Why we should allow performance enhancing drugs in sport

J Savulescu, B Foddy, M Clayton

The legalisation of drugs in sport may be fairer and safer

In 490 BC, the Persian Army landed on the plain of Marathon, 25 miles from Athens. The Athenians sent a messenger named Feidipides to Sparta to ask for help. He ran the 150 miles in two days. The Spartans were late. The Athenians attacked and, although outnumbered five to one, were victorious. Feidipides was sent to run back to Athens to report victory. On arrival, he screamed “We won” and dropped dead from exhaustion.

The marathon was run in the first modern Olympics in 1896, and in many ways the athletic ideal of modern athletes is inspired by the myth of the marathon. Their ideal is superhuman performance, at any cost.

DRUGS IN SPORT

The use of performance enhancing drugs in the modern Olympics is on record as early as the games of the third Olympiad, when Thomas Hicks won the marathon after receiving an injection of strychnine in the middle of the race. The first official ban on “stimulating substances” by a sporting organisation was introduced by the International Amateur Athletic Federation in 1928.

Using drugs to cheat in sport is not new, but it is becoming more frequent. In 1976, the East German swimming team won 11 out of 13 Olympic events, and later sued the government for giving them anabolic steroids. Yet despite the health risks, and despite the regulating bodies’ attempts to eliminate drugs from sport, the use of illegal substances is widely known to be rife. It hardly raises an eyebrow now when substances is widely known to be rife. It raises an eyebrow now when substances is widely known to be rife. It raises an eyebrow now when substances is widely known to be rife. It raises an eyebrow now when substances is widely known to be rife. It raises an eyebrow now when substances is widely known to be rife. It raises an eyebrow now when substances is widely known to be rife. It raises an eyebrow now when substances is widely known to be rife.

CONDEMNED TO CHEATING?

We are far from the days of amateur sporting competition. Elite athletes can earn tens of millions of dollars every year in prize money alone, and millions more in sponsorships and endorsements. The lure of success is great. But the penalties for cheating are small. The enormous rewards for the winner, the effectiveness of the drugs, and the low rate of testing all combine to create a cheating “game” that is irresistible to athletes. Kjetil Haugen investigated the suggestion that athletes face a kind of prisoner’s dilemma regarding drugs. His game theoretic model shows that, unless the likelihood of athletes being caught doping was raised to unrealistically high levels, or the payoffs for winning were reduced to unrealistically low levels, athletes could all be predicted to cheat. The current situation for athletes ensures that this is likely, even though they are worse off as a whole if everyone takes drugs.

Drugs such as erythropoietin (EPO) and growth hormone are natural chemicals in the body. As technology advances, drugs have become harder to detect because they mimic natural processes. In a few years, there will be many undetectable drugs. Haugen’s analysis predicts the obvious: that when the risk of being caught is zero, athletes will all choose to cheat.

The recent Olympic games in Athens were the first to follow the introduction of a global anti-doping code. From the lead up to the games to the end of competition, 3000 drug tests were carried out: 2600 urine tests and 400 blood tests for the endurance enhancing drug EPO. From these, 23 athletes were found to have taken a banned substance—the most ever in an Olympic games. Ten of the men’s weightlifting competitors were excluded.

The goal of “cleaning” up the sport is unattainable. Further down the track the spectre of genetic enhancement looms dark and large.

THE SPIRIT OF SPORT

So is cheating here to stay? Drugs are against the rules. But we define the rules of sport. If we made drugs legal and freely available, there would be no cheating.

The World Anti-Doping Agency code declares a drug illegal if it is performance enhancing, if it is a health risk, or if it violates the “spirit of sport.” They define this spirit as follows. The spirit of sport is the celebration of the human spirit, body, and mind, and is characterised by the following values:

- ethics, fair play and honesty
- health
- excellence in performance
- character and education
- fun and joy
- teamwork
- dedication and commitment
- respect for rules and laws
- respect for self and other participants
- courage
- community and solidarity

Would legal and freely available drugs violate this “spirit”? Would such a permissive rule be good for sport?

Human sport is different from sports involving other animals, such as horse or dog racing. The goal of a horse race is to find the fastest horse. Horses are lined up and flogged. The winner is the one with the best combination of biology, training, and rider. Basically, this is a test of biological potential. This was the old naturalistic Athenian vision of sport: find the strongest, fastest, or most skilled man.

