calcium requires adenosine triphosphate (ATP) to fuel the sarcoplasmic reticulum and sarcolemmal calcium ATPases which transport calcium into the sarcoplasmic reticulum or across the sarcolemma, respectively. Calcium removal may also occur via Na^+/Ca^{2+} exchange, and ATP is required to fuel the NA^+ pump which maintains a low intracellular Na^+ level which is favourable to Ca^{2+} extrusion by this mechanism.[38]

Shapiro and McKenna[39] suggested that the measurement of diastolic function could have an advantage over the assessment of systolic function, as changes in diastolic function may be detectable before changes in systolic function are evident. The interpretation of diastolic functional data in EICF studies is, however, potentially problematic. Diastolic function is technically difficult to assess during prolonged exercise and thus most studies have reported pre- and post-exercise comparisons of Doppler-derived variables such as the E **:** A ratio. This represents the ratio of early (passive) to late (atrial contraction) peak filling velocities. A reduction in the E **:** A ratio has been associated with left ventricular diastolic stiffness often observed in pathological conditions;[40] however, this represents only a global index of diastolic function and is affected by loading and heart rate amongst other factors.[41] This latter point is potentially problematic post-exercise as left ventricular filling time decreases rapidly with the increased heart rate.[42]

Evidence for diastolic dysfunction occurring after prolonged exercise has been reported in a number of the studies in table II.[3,19,20,23-26,29,34] Of these, Niemelä et al.[19] reported a reduction in the peak rate of dimensional increase of the left ventricle and a prolonged filling time, suggesting impaired left ventricle relaxation and filling in the earlier race finishers. They also reported a reduction in posterior wall thinning that may have been the result of altered behaviour of the myocardium during relaxation. A more common finding is a reduction in E **:** A ratio[3,24,26,29,31,34] with the majority noting that any depression was independent of an elevated post-exercise heart rate. For example, Douglas et al.[3] reported that the E **:** A ratio decreased from a resting value of 1.9 ± 0.6 to 1.5 ± 0.6 after an Ironman triathlon. Whyte et al.[26] also noted a depression in the E **:** A ratio from 1.9 ± 0.3 to 1.4 ± 0.2 after a half-Ironman and from 1.9 ± 0.3 to 1.5 ± 0.2 after a full Ironman. Interestingly, a decrease in the E **:** A ratio independent of heart rate, was reported by Lucia et al.[24] in the absence of systolic dysfunction. Vanoverschelde et al.[31] also noted that caution should be used when interpreting transmitral filling patterns. Despite these problems they concluded that a lack of correlation between the decrease in left ventricular preload and transmitral inflow dynamics after prolonged exercise implies preload cannot be solely responsible for any changes.[31]

1.3 Exercise-Related Factors that May Predispose to Cardiac Fatigue

Current evidence suggests that a likely consequence of prolonged exercise may be a transient depression in left ventricular function. It is possible that many different combinations of factors could precipitate EICF and thus explain the differences seen in table II. The results of any study could be influenced by factors such as duration, intensity and volume of exercise as well as subject fitness and environmental factors. It is, therefore, pertinent to investigate any direct or indirect evidence within available EICF literature on the basis of these methodological factors.

1.3.1 Duration and Intensity of Exercise

Despite the emphasis on prolonged laboratory or field-based exercise some authors have investigated the effect of brief exercise (with duration ranging from 5–18 minutes) and found no evidence of EICF.[3,30,31,33,34] This suggests that it is not exercise *per se* that causes the depression in cardiac function, but rather some specific (but prolonged) duration of exercise that is likely to be a major factor in the development of left ventricular dysfunction. This hypothesis is supported by Niemelä et al.[18] who reported that left ventricular function became somewhat more depressed during the last 6–8 hours of a 24-hour race in selected subjects who rested briefly mid-race for echocardiographic assessment. In the only study to investigate the same subjects in two exercise bouts, Whyte et al.[26] observed a depression in systolic function after a full Ironman (10 hours and 40 minutes) but not after a half-Ironman triathlon (5 hours and 29 minutes). In a recent study of a mountain marathon race over two days there was some evidence that the alterations in systolic and diastolic function were more pronounced after the second day of activity.[29]

Studies that report no evidence of EICF have generally adopted exercise regimes with shorter durations than full or half-Ironman triathlons. No change in EF was reported in trained subjects following upright bicycle exercise after 60,[10] 120[9] and 150[7] minutes or after marathon running.[14,22,24] Whether the marathon distance might represent an inadequate duration of exercise to induce cardiac fatigue is, however, contradicted by the dysfunction reported after similar exercise durations.[30,31] Whilst prolonged duration is likely to be an important factor for the development of EICF there is no consensus as to what duration might be critical in the onset of EICF and even if a threshold concept is plausible.

The impact of exercise intensity is virtually impossible to divorce from duration given that many studies are completed at a self-selected and competitive intensity. The addition of competitive stress may intuitively add to the work imposed on the left ventricle if heart rates are increased. To date, there is no specific investigation of exercise intensity alone upon the development of EICF. There is evidence of cardiac fatigue in competitive situations[26,28] as well as non-competitive exercise.[30] Conversely, left ventricular systolic dysfunction has not been reported after some competitive races.[24] Some indirect evidence supportive of a role for exercise intensity is worthy of note. Niemelä et al.[19] reported greater evidence of EICF in those athletes who covered greater distances in a 24-hour run and Douglas et al.[3] reported that the reduction in ventricular shortening tended to be greater in those with the fastest race times.

