High intensity training and the heart

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Absence may make the heart grow fonder, but exercise makes the heart grow stronger. This review discusses the cardiac impact of high intensity training, and discusses the possible mechanisms underlying the risk and benefit of such training.

Exercise has become highly fashionable. The ROOFEr generation (Red wine, Olive Oil, Fish and Exercise) have accepted that the idea of health is best represented by television's 'Gladiators'. But is this wise? Is exercise beneficial? And if so, how much exercise is best? What are the effects of very high intensity exercise, and how might these effects be mediated?

This article will discuss the cardiac morphological effects of regular training. It will then proceed to discuss the risks and benefits of exercise, and attempt to define the optimum intensity of exercise. Recent data which help explain the impact of intense exercise on cardiac risk profile are presented.

CARDIAC MORPHOLOGICAL RESPONSES TO EXERCISE

Like any muscle, the heart will grow with training and waste with rest. In this respect, the responsiveness of the heart is remarkable, with falls in cardiac mass detectable within only 4 days of ceasing a training programme (Huston et al, 1985).

Cardiac growth comprises two factors: a change in cavity size and a change in wall thickness. The balance of these two components is determined by the nature and intensity of the training undertaken. All exercise increases heart rate and systolic blood pressure (SBP). However, dynamic exercise (sustained rhythmic shortening of muscles as in running) is generally associated with a fall in total peripheral vascular resistance and hence also in diastolic blood pressure (DBP) and mean blood pressure (Schaible and Scheur, 1985). The absence of pressure burden leads to a predominant rise in left ventricular end-diastolic dimensions (LVEDD).

By contrast, isometric exercise (e.g. training against high resistances) is associated with greater SBP rise coupled with a rise in DBP and little change in total peripheral vascular resistance (Nutter et al, 1972). Indeed, contraction effort of >70% maximum may halt muscle blood supply altogether, so that stroke volume actually falls. The predominant pressure burden leads to increased septal and free-wall thickness. Consequently, different sports yield quite different patterns and degrees of left ventricular (LV) response. In general, LV mass (LVM) increases proportionately to body mass in those taking only isometric exercise, while LVEDD rises significantly in those taking predominantly dynamic exercise.

The hypertrophic response is of some rapidity and magnitude, with LVM rising by up to 60% depending on nature and intensity of training. In general, athletes have LVEDDs 10% larger, wall thicknesses 15–20% larger than matched control subjects, and LVM 45% larger (Maron, 1986). Regression of LVM may be equally quick, falling within 4 days of training reduction (Huston et al, 1985) and by 20% in highly-trained athletes within 3 weeks of inactivity (Martin et al, 1986).

Regular exercise training is thus associated with changes in cardiac morphology and performance, which are more marked with higher intensity exercise. But are these changes beneficial?

High-intensity exercise is associated with a short-term increase in cardiac risk. However, sudden death is rare occurring in between 1 and 5 per million athletes per year. The mechanism of sudden death is usually arrhythmic, although the underlying cause varies with age.

Below the age of 30 years, hypertrophic cardiomyopathy is the commonest single cause.

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Idiopathic right ventricular dysplasia, Marfan's syndrome and congenital abnormalities of the coronary circulation account for the majority of the other cases. The marked changes in cardiac morphology in those who train hard and regularly can, however, make it difficult to decide quite what is 'normal'. LVEDDs may rise well beyond 7 cm, and wall thicknesses to levels well beyond that of a sedentary population (Maron, 1986).

Above the age of 30 years, coronary disease accounts for the majority of deaths. But what is the overall impact of intense training on coronary risk?

HIGH-INTENSITY TRAINING AND CORONARY DISEASE

As early as 1953, it was shown that bus conductors had only 70% of the age-adjusted risk of coronary disease when compared to bus drivers, and half the risk of myocardial infarction or coronary mortality (Morris et al, 1953). Subsequent studies of occupational exercise suggest that the relative risk of death from coronary heart disease may approach 1.9 for sedentary workers when compared to those of more active occupation, and that a 'dose–response curve' relates exercise and protection (Berlin and Colditz, 1990).

In a study of 16 936 college graduates, Paffenbarger and colleagues confirmed a dose–response curve of benefit with recreational exercise, and showed that expending more than 2000 kcal/week reduced mortality during 12–16-year follow-up by up to one third. Overall, adequate exercise might extend life by more than 2 years (Paffenbarger et al, 1986). However, it has become clear that regular high intensity exercise is less beneficial. A U-shaped curve relates number of calories burned each week with coronary risk, with a progressive fall in risk up to 2500 kcal/week, after which risk begins to climb again (Paffenbarger et al, 1986).