Training aims to bring out this potential. Drugs that improve our natural potential are against the spirit of this model of sport. But this is not the only view of sport. Humans are not horses or dogs. We make choices and exercise our own judgment. We choose what kind of...
training to use and how to run our race. We can display courage, determination, and wisdom. We are not flogged by a jockey on our back but drive ourselves. It is this judgment that competitors exercise when they choose diet, training, and whether to take drugs. We can choose what kind of competitor to be, not just through training, but through biological manipulation. Human sport is different from animal sport because it is creative. Far from being against the spirit of sport, biological manipulation embodies the human spirit—the capacity to improve ourselves on the basis of reason and judgment. When we exercise our reason, we do what only humans do.

The result will be that the winner is not the person who was born with the best genetic potential to be strongest. Sport would be less of a genetic lottery. The winner will be the person with a combination of the genetic potential, training, psychology, and judgment. Olympic performance would be the result of human creativity and choice, not a very expensive horse race.

Classical musicians commonly use β blockers to control their stage fright. These drugs lower heart rate and blood pressure, reducing the physical effects of stress, and it has been shown that the quality of a musical performance is improved if the musician takes these drugs. Although elite classical music is arguably as competitive as elite sport, the rewards are similar, there is no stigma attached to the use of these drugs. We do not think less of the violinist or pianist who uses them. If the audience judges the performance to be improved with drugs, then the drugs are enabling the musician to express him or herself more effectively. The competition between elite musicians has rules—you cannot mime the violin to a backing CD. But there is no rule against the use of chemical enhancements.

Is classical music a good metaphor for elite sport? Sachin Tendulkar is known as the “Maestro from Mumbai”. The Associated Press called Maria Sharapova’s 2004 Wimbledon final a “virtuoso performance”. Jim Murray wrote the following about Michael Jordan in 1996:

“’You go to see Michael Jordan play for the same reason you went to see Astaire dance, Olivier act or the sun set over Canada. It’s art. It should be painted, not photographed. It’s not a game, it’s a recital. He’s not just a player, he’s a virtuoso. Heifetz with a violin. Horowitz at the piano.’”

Indeed, it seems reasonable to suggest that the reasons we appreciate sport at its elite level have something to do with competition, but also a great deal to do with the appreciation of an extraordinary performance.

Clearly the application of this kind of creativity is limited by the rules of the sport. Riding a motorbike would not be a “creative” solution to winning the Tour de France, and there are good reasons for proscribing this in the rules. If motorbikes were allowed, it would still be a good sport, but it would no longer be a bicycle race.

We should not think that allowing cyclists to take EPO would turn the Tour de France into some kind of “drug race”, any more than the various training methods available turn it into a “training race” or a “money race”. Athletes train in different, creative ways, but ultimately they still ride similar bikes, on the same course. The skill of negotiating the steep winding descent will always be there.

UNFAIR?

People do well at sport as a result of the genetic lottery that happened to deal them a winning hand. Genetic tests are available to identify those with the greatest potential. If you have one version of the ACE gene you will be better at long distance events. If you have another, you will be better at short distance events. Black Africans do better at short distance events because of biologically superior muscle type and bone structure. Sport discriminates against the genetically unfit. Sport is the province of the genetic elite (or freak).

The starkest example is the Finnish skier Eero Maenityranta. In 1964, he won three gold medals. Subsequently it was found he had a genetic mutation that meant that he “naturally” had 40–50% more red blood cells than average. Was it fair that he had significant advantage given to him by chance?

The ability to perform well in sporting events is determined by the ability to deliver oxygen to muscles. Oxygen is carried by red blood cells. The more red blood cells, the more oxygen you can carry. This in turn controls an athlete’s performance in aerobic exercise. EPO is a natural hormone that stimulates red blood cell production, raising the packed cell volume (PCV)—the percentage of the blood comprised of red blood cells. EPO is produced in response to anemia, haemorrhage, pregnancy, or living at altitude. Athletes began injecting recombinant human EPO in the 1970s, and it was officially banned in 1985.

At sea level, the average person has a PCV of 0.4–0.5. It naturally varies; 5% of people have a packed cell volume above 0.5, and that of elite athletes is more likely to exceed 0.5, either because their high packed cell volume has led them to succeed in sport or because of their training.