It is interesting to note that three studies of relatively limited duration that controlled exercise intensity in laboratory studies reported no evidence of EICF.[7,9,10] Thus, a pattern of combined and potentially interactive exercise-related factors may well be important in placing significant stress on the left ventricle to elicit EICF.

1.3.2 Fitness and/or Training Status of the Subjects

The concept that the impact of exercise may be different depending on the nature of the competitor based on factors such as age, sex and training status is interesting but not supported by any investigation. This is due to the lack of specific investigation of these factors and the fact that both males and females of a broad age range have been studied within individual studies.

The choice of subjects in table II has included both well-trained[3,26] and recreational or untrained[10,30-34] participants. In addition, many of the

previous studies have simply not recorded the fitness levels of the subjects thus making it difficult to assess the impact of fitness upon EICF. Despite this, EICF has been reported in athletes who completed extremely demanding events such as an Ironman triathlon and 24-hour running[3,18-20,26] as well as untrained individuals completing short duration (60-minute) cycle ergometry.[32] It is interesting to postulate that in untrained individuals the amount of exercise needed to impair cardiac function may be less than that needed in highly trained athletes but current data do not support this contention. Unpublished observations from our laboratory reported no difference in either systolic or diastolic function between sedentary and well-trained individuals who completed a 4-hour cycle ride at 90% of their lactate threshold.

1.3.3 Environmental Factors

Due to the field-based nature of much of the EICF literature, it was proposed that the effects of any environmental strain might be more important than exercise duration in the development of cardiac fatigue.[24] Prolonged exercise in conjunction with severe climatic conditions might result in electrolyte disturbances and/or severe loss of plasma volume that could contribute to altered haemodynamic load, thus precipitating a reduced SV, as well as potentially augmenting the mechanism(s) underpinning reduced inotropic activity seen in EICF. Studies with well documented environmental temperature data are interesting but far from conclusive. Perrault et al.[14] did not witness any reduced left ventricular function despite environmental conditions of 27°C temperature and a humidity of 94% in the Montreal International Marathon. Conversely, Niemelä et al.[18] reported systolic dysfunction in athletes competing for 24 hours in cooler conditions 7–15°C (humidity of 50–60%).

Prolonged exercise at altitude has been shown to produce acute pulmonary oedema[43] and Davila-Roman et al.[17] reported depressed right ventricular function (with no left ventricular dysfunction) in runners who completed an ultra-endurance alpine marathon (163km at 2350–4300m). The presence of right ventricular dysfunction in these athletes may be related to the presence of pulmonary oedema; however, definitive answers remain elusive. The lack of left ventricular dysfunction in such circumstances is a little surprising given the low partial pressure of oxygen at altitude. It has been hypothesised that an increased rate-pressure product and hyperventilation in non-acclimatised individuals could lead to coronary vasospasm which would result in ischaemia.[44,45] With such contradictory evidence, it is impossible at this stage to draw specific conclusions about the impact of environmental strain on the development of EICF.

2. Mechanisms Underpinning Cardiac Fatigue

Whilst there is a burgeoning body of evidence that supports the existence of EICF, to date we have limited insight into the potential underlying mechanisms. The most common approach to aetiological investigation has been to look for evidence of myocardial damage, possibly related to ischaemia, through changes in electrocardiogram (ECG) or the appearance of blood-borne markers indicative of myocardial cell damage. Again, the data are inconsistent possibly as a result of the limitations of field studies. In answering more mechanistic questions, the use of animal models may prove to be extremely valuable and the review of Starnes and Bowles[2] provides some insightful comments on such work.

2.1 Myocardial Damage or Disruption

As in clinical scenarios, if myocardial damage occurs with prolonged exercise, this would result in the release of myocardial cellular proteins into the general circulation, where they can be detected. Myocardial damage could underpin the left ventricular systolic and diastolic dysfunction reported in a range of descriptive studies. Starnes and Bowles[2] suggested that transient ischaemia was a likely mechanism for EICF and could result from a process called myocardial 'stunning'. Stunning can affect calcium metabolism that would underpin alterations in contractile function. In addition, ischaemia can cause a functional impairment in myocyte relaxation[38] possibly as the result of altered myofilament

responsiveness to Ca^{2+} as well as cytosolic Ca^{2+} overload.[46] The theory of 'stunning' is attractive on the basis that it does not result in necrosis and permanent cellular damage and is transient in nature. This hypothesis is indirectly supported by the few studies that have reported normalisation of left ventricular function 24–48 hours post-exercise.[3,26] Care must be taken, however, as there is limited direct evidence of any myocardial ischaemia in any EICF studies including ECG data.[3,18,26] Osbakken and Locko[47] employed stress-redistributed thallium scans and reported possible evidence of myocardial perfusion defects in trained athletes after 40 ± 7 minutes of fatigue-limited submaximal bicycle exercise. They suggested that this might be caused by ischaemia or coronary vasospasm. However, the lack of any other evidence of cardiac dysfunction led them to conclude that the changes may be due to uneven ventricular hypertrophy resulting from the pressure and volume loads imposed by exercise.