Furthermore, a single episode of intense exercise is associated with an immediate risk of acute myocardial infarction. This risk is dependent upon the amount of training previously done. A 6 metabolic equivalent (mets) workload increases the relative risk of acute myocardial infarction in the following hour to 5.9, but by 107 fold for those who exercise less than once each week, to 2.4 for those who exercise more than five times each week (Mittleman et al, 1993).

By and large, then, high intensity training increases both immediate cardiac risk and lifetime coronary risk when compared to more moderate exercise, although risks remain lower than in a sedentary population.

How can we explain these data? Two areas are currently of great interest.

EXERCISE AND INFLAMMATION

The physiological response to a wide variety of different inflammatory stimuli remains qualitatively similar. Cytokines drive the hepatic production of acute phase proteins including C-reactive protein and fibrinogen. Inflammatory markers are associated with both the development of coronary disease, with disease severity and with the occurrence of coronary events. In addition, chronic gastric, lung and gum infections are all associated with both a chronic inflammatory response and with the development of coronary artery disease.

Systemic inflammatory responses may also play a role in the conversion of stable coronary disease to an unstable coronary syndrome (Mittleman et al, 1993). Fibrinogen is an hepatically-derived acute phase protein whose levels represent an independent risk factor for ischaemic heart disease. Fibrinogen is a plausible mediator of coronary atherosclerosis. Fibrinogen and its breakdown products penetrate the vascular wall, and can increase vascular permeability, collagen synthesis, endothelial injury, and smooth muscle cell proliferation and migration.

It has thus been postulated that inflammation may cause coronary disease through changes in fibrinogen levels. If true, could the effects of exercise on coronary risk be mediated by changes in fibrinogen concentration? We studied male army recruits undergoing 10 weeks of intensive training, the last week of which includes an exhausting 2-day military exercise (ME), comprising prolonged and intensive physical exertion. Cohorts of troops were studied at intake, and again in the last week of training when fitness had improved greatly.

This final assessment was staggered, with 5 cohorts of troops (A–E respectively) studied at different time-points in relation to ME (*Figure 1*). Fibrinogen concentrations rose significantly from baseline values on days 1–3 after the intensive physical effort of the 2-day ME (27.2%, $P<0.001$; 37.1%, $P<0.001$; 19.9%, $P=0.04$ respectively), and were lower at day 5 (–11.9%, $P=0.04$). There was no significant change in fibrinogen concentration at t=12 hours and t=4 days after ME. The peak percentage rise in fibrinogen concentration on day 2 was significantly greater than at any other

timepoint ($P<0.05$ for all comparisons) (Montgomery et al, 1996). Thus, fibrinogen levels are significantly reduced (–11.9%) after 10 weeks of training, if 5 days without severe exertion intervene.

These findings are in keeping with a beneficial effect of chronic training on fibrinogen levels (Lee et al, 1990). While chronic regular exercise reduces fibrinogen levels, intense exercise paradoxically causes an 'acute phase' rise. Given that a change in fibrinogen concentration of just 0.1 g/litre might correspond to a cardiovascular risk alteration of 15% (Ernst, 1993), at least part of the cardiovascular benefit of regular exercise (and detrimental effects of chronic and acute intensive exercise) may derive from an associated change in fibrinogen levels.

THE RENIN–ANGIOTENSIN SYSTEM AND CORONARY DISEASE

As discussed above, cardiac hypertrophy is generally associated with increased cardiac morbidity and mortality (*Table 1*). Overall, LVH is associated with a 10-fold increase in mortality rate (Massie et al, 1989). Recent data suggest that increased tissue renin–angiotensin system activity may connect cardiac hypertrophy with increased coronary vascular risk.

The circulating human renin–angiotensin system plays an important role in circulatory homeostasis. Angiotensin-converting enzyme (ACE) degrades vasodilator kinins and generates vasoconstrictor angiotensin II (Ang II). However, local renin–angiotensin systems exist in tissues including human myocardium, and these may regulate LV growth. A polymorphism of the human ACE gene has been identified in which the absence (Deletion, D allele) rather than the presence (Insertion, I allele) of a 287 base pair fragment is associated with higher tissue ACE activity (Danser et al, 1995).