Raising the PCV too high can cause health problems. The risk of harm rapidly rises as PCV gets above 50%. One study showed that in men whose PCV was 0.51 or more, risk of stroke was significantly raised (relative risk = 2.5), after adjustment for other causes of stroke. At these levels, raised PCV combined with hypertension would cause a ninefold increase in stroke risk. In endurance sports, dehydration causes an athlete’s blood to thicken, further raising blood viscosity and pressure. What begins as a relatively low risk of stroke or heart attack can rise acutely during exercise.

In the early 1990s, after EPO doping gained popularity but before tests for its presence were available, several Dutch cyclists died in their sleep due to inexplicable cardiac arrest. This has been attributed to high levels of EPO doping. The risks from raising an athlete’s PCV too high are real and serious.

Use of EPO is endemic in cycling and many other sports. In 1998, the Festina team was expelled from the Tour de France after trainer Willy Voet was caught with 400 vials of performance enhancing drugs. The following year, the World Anti-Doping Agency was established as a result of the scandal. However, EPO is extremely hard to detect and its use has continued. Italy’s Olympic anti-doping director observed in 2003 that the amount of EPO sold in Italy outweighed the amount needed for sick people by a factor of six.

In addition to trying to detect EPO directly, the International Cycling Union requires athletes to have a PCV no higher than 0.5. But 5% of people naturally have a PCV higher than 0.5. Athletes with a naturally high PCV cannot race unless doctors do a number of tests to show that their PCV is natural. Charles Wegelius was a British rider who was banned and then cleared in 2003. He had had his spleen removed in 1998 after an accident, and as the spleen removes red blood cells, its absence resulted in an increased PCV. There are other ways to increase the number of red blood cells that are legal. Altitude training can push the PCV to dangerous, even fatal, levels. More recently, hypoxic air machines have been used to simulate altitude training. The body responds by releasing natural EPO and growing more blood cells, so that it can absorb more oxygen with
every breath. The Hypoxicarn promotional material quotes Tim Seaman, a US athlete, who claims that the hypoxic air tent has ‘‘given my blood the legal ‘boost’ that it needs to be competitive at the world level.’’

There is one way to boost an athlete’s number of red blood cells that is completely undetectable: autologous blood doping. In this process, athletes remove some blood, and reinfuse it after their body has made new blood to replace it. This method was popular before recombinant human EPO became available.

‘‘By allowing everyone to take performance enhancing drugs, we level the playing field.’’

There is no difference between elevating your blood count by altitude training, by using a hypoxic air machine, or by taking EPO. But the last is illegal. Some competitors have high PCVs and an advantage by luck. Some can afford hypoxic air machines. Is this fair? Nature is not fair. Ian Thorpe has enormous feet which give him an advantage that no other swimmer can get, no matter how much they exercise. Some gymnasts are more flexible, and some basketball players are seven feet tall. By allowing everyone to take performance enhancing drugs, we level the playing field. We remove the effects of genetic inequality. Far from being unfair, allowing performance enhancement promotes equality.

JUST FOR THE RICH?

Would this turn sport into a competition of expensive technology? Forget the romantic ancient Greek ideal. The Olympics is a business. In the four years before the Athens Olympics, Australia spent $547 million on sport funding, with $13.8 million just to send the Olympic team to Athens. With its highest ever funding, the Australian team brought home 17 gold medals, also its highest. On these figures, a gold medal costs about $32 million. Australia came 4th in the medal tally in Athens despite having the 52nd largest population. Neither the Australian multicultural genetic heritage nor the flat landscape and desert could have endowed Australians with any special advantage. They won because they spent more. Money buys success. They have already embraced strategies and technologies that are inaccessible to the poor.

Paradoxically, permitting drugs in sport could reduce economic discrimination. The cost of a hypoxic air machine and tent is about US$7000. Sending an athlete to a high altitude training location for months may be even more expensive. This arguably puts legal methods for raising an athlete’s PCV beyond the reach of poorer athletes. It is the illegal forms that level the playing field in this regard.