Several studies have reported data for markers of myocardial damage (table III). Early studies investigated the hybrid type (MB) isoenzyme of creatine kinase (CKMB) as it has been used to detect myocardial damage subsequent to myocardial infarction.[48] Increases in CKMB have been found above reference levels[49] and into the range suggestive of myocardial damage after marathon running.[50,51] However, there is a small proportion of the MB isoenzyme present in skeletal muscle and it is possi-

Table III. Studies investigating cardiac troponins and natriuretic peptides as biochemical markers of myocardial damage after prolonged exercise

Study	Blood measurement	Exercise	Findings
Cummins et al.[51]	cTnI	Marathon	Mean cTnI levels not elevated
Mair et al.[55]	cTnT (2nd gen)	230km cycle	cTnT elevated in 1/28 cyclists
Koller et al.[56]	cTnT (1st gen), cTnI	Marathon	cTnT cTnI elevated in 1/19 subjects
Siegel et al.[22]	cTnT (1st gen)	Marathon	cTnT in range of AMI in 3/4 subjects
Bonetti et al.[57]	cTnT (2nd gen)	Giro d'Italia	cTnT elevated in 5/28 cyclists
Laslett et al.[58]	cTnT (1st gen)	100 miles (161km) [18–30h]	cTnT elevated in all subjects
Laslett and Eisenbud[59]	cTnT (2nd gen)[a]	100 miles (161km) [18–30h]	No elevation in cTnT when use 2nd gen
Davila-Roman et al.[17]	cTnI	163km high altitude run	cTnI increased in only 1 subject
Mair et al.[60]	cTnT (2nd gen)	67km Alpine marathon	No elevation cTnT or cTnI
Siegel et al.[61]	cTnT (1st gen/2nd gen), cTnI	Marathon	1st gen cTnT elevated in 20%. 2nd Gen no elevation
Koller et al.[62]	cTnT (2nd gen), cTnI	67km alpine run/230km cycle	No elevation cTnT or cTnI
Denvir et al.[63]	cTnI	Triathlon	cTnI elevated in 6 out of 25 athletes
Lucía et al.[24]	cTnT (2nd gen), cTnI	Marathon	No elevation in cTnT, cTnI elevated in 1 subject
Rifai et al.[25]	cTnT (2nd gen), cTnI	Ironman triathlon	cTnT elevated in 6 subjects cTnI elevated in 2 subjects
Whyte et al.[26]	cTnT (1st gen)	Half/full Ironman	cTnT elevated both races. Normal by 24h post-race
Ohba et al.[64]	BNP, ANP, cTnT (2nd gen)	100km marathon	Increased ANP/BNP, cTnT elevated in 9/10 runners
Siegel et al.[65]	BNP, cTnT, cTnI (range of assays)	Marathon (4-year study)	BNP normal. No change in cTnT. 6-fold rise in cTnI (high-sensitive method)
Neumayr et al.[66]	CTnI	Radmarathon (230km)	cTnI elevated in 13/38 subjects
Neumayr et al.[67]	cTnI and cTnT (3rd gen)	Race across the Alps (509km)	cTnI elevated in 6/10 and cTnT elevated in 1/10
Shave et al.[29]	cTnT (3rd gen)	Two day race in Scottish Hills	cTnT elevated in 13/26 after day 1, 1/26 after day 2

a Re-test of Laslett et al.[58]

1st gen = first generation assay; **2nd gen** = second generation assay; **3rd gen** = third generation assay; **AMI** = acute myocardial infarction; **ANP** = atrial natriuretic peptide; **BNP** = brain natriuretic peptide; **cTnI** = cardiac troponin I; **cTnT** = cardiac troponin T.

ble that damage to skeletal muscle could result in an elevation of CKMB.[52] This suggestion was supported by several authors who have found CKMB levels indicative of cardiac damage that conflicted with other findings using techniques such as CKMB mass/total creatine kinase ratio,[18,24,53] technetium 99m pyrophosphate scintigraphy[50,51,54] or thallium myocardial perfusion imaging.[22]

Most recent studies (table III) have investigated the myofibrillar proteins cardiac troponin T (cTnT) and troponin I (cTnI) as they are considered to be more specific markers[68] of myocardial damage. Cardiac troponins have been found to be present in the circulation after ischaemia and post-myocardial infarction.[69] The advantage of the specific cTnT and cTnI assays over CKMB measurements is that the greater sensitivity may allow the detection of small areas of myocardial damage potentially related to microvascular spasm.[8] Inconsistent evidence of elevated cTnT and cTnI after prolonged exercise is evident. Several of the studies in table III used the first generation cTnT ELISA immunoassay to examine myocardial damage,[22,26,56,58] which has now been shown to have a 12% cross reactivity with skeletal troponin T.[69] These confounding results may be due to unspecified binding of skeletal troponin T to the wall of the test tube which occurs in the presence of a total creatine kinase serum level greater than 5 μg/L. Therefore, there is the probability of false positive identification of cardiac damage in these studies. Consequently, a second-generation immunoassay was developed and subsequently used to assess EICF following endurance exercise.[24,25,55,57,59-61,64] Using the second-generation immunoassay, Rifai et al.[25] demonstrated elevated cTnT in six subjects following the Hawaii Ironman triathlon. Conversely, Laslett et al.[59] Siegel et al.[61] and Lucía et al.[24] reported limited evidence of myocardial damage using the second generation ELISA. The second-generation immunoassay uses a bovine cTnT as the calibration material, therefore its specificity for identifying human cTnT has recently been questioned.[68] A new third generation immunoassay has been developed using recombinant human cTnT and has been validated in a clinical setting.[68] Recently, Shave et al.[70] reported that despite significant elevations in both total creatine kinase and CKMB following eccentric exercise that induced skeletal muscle damage, the new third generation cTnT immunoassay remained unchanged, suggesting a high degree of cardiospecificity.