Cardiac ACE and angiotensinogen gene expression increase during LV hypertrophy, as do Ang II receptor numbers. Ang II increases physiological cardiac hypertrophy while renin–angiotensin system antagonists impair such growth (Beinlich et al, 1991). Such data strongly support a role for renin–angiotensin system in the control of both physiological and

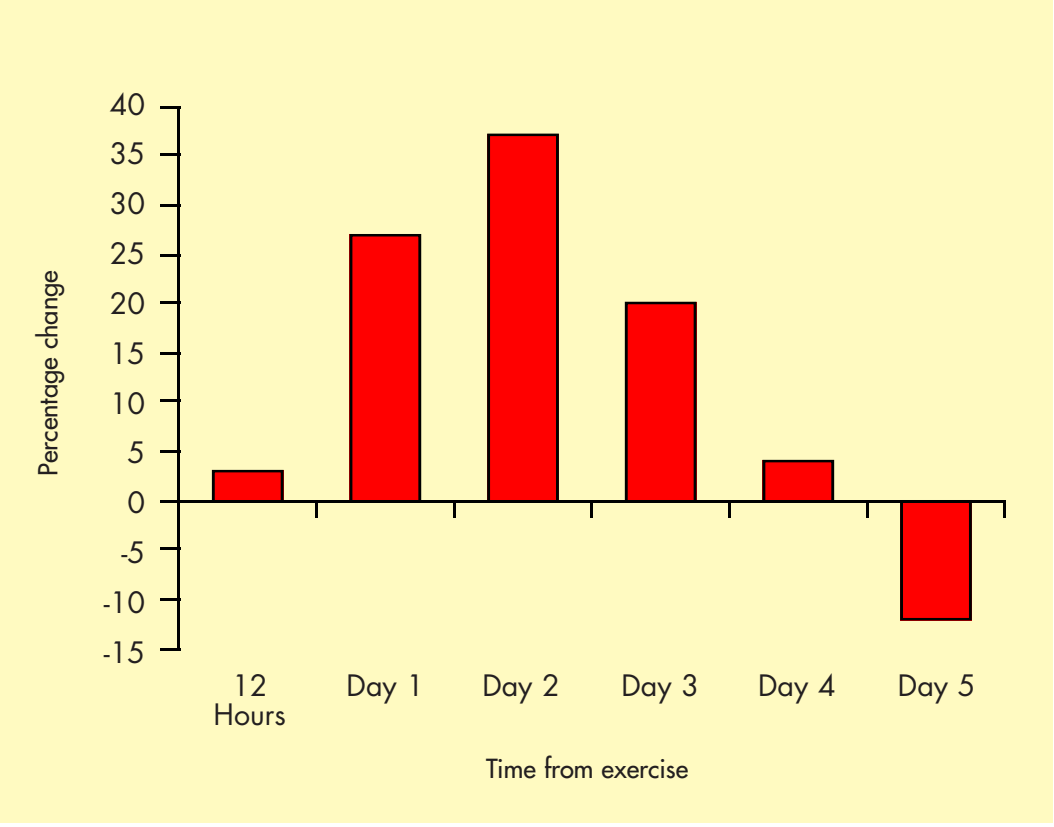

Figure 1. The percentage change in serum fibrinogen concentration (mean of individual percentage changes from pre-training levels) with time after an intensive 2-day military exercise (ME) is shown. Recruits were all in the last of 10 weeks of physical training when the exercise was undertaken (see text). An 'acute phase' rise in fibrinogen concentration followed ME. At 5 days, fibrinogen levels were significantly lower than at entry, consistent with a beneficial effect of training.

TABLE 1.
Risk factor-adjusted relative risks associated with a 50g/m increase in height-adjusted left ventricular mass

	Increase in relative risk	
Variable	**Male**	**Female**
Cardiovascular disease	1.49	1.57
Death from cardiovascular disease	1.73	2.12
Death from all causes	1.49	2.01

From Levy et al (1990)

pathophysiological growth, and are supported by studies in humans. The magnitude of the LV growth response associated with a 10-week exercise training programme is strongly influenced by ACE genotype: mean LVM increased by +2.0 g in those of II genotype, and +42.3 g in those of DD genotype (Montgomery et al, 1997). In those exposed to a hypertrophic stimulus (such as hypertension or inherited hypertrophic cardiomyopathy), the D allele is also associated with the scale of LV hypertrophic response (Montgomery et al, 1997). Tissue renin–angiotensin system activity may thus powerfully influence the LV hypertrophic response.