One popular form of recombinant human EPO is called Epogen. At the time of writing, the American chain Walgreens offers Epogen for US$86 for 6000 international units (IU). The maintenance dose of EPO is typically 20 IU per kg body weight, once a week. An athlete who weighs 100 kg therefore needs 2000 IU a week, or 8600 IU a month. Epogen costs the athlete about US$122 a month. Even if the Epogen treatment begins four years before an event, it is still cheaper than the hypoxic air machine. There are limits on how much haemoglobin an athlete can produce, however much EPO they inject, so there is a natural cap on the amount of money they can spend on this method.

Meanwhile, in 2000, the cost of an in competition recombinant EPO test was about US$130 per sample. This test is significantly more complex than a simple PCV test, which would not distinguish exogenous or endogenous EPO. If monetary inequalities are a real concern in sport, then the enormous sums required to test every athlete could instead be spent on grants to provide EPO to poorer athletes, and PCV tests to ensure that athletes have not thickened their blood to unsafe levels.

UNSAFE?

Should there be any limits to drugs in sport?

There is one limit: safety. We do not want an Olympics in which people die before, during, or after competition. What matters is health and fitness to compete. Rather than testing for drugs, we should focus more on health and fitness to compete. Forget testing for EPO, monitor the PCV. We need to set a safe level of PCV. In the cycling world, that is 0.5. Anyone with a PCV above that level, whether through the use of drugs, training, or natural mutation, should be prevented from participating on safety grounds. If someone naturally has a PCV of 0.6 and is allowed to compete, then that risk is reasonable and everyone should be allowed to increase their PCV to 0.6. What matters is what is a safe concentration of growth hormone—not whether it is natural or artificial.

We need to take safety more seriously. In the 1960s, East German athletes underwent systematic government sanctioned prescription of anabolic steroids, and were awarded millions of dollars in compensation in 2002. Some of the female athletes had been compelled to change their sex because of the large quantities of testosterone they had been given.

We should permit drugs that are safe, and continue to ban and monitor drugs that are unsafe. There is another argument for this policy based on fairness: provided that a drug is safe, it is unfair to the honest athletes that they have to miss out on an advantage that the cheaters enjoy.

Taking EPO up to the safe level, say 0.5, is not a problem. This allows athletes to correct for natural inequality. There are of course some drugs that are harmful in themselves—for example, anabolic steroids. We should focus on detecting these because they are harmful not because they enhance performance.

Far from harming athletes, paradoxically, such a proposal may protect our athletes. There would be more rigorous and regular evaluation of an athlete’s health and fitness to perform. Moreover, the current incentive is to develop undetectable drugs, with little concern for safety. If safe performance enhancement drugs were permitted, there would be greater pressure to develop safe drugs. Drugs would tend to become safer.

This is perhaps best illustrated by the case of American sailor Kevin Hall. Hall lost his testicles to cancer, meaning that he required testosterone injections to remain healthy. As testosterone is an anabolic steroid, he had to prove to four separate governing bodies that he was not using the substance to gain an advantage. Any tests that we do should be sensitive to the health of the athlete; to focus on the substances themselves is dogmatic.

Not only this, but health testing can help to mitigate the dangers inherent in sport.

For many athletes, sport is not safe enough without drugs. If they suffer from asthma, high blood pressure, or cardiac arrhythmia, sport places their bodies under unique stresses, which raise the likelihood of a chronic or catastrophic harm. For example, between 1985 and 1995, at least 121 US athletes collapsed and died directly after or during a training session or competition—most often because they had hypertrophic cardiomyopathy or heart malformations. The relatively high incidence of sudden cardiac death in young athletes has prompted the American Heart Association to recommend that all athletes undergo cardiac screening before being allowed to train or compete.

Sometimes, the treatments for these conditions will raise the performance of an athlete beyond that which they could
CHILDREN

Linford Christie, who served a two year drug ban from athletics competition, said that athletics “is so corrupt now I wouldn’t want my child doing it”. But apart from the moral harms to children in competing in a corrupt sport, should we withhold them from professional sport for medical reasons?

The case where the athletes are too young to be fully autonomous is different for two important reasons. Firstly, children are much less capable of rejecting training methods and treatments that their coach wishes to use. Secondly, we think it is worth protecting the range of future options open to a child.