Despite less frequent use (table III) cardiac TnI is thought to be an even more specific marker of myocardial damage as it is not found in skeletal muscle. No or limited overall alterations in serum cTnI concentrations have been reported after exercise such as a marathon[24,51] or altitude ultra-marathon running.[17] However, elevated levels of cTnI have been reported in a few samples in several different studies[63,65-67] The variation in findings could be due to the diversity of platforms used, which has added to the limited clinical evaluation of cTnI compared with cTnT.[68] A further problem with several of the troponin studies is the timing of samples taken. Cardiac troponin T takes 3–4 hours to enter into the circulation after myocardial damage and reaches an early peak between the 12–18 hours, depending on the release of the cytoplasmic component, following membrane depolarisation.[57] Cardiac TnT has a half-life in the circulation of 120 minutes.[71] It appears that the prolonged window of detection for cTnT is due to continuous release of cTnT from the myofibrillar pool as the contractile apparatus undergoes degradation. The clearance rate of cTnI is not known. Many of the previous EICF studies took blood samples immediately post-exercise and in those protocols of less than 3 hours the authors may have missed the detection of myocardial damage. Combined with the consideration of technical issues is a contentious debate about the exact origin of cTnT and cTnI. Because most cTnI and cTnT data do not make the cut-off levels for diagnosis of myocardial infarction there is some discussion as to whether the troponin concentrations represent markers of disruption of contractile proteins or the simple membrane leakage of the cytosolic component of cardiac troponins. There is no definitive answer to this question but release of the cytosolic component subsequent to some altera-

tion in membrane permeability would not, theoretically, alter contractile function. Neumayr et al.[66,67] suggested that the kinetics of cTnI and cTnT release could be explained by a transient increase in membrane permeability so that cytosolic troponins could leak into the circulation. They further postulated that the transitory, reversible shift in membrane permeability was caused by a stress-induced increase in free radicals although this was not specifically assessed.

As only a few studies have looked at functional and biochemical indices in the same study,[17,22,24-26,29] it is difficult to confirm a causal link between the two. The study by Rifai et al.[25] is worthy of individual consideration because second generation cTnT as well as cTnI assays were compared with quantitative echocardiographic segmental wall motion analysis. They reported greater echo 'scores', indicative of worsening left ventricular function, in those subjects with a significant increase in cTnT and/or cTnI compared with those without. This suggests some link between functional decrements and the presence of markers of myocardial damage.

Atrial and brain natruiretic peptides (ANP, BNP) have been used widely as markers of cardiac dysfunction in the clinical literature but infrequently in EICF studies.[64,65] Siegel et al.[65] reported elevated BNP after a marathon but this was still within normal limits. Conversely, Obha et al.[64] reported a significant increase in both ANP and BNP after a 100km race. The ANP and BNP concentrations were strongly associated with increases in cTnT. Obha et al.[64] noted that this additional biochemical evidence was strongly suggestive of myocardial damage.

2.2 β-Adrenergic Down-Regulation

An alternate mechanism proposed to result in a decreased inotropic state is a desensitisation (down regulation and uncoupling) of cardiac β-adrenoceptors. Support for this theory was provided by Friedman et al.[72] who reported that a single 60-minute bout of dynamic exercise in dogs produced decreased chronotropic responsiveness to isoproterenol. Given that prolonged exercise provides a lengthy exposure to elevated catecholamines it is possible that there is a post-exercise paradoxical down-regulation of β-adrenoceptors to below pre-exercise levels.[73] It is tempting to postulate that conflicting evidence of the incidence of EICF in the literature could be explained by some studies employing exercise that is of insufficient duration to result in a down-regulation of β-adrenoceptors.

Confirmation of such a hypothesis in humans is difficult as there are methodological problems with assessing left ventricular inotropic response to β-adrenoceptor stimulation. However, the method of assessing chronotropic responses to isoproterenol infusion offers a viable alternative.[23,34] Eysmann et al.[34] reported decreased chronotropic responsiveness to prolonged exercise in sedentary individuals and Douglas et al.[23] reported decreased chronotropic responsiveness after a Hawaii Ironman Triathlon. Both studies reported decreased EF and diastolic function post-exercise but only in the Eysmann et al.[34] study did this correlate significantly with the degree of transient depression in chronotropic response. Taken together, these studies suggest that left ventricular dysfunction observed after prolonged exercise may, at least in part, be explained by altered sympathoadrenal activity and responses.[34] It is thought that exposure to excessive catecholamines might trigger this β-adrenoceptor down-regulation. Catecholamines have been shown to rise considerably, with endurance exercise[30,74] often in proportion to exercise intensity.[75] Whether this process could lead to a reduced heart rate reported with ultra-endurance activity[7] has not been elucidated.

2.3 Other Factors

Prolonged exercise results in increased plasma free fatty acid concentrations.[30] Elevated levels of free fatty acids can result in a decreased inotropic state.[76] Both McKechnie[43] and Seals et al.[30] suggested that the depression in left ventricular function found in their study was caused by a significantly increased concentration of free fatty acids. Free fatty acids may reduce the efficiency of mitochondrial respiration through uncoupling of electron transport,

acting through cellular accumulation of long-chain fatty acyl CoA and carnitine.[76] Interestingly, Niemelä et al.[18] reported echocardiographic evidence of EICF but the 2-fold increase in free fatty acids found was assumed to be too low to have caused an alteration in left ventricular function.

Prolonged exercise also results in elevated free radical production and this has been speculated as a potential aetiological factor for EICF.[2] There is, however, no data available in human studies relating free radical production to either functional alterations in the left ventricle or the appearance of cardiac troponins. If free radical damage were underpinning EICF then the use of antioxidants might be a valuable avenue for future research.