Tissue renin–angiotensin system activity may also influence the pathogenesis of coronary disease. A local vascular renin–angiotensin system exists (Swales and Samani, 1993) which drives local Ang II production, and which is upregulated by increasing hypertension or vascular injury (Nishimura et al, 1992; Rakugi et al, 1993). In hypertensive animals, aortic vascular smooth muscle cell size, collagen content and medial thickness are reduced by treatment with ACE inhibitors, even at doses that do not inhibit plasma ACE (Albaladejo et al, 1994). DNA synthesis is increased by balloon-injury and by ATII infusion in the rat thoracic aorta and carotid, with the two stimuli exerting synergistic effects (Daemen et al, 1991). The D allele of the ACE gene may also be associated increased the risk of restenosis at the site of emergency coronary angioplasty (Ohishi et al, 1993).

In models of accelerated atherosclerosis, vascular growth (and development of the neointima) is reduced by ACE inhibition, endothelial migration is increased, plasminogen activator levels raised, and vascular smooth muscle cell migration reduced. In high cholesterol models, endothelial function (such as flow-dependent relaxation) is relatively preserved by treatment with ACE inhibitors. Further, in the Watanabe heritable hyperlipidaemic rabbit and in cholesterol-fed cyomolgus monkeys, ACE inhibitors (but not β-blocking agents or calcium-channel blockers) demonstrate a potent antiatherosclerotic action. Although free-radical scavenging by the sulphydryl group of captopril may have played a protective role in these studies, it seems likely that much of the benefit of these drugs is derived from inhibition of vascular ACE (Sharpe, 1993). In humans, too, tissue ACE activity may influence the progression of coronary disease: the D allele may be associated with increased risk of myocardial infarction (Cambien et al, 1992; Tiret et al, 1993, 1994).

Thus tissue renin–angiotensin system activity is implicated in both the development of cardiac hypertrophy and of coronary vascular disease. Could this be the connecting factor linking high intensity training and the reduced benefit of high intensity training? The answer is not known, but ongoing work makes the issue even more intriguing. It has recently been observed that the I allele of the ACE gene (associated with lower ACE activity), has beneficial effects on the response to exercise training (Montgomery et al, 1998). These data suggest that those of II genotype may be more able to complete endurance tasks than those of DD genotype. Although the ACE gene I/D polymorphism does not seem associated with resting blood pressure, the blood pressure response to exercise may be associated with the D allele (Friedl et al, 1996).

These data, together with unpublished observations made by the authors, suggest that the blood pressure response to a given external work load may be higher in those of DD genotype than those of II genotype, and that the amount of cardiac work performed to achieve the same external work by the body may be greater in those with one or more D alleles. Those with the higher tissue ACE levels (as marked by the D allele) may thus produce greater cardiac pressure burden (and consequent hypertrophy), and greater vascular wall stress (and hence vascular injury) during intensive exercise training. Such severe exercise may

thus be more likely to be associated with excess cardiovascular mortality.

CONCLUSIONS

Regular aerobic (dynamic) exercise at moderate levels of intensity profoundly reduces coronary risk. The long-term benefits of regular exercise are reduced when exercise intensity is much greater. Acutely, exercise is associated with an immediate risk of myocardial infarction, but this risk is much lower in those who take regular exercise and is greater when exercise is more intense. Some of these effects may be explained by changes in fibrinogen levels, and by the activity of renin–angiotensin systems.

In general, inactivity is dangerous, and regular moderate activity beneficial. The benefits of irregular intense exercise are by no means as clear. Those who briskly walk the dog in the park each day may yet stand at the graves of the gym generation. HM

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KEY POINTS

- Regular moderate exercise is associated with a marked reduction in cardiovascular risk.
- Very intense exercise carries with it an immediate risk of myocardial infarction and sudden cardiac death.
- Regular intense exercise is less beneficial in the long-term than regular more moderate exercise.
- Fibrinogen levels are associated with lifetime cardiac risk.
- Fibrinogen levels fall in those training regularly, but rise in a significant and sustained fashion with very intense exercise. Such changes may mediate some of the effects of exercise on coronary risk.
- Genetic markers of lower angiotensin-converting enzyme activity may be associated with reduced cardiac and vascular pressure burden with exercise. Lower angiotensin-converting enyme levels may thus be associated with reduced cardiac risk in those exercising at higher intensity.