There is a serious ethical problem with allowing children to make any kind of choice that substantially closes off their options for future lifestyles and career choices. If we do not consider children competent for the purposes of allowing them to make choices that cause them harm, then we should not allow them to decide to direct all of their time to professional gymnastics at age 10. The modifications such a choice can make to a child’s upbringing are as serious, and potentially as harmful, as many of the available performance enhancing drugs. Children who enter elite sport miss large parts of the education and socialisation that their peers receive, and are submitted to intense psychological pressure at an age when they are ill equipped to deal with it.

We argue that it is clear that children, who are not empowered to refuse harmful drugs, should not be given them by their coaches or parents. But the same principles that make this point obvious should also make it obvious that these children should not be involved in elite competitive sport in the first place. However, if children are allowed to train as professional athletes, then they should be allowed to take the same drugs, provided that they are no more dangerous than their training is.

Haugen’s model showed that one of the biggest problems in fighting drug use was that the size of the rewards for winning could never be overshadowed by the penalties for being caught. With this in mind, we can begin to protect children by banning them from professional sport.

CLIMATE OF CHEATING

If we compare the medical harms of the entire worldwide doping problem, they would have to be much less than the worldwide harms stemming from civilian illicit drug use. And yet, per drug user, the amount of money spent on combating drugs in sport outweighs the amount spent on combating civilian drug use by orders of magnitude.

We can fairly assume that if medical harms and adherence to law were the only reasons we felt compelled to eradicate doping, then the monetary value we place on cleaning up sport should be the same, per drug user, as the monetary value we place on eradicating recreational drug use. And yet it is not.

Because of this, it should be obvious that it is not medical harms that we think are primarily at stake, but harm to sport as a whole, a purported violation of its spirit. It is a problem for the credibility of elite sport, if everyone is cheating.

If it is this climate of cheating that is our primary concern, then we should aim to draft sporting rules to which athletes are willing to adhere.

PROHIBITION

It is one thing to argue that banning performance enhancing drugs has not been successful, or even that it will never be successful. But it should also be noted that the prohibition of a substance that is already in demand, that athletes have to be solely and legally responsible for what they consume—must remain supreme.

“The rule of strict liability—under which athletes have to be solely and legally responsible for what they consume—must remain supreme. We cannot, without blinding reason and cause, move one millimetre from strict liability—if we do, the battle to save sport is lost.”

The best reason for adhering to this rule is that, if coaches were made responsible for drugs that they had given to their athletes, then the coach would be banned or fined, and the athlete could still win the event. In this situation, other athletes would still be forced to take drugs in order to be competitive, even though the “cheat” had been caught.

But the doctrine of strict liability makes victims of athletes such as those of the East German swim team, who are competing in good faith but have been forced to take drugs. It also seems dogmatically punitive for athletes like British skier Alain Baxter, who accidentally inhaled a banned stimulant when he used the American version of a Vicks decongestant inhaler, without realising that it differed from the British model.

It seems that strict liability is unfair to athletes, but its absence is equally unfair. Our proposal solves this paradox—when
we exclude athletes only on the basis of whether they are healthy enough to compete, the question of responsibility and liability becomes irrelevent. Accidental or unwitting consumption of a risky drug is still risky; the issue of good faith is irrelevant.

**ALTERNATIVE STRATEGIES**

Michael Ashenden\(^4\) proposes that we keep progressive logs of each athlete's PCV and hormone concentrations. Significant deviations from the expected value would require follow up testing. The Italian Cycling Federation decided in 2000 that all juniors would be tested to provide a baseline PCV and given a "Hematologic Passport". Although this strategy is in many ways preferable to the prohibition of doping, it does nothing to correct the dangers facing an athlete who has an unsafe baseline PCV or testosterone concentration.

**TEST FOR HEALTH, NOT DRUGS**

The welfare of the athlete must be our primary concern. If a drug does not expose an athlete to excessive risk, we should allow it even if it enhances performance. We have two choices: to vainly try to turn the clock back, or to rethink who we are and what sport is, and to make a new 21st century Olympics. Not a super-Olympics but a more human Olympics. Our crusade against drugs in sport has failed. Rather than fearing drugs in sport, we should embrace them. In 1998, the president of the International Olympic Committee, Juan Antonio Samaranch, suggested that athletes be allowed to use non-harmful performance enhancing drugs.\(^1\) This view makes sense only