A myriad of other factors could also be involved in the genesis of EICF but have not received specific research attention. It is possible that changes in set point, operating point, or gain of parasympathetic tone and a variety of autonomic reflexes, including the arterial baroreflex and carotid chemoreflex could also result in changes in the inotropic state.[23] The influence of neural control and variables such as heart rate variability may be worthy of systematic investigation

The explanation for diastolic functional alterations after exercise is unclear but may be underpinned by altered Ca^{2+} metabolism. As has been suggested, Ca^{2+} metabolism can be impaired as a consequence of ischaemia but other factors that such as increased pH or inorganic phosphates can alter myofilament sensitivity to calcium and possibly influence both systolic and diastolic tension.[77]

3. Clinical Significance of Cardiac Fatigue

Part of the rationale for EICF research is based upon the concern that prolonged exercise may be deleterious to the health of the heart. Most authors make the assumption that any elevation of cTnT or cTnI represents some insult to the myocardial cell, however, debate centres on the nature and long-term significance of such insults. In earlier papers, Rowe[8,45] expressed significant concern about the possibility of exercise-induced coronary vasospasm when relating details of Sy Mah (world record holder for completing most marathons). It was reported that Sy Mah had focal fibrosis of the papillary muscles with an absence of atherosclerosis at his autopsy. Rowe[8] postulated that this was due to exercise-induced vasospasm causing localised and silent ischaemia. Concern for the effects of exercise on the health of the heart were also aroused by the earlier data from McKechnie et al.[43] who reported two case studies of athletes who had developed clinical signs of left ventricular heart failure after a 90km race. McKechnie et al.[43] suggested that the pulmonary oedema found in these athletes was a result of exercise-induced cardiac dysfunction and again Rowe[8] postulated exercise-induced coronary vasospasm as the cause. A number of echocardiographic studies have reported wall motion abnormalities.[20,21,25] Manier et al.[21] reported septal akinesia in one athlete after a marathon and Rifai et al.[25] reported significant decrements in quantitative echocardiographic wall motion analysis, associated with elevated cTnT and cTnI and stated that it was clear that some form of myocardial injury was present but the extent of the damage, the reversibility and the long-term consequences were impossible to determine. Damm et al.[78] reported that five of eight elite male Swedish orienteers with resting wall motion abnormalities, as assessed by radionuclide angiography, could not significantly increase their EF with dynamic exercise and had evidence of concealed left ventricular damage. Rowe[8] stated that whilst plausible explanations for such localised necrosis had been provided, further necropsy studies would be required.

From these data it is possible to take two different clinical standpoints. Firstly, the depression in function and elevation in cardiac troponin levels are quite small in clinical terms. Added to this is the finding that when the symptoms are present they return to baseline levels within 24–48 hours after completion of the exercise bout.[3,17,18,26] Thus, to date we have no evidence that any individual event produces long-lasting dysfunction. However, an alternative viewpoint has been expressed in the recent work of Neumayr and coworkers.[66,67] Neumayr et

al.[67] stated "the crucial question is not whether this exercise-induced release of cardiac troponins represents myocardial damage or not. The more decisive point in this context … is whether they reflect reversible versus irreversible cardiac injury". Although they postulated that membrane leakage of cytosolic troponins may be more likely than myofibrillar degradation they were clear to note the lack of any conclusive data. Neumayr et al.[67] further suggested that a continuum of reversible-irreversible myocardial injuries may occur in exercise although, delineation of these may be very difficult, and that "as long as the clinical meaning of exercise-induced release of cardiac troponin is uncertain it should be considered as biochemical evidence for subclinical myocardial damage".

4. Future Research

Given the limited amount of data currently available in this area, there is significant scope for future research related to a range of important issues. While controversy still exists as to the actual existence of EICF there is a continuing need for descriptive research that documents the nature and magnitude of EICF. At a very simplistic level we do not know the repeatability of the current functional and biochemical data in any subject population or exercise setting.

Beyond this, it is pertinent for future research to take a systematic and more controlled approach to the investigation of, and interaction between, a range of exercise-related factors that may or may not, predispose the athlete to develop EICF. Future research should continue to investigate the impact of exercise duration (and intensity) on EICF in a range of controlled studies. There has also been no structured approach to the assessment of the impact of exercise mode on EICF. Given the fact that different exercise modes may place different haemodynamic loads upon the left ventricle means that this issue is worthy of further investigation. The impact of prolonged exercise upon left ventricular function in untrained individuals is far from clear due to a severely limited database. If EICF occurs earlier or is more pronounced in untrained individuals this may have important performance and clinical implications. Whilst a sensible area for future research, it is important to note the limitations of direct comparisons between trained and untrained individuals as both duration and intensity of effort are likely to differ. Similarly, a structured approach to the assessment of environmental strain imposed upon prolonged exercise in the development of EICF would be a useful line of research to prosecute.

Wherever possible, specific methodological concerns need to be addressed in future work. Control of preload is an area of some importance in the understanding of EICF. This is, however, difficult to both achieve and assess and may require some invasive techniques that are best suited to animal research. Limited data exit for left ventricular function during exercise and this should be extended in future studies potentially with greater duration of exercise employed. Although difficult to assess, the impact of exercise upon the right ventricle is worthy of study to build on a limited database.[15-17] It is also pertinent to look at diastolic dysfunction in more detail at is a relatively poorly understood area that receives less research attention. Within the clinical setting, diastolic function can precede inotropic failure after mild ischaemia and some evidence suggests that it may occur prior to systolic dysfunction during prolonged exercise. The mechanisms underpinning diastolic functional changes with prolonged exercise should also be elucidated. It may also be valuable to extend to other methods of data collection such as tissue Doppler.[79]

The study of the mechanisms underlying EICF is the least explored area within the literature and future research needs to rectify this. This will likely have a significant impact on our understanding of the clinical significance of EICF. Future research should investigate a range of markers for myocardial damage such as ANP, BNP and potentially other assays such as cardiotrophin-I,[80] to potentially provide a broader picture of the consequences of prolonged exercise for the integrity of myocardial cells. Development of the initial work on β-adrenoceptor down-regulation post-prolonged exercise is also a valuable avenue to pursue. There is also scope for

broadening research interests to include areas such as elevated free radicals[81] and potassium[82] concentrations and their impact on left ventricular inotropism.

Whilst concern is justified, the clinical impact of prolonged exercise is far from certain and requires a substantial amount of future work. What the consequences of repeated exposure to prolonged endurance activities, possibly over a number of years, are as yet undetermined.

5. Conclusions

It is clear that there are still many gaps in the description, understanding, causes and consequences of EICF. Despite this, there is a growing body of evidence that has reported aspects of left and right ventricular systolic and diastolic dysfunction after a range of exercise bouts in a variety of settings and subjects. In a similar range of exercise settings, there is also a small but noticeable body of data that suggest prolonged exercise may be related to some form of transient myocardial insult as denoted by the presence of cardiac troponins in the systemic circulation. Why only some subjects present elevated cardiac troponins and whether this underpins left ventricular functional changes is not presently known. This topic remains an interesting and important area of future research and understanding in the clinical and scientific community.

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References

1. Overgaard K, Lindstrom T, Ingemann-Hansen T, et al. Membrane leakage and increased content of Na+-K+ pumps and Ca2+ in human muscle after a 100-km run. J Appl Physiol 2002; 92: 1891-8
2. Starnes JW, Bowles DK. Role of exercise in the cause and prevention of cardiac dysfunction. Exerc Sport Sci Rev 1995; 23: 349-74
3. Douglas PS, O'Toole ML, Hiller WDB, et al. Cardiac fatigue after prolonged exercise. Circulation 1987; 76: 1206-13
4. Coyle EF, Gonzalez-Alonso J. Cardiovascular drift during prolonged exercise: new perspectives. Exerc Sport Sci Rev 2001; 29: 92-9
5. Saltin B, Stenberg J. Circulatory response to prolonged severe exercise. J Appl Physiol 1964; 19: 833-8
6. Laursen PB, Rhodes EC. Factors affecting performance in an ultra endurance triathlon. Sports Med 2001; 31: 195-209
7. Goodman JM, McLaughlin PR, Liu PP. Left ventricular performance during prolonged exercise: absence of systolic dysfunction. Clin Sci (Lond) 2001; 100: 529-37
8. Rowe WJ. Endurance exercise and injury to the heart. Sports Med 1993; 16: 73-9
9. Upton MT, Rerych SK, Roeback JR, et al. Effect of brief and prolonged exercise on left ventricular performance. Am J Cardiol 1980; 45: 1154-60
10. Palatini P, Bongiovi S, Marcor F, et al. Left ventricular performance during prolonged exercise and early recovery in healthy subjects. Eur J Appl Physiol 1994; 69: 396-401
11. Warburton DER, Haykowsky MJF, Quinney HA, et al. Reliability and validity of measures of cardiac output during incremental to maximal aerobic exercise. Part I: conventional techniques. Sports Med 1999; 27: 23-41
12. Warburton DER, Haykowsky MJF, Quinney HA, et al. Reliability and validity of measures of cardiac output during incremental to maximal aerobic exercise. Part II: novel techniques and new advances. Sports Med 1999; 27: 241-60
13. Crawford MH, White DH, Amon KW. Echocardiographic evaluation of left ventricular size and performance during handgrip and supine and upright bicycle exercise. Circulation 1979; 59: 1188-96
14. Perrault H, Peronnet F, Lebeau R, et al. Echocardiographic assessment of left ventricular performance before and after marathon running. Am Heart J 1986; 112: 1026-31
15. Carrió I, Serra-Grima R, Berna L, et al. Transient alterations in cardiac performance after a six-hour race. Am J Cardiol 1990; 65: 1471-4
16. Douglas PS, O'Toole ML, Hiller WDB, et al. Different effects of prolonged exercise on the right and left ventricles. J Am Coll Cardiol 1990; 15: 64-9
17. Davila-Roman VG, Guest TM, Tuteur PG, et al. Transient right but not left ventricular dysfunction after strenuous exercise at high altitude. J Am Coll Cardiol 1997; 30: 468-73
18. Niemelä KO, Palatsi IJ, Ikaheimo MJ, et al. Evidence of impaired left ventricular performance after an uninterrupted competitive 24 hour run. Circulation 1984; 70: 350-6
19. Niemelä K, Palasti I, Ikaheimo M, et al. Impaired left ventricular diastolic function in athletes after utterly strenuous prolonged exercise. Int J Sports Med 1987; 8: 61-5
20. Douglas PS, O'Toole M, Woolard J. Regional wall motion abnormalities after prolonged exercise in the normal left ventricle. Circulation 1990; 82: 2108-14
21. Manier G, Wickers F, Lomenech AM, et al. Echocardiographic assessment of myocardial performance after prolonged strenuous exercise. Eur Heart J 1991; 12: 1183-8
22. Siegel AJ, Lewandrowski KB, Strauss HW, et al. Normal post-race antimyosin myocardial scintigraphy in asymptomatic marathon runners with elevated serum creatine kinase MB isoenzyme and troponin T levels. Circulation 1995; 86: 451-6
23. Douglas PS, O'Toole ML, Katz SE. Prolonged exercise alters cardiac chronotropic responsiveness in endurance athletes. J Sports Med Phys Fitness 1998; 38: 158-63

24. Lucía A, Serratosa L, Saborido A, et al. Short-term effects of marathon running: no evidence of cardiac dysfunction. Med Sci Sports Exerc 1999; 31: 1414-21
25. Rifai N, Douglas PS, O'Toole M, et al. Cardiac troponin T and I, electrocardiographic wall motion analyses, and ejection fractions in athletes participating in the Hawaii Ironman triathlon. Am J Cardiol 1999; 83: 1085-9
26. Whyte GP, George K, Sharma S, et al. Cardiac fatigue following prolonged endurance exercise of differing distances. Med Sci Sports Exerc 2000; 32: 1067-72
27. Warburton DER, Welch RC, Haykowsky MJ, et al. Effects of half triathlon on the development of late potentials. Med Sci Sports Exerc 2000; 32: 1208-13
28. Haykowsky M, Welsh R, Humen D, et al. Impaired left ventricular systolic function after a half-Ironman race. Can J Cardiol 2001; 17: 687-90
29. Shave R, Dawson E, Whyte G, et al. Evidence of exercise-induced cardiac dysfunction and elevated cTnT in separate cohorts competing in an ultra-endurance mountain marathon race. Int J Sport Med 2002; 23: 489-94
30. Seals DR, Rogers MA, Hagberg JM, et al. Left ventricular dysfunction after prolonged strenuous exercise in healthy subjects. Am J Cardiol 1988; 61: 875-9
31. Vanoverschelde JLJ, Younis LT, Melin JA, et al. Prolonged exercise induces left ventricular dysfunction in healthy subjects. J Appl Physiol 1991; 70: 1356-63
32. Ketelhut R, Losem CJ, Messerli FH. Depressed systolic and diastolic cardiac function after prolonged aerobic exercise in healthy subjects. Int J Sports Med 1992; 13: 293-7
33. Ketelhut R, Losem CJ, Messerli FH. Is a decrease in arterial pressure during long-term aerobic exercise caused by a fall in cardiac pump function? Am Heart J 1994; 127: 567-71
34. Eysmann SB, Gervino E, Vatner DE, et al. Prolonged exercise alters β-adrenergic responsiveness in healthy sedentary humans. J Appl Physiol 1996; 80: 616-22
35. Longo MR, Guzman AW, Triebwasser JH. Normal values and commonly used echocardiographic formulae for adults. Aviat Space Environ Med 1975; 46: 1062-4
36. Robotham JL, Takata M, Berman M, et al. Ejection fraction revisited. Anesthesiology 1991; 74: 172-83
37. Penny DJ. The basics of ventricular function. Cardiol Young 1999; 9: 210-23
38. Apstein CS, Eberli FR. Diastolic function and dysfunction with exercise, hypertrophy, ischemia, and heart failure. Cardiologia 1998; 43: 1269-79
39. Shapiro LM, McKenna WJ. Left ventricular hypertrophy: relation of structure to diastolic function in hypertension. Br Heart J 1984; 51: 637-42
40. Maron BJ. Structural features of the athlete heart as defined by echocardiography. J Am Coll Cardiol 1986; 7: 190-203
41. Lim MJ, Buda AJ. Doppler echocardiography in the evaluation of left ventricular diastolic function. Curr Opin Cardiol 1991; 6: 937-45
42. Libonati JR. Myocardial diastolic function and exercise. Med Sci Sports Exerc 1999; 31: 1741-7
43. McKechnie JK, Leary WP, Noakes TD, et al. Acute pulmonary oedema in two athletes during a 90-km running race. S Afr Med J 1979; 56: 261-5
44. Yasue H, Omote S, Takizawa A, et al. Circadian variation of exercise capacity in patients with prinzmetal's variant angina: role of exercise-induced coronary arterial spasm. Circulation 1979; 59: 938-48
45. Rowe WJ. Extraordinary unremitting endurance exercise and permanent injury to normal heart. Lancet 1992; 340: 712-4
46. Paulus WJ, Shah AM. NO and cardiac diastolic function. Cardiovasc Res 1999; 43: 595-606
47. Osbakken M, Locko R. Scintigraphy determination of ventricular function and coronary perfusion in long-distance runners. Am Heart J 1984; 108: 296-304
48. Roberts R. Diagnostic assessment of myocardial infarct based on lactate dehydrogenase and creatine kinase isoenzymes. Heart Lung 1981; 10: 486-506
49. Apple FS, Rogers MA, Sherman WM, et al. Profile of creatine kinase isoenzymes in skeletal muscle of marathon runners. Clin Chem 1984; 30: 413-6
50. Ohman EM, Teo KK, Johnson AH, et al. Abnormal cardiac enzyme responses after strenuous exercise: alternative diagnostic aids. BMJ 1982; 285: 1523-6
51. Cummins P, Young A, Auckland ML, et al. Comparison of serum cardiac specific troponin-I with creatine kinase, creatine kinase-MB isoenzyme, tropomyosin, myoglobin and C-reactive protein release in marathon runners: cardiac or skeletal muscle trauma? Eur J Clin Invest 1987; 17: 317-24
52. Schneider CM, Dennehy CA, Rodearmel SJ, et al. Effects of physical activity on creatine phosphokinase and the isoenzyme creatine kinase-MB. Ann Emerg Med 1995; 25: 520-1
53. Ordonez-Llanos J, Serra-Grima JR, Merce-Muntanola J, et al. Ratio of creatine kinase 2 mass concentration to total creatine kinase activity not altered by heavy physical exercise. Clin Chem 1992; 38: 2224-7
54. Siegel AJ, Silverman LM, Holman BL. Elevated creatine kinase MB isoenzyme levels in marathon runners. JAMA 1981; 246: 2049-51
55. Mair J, Wohlfarter T, Koller A, et al. Serum cardiac troponin T after extraordinary endurance exercise [letter]. Lancet 1992; 340: 1048
56. Koller A, Mair J, Mayr M, et al. Diagnosis of myocardial injury in marathon runners. Ann N Y Acad Sci 1995; 752: 234-5
57. Bonetti A, Tirelli F, Albertini R, et al. Serum cardiac troponin T after repeated endurance exercise events. Int J Sports Med 1996; 17: 259-62
58. Laslett L, Eisenbud E, Lind R. Evidence of myocardial injury during prolonged strenuous exercise. Am J Cardiol 1996; 78: 488-90
59. Laslett L, Eisenbud E. Lack of detection of myocardial injury during competitive races of 100 miles lasting 18 to 30 hours. Am J Cardiol 1997; 80: 379-80
60. Mair J, Schobersberger W, Koller A, et al. Risk for exercise-induced myocardial injury for athletes performing prolonged strenous endurance exercise. Am J Cardiol 1997; 80: 543-4
61. Siegel AJ, Scholar M, Yang J, et al. Elevated serum cardiac markers in asymptomatic marathon runners after competition: is the myocardium stunned? Cardiology 1997; 88: 487-91
62. Koller A, Mair J, Schobersberger W, et al. Effects of prolonged strenuous endurance exercise on plasma myosin heavy chain fragments and other muscle proteins. J Sports Med Phys Fitness 1998; 38: 10-7
63. Denvir MA, Galloway PJ, Meighan AS, et al. Changes in skeletal and cardiac muscle enzymes during the Scottish coast to coast triathlon. Scott Med J 1999; 44: 49-51
64. Obha H, Takada H, Musha H, et al. Effects of prolonged strenuous exercise on plasma levels of atrial natriuretic peptide and brain natriuretic peptide in healthy men. Am Heart J 2001; 141: 751-8

65. Siegel AJ, Lewandrowski EL, Chun KY, et al. Changes in cardiac markers including B-natriuetic peptide in runners after the Boston marathon. Am J Cardiol 2001; 88: 920-3

66. Neumayr G, Pfister R, Mitterbauer G, et al. Effect of the 'Race Across The Alps' in elite cyclists on plasma cardiac troponins I and T. Am J Cardiol 2002; 89: 484-6

67. Neumayr G, Gaenzer H, Pfister R, et al. Plasma levels of cardiac troponin I after prolonged strenuous exercise. Am J Cardiol 2001; 87: 369-71

68. Collinson PO, Boa FG, Gaze DC. Measurement of cardiac troponins. Ann Clin Biochem 2001; 38: 423-49

69. Wu AHB, Valdes R, Apple FS, et al. Cardiac Troponin-T immunoassay for diagnosis of acute myocardial infarction. Clin Chem 1994; 40: 900-7

70. Shave R, Dawson E, Whyte G, et al. The cardiospecificity of the third-generation cTnT assay after exercise-induced muscle damage. Med Sci Sports Exerc 2002; 34: 651-4

71. Zimmermann R, Baki S, Dengler TJ, et al. Troponin T release after heart transplantation. Br Heart J 1993; 69: 395-8

72. Friedman DB, Ordway GA, Williams RS. Exercise-induced functional desensitization of canine cardiac b-adrenergic receptors. J Appl Physiol 1987; 62: 1721-3

73. Fraser J, Nadeau J, Robertson D, et al. Regulation of human leucocyte beta receptors by endogenous catecholamines. J Clin Invest 1981; 67: 1777-84

74. Dearman J, Francis KT. Plasma levels of catecholamines, cortisol and beta-endorphins in male athletes after running 26.2, 6 and 2 miles. J Sports Med 1983; 23: 30-8

75. Meyer R, Mayer U, Weib M, et al. Sympathoadrenergic regulation of metabolism and cardiocirculation during and following running exercises of different intensity and duration. Int J Sports Med 1988; 9: 132-40

76. Liedtke AJ, Nellis S, Neely JR. Effects of excess free fatty acids on mechanical and metabolic function in normal and ischemic myocardium in swine. Circ Res 1978; 43: 652-61

77. Ferrari R. Healthy versus sick myocytes: metabolism, structure and function. Eur Heart J Suppl 2002; 4: G1-G12

78. Damm S, Andersson LG, Henriksen E, et al. Wall motion abnormalities in male elite orienteers are aggravated by exercise. Clin Physiol 1999; 19: 121-6

79. Vinereanu D, Florescu N, Sculthorpe N, et al. Left ventricular long axis diastolic function is augmented in the hearts of endurance-trained compared with strength-trained athletes. Clin Sci (Lond) 2002; 103: 249-57

80. Talwar S, Squire IB, O'Brien RJ, et al. Plasma cardiotrophin-I following acute myocardial infarction: relationship with left ventricular dysfunction. Clin Sci 2002; 102: 9-14

81. Alessio HM. Exercise-induced oxidative stress. Med Sci Sports Exerc 1993; 25: 218-24

82. Lindinger MI. Potasssium regulation during exercise and recovery in humans: implications for skeletal and cardiac muscle. J Mol Cell Cardiol 1995; 27: 1011-22

Correspondence and offprints: *Keith George*, Research Institute for Sport and Exercise Science, Liverpool John Moores University, Liverpool, L3 2ET, England.
E-mail: k.george@livjm.ac.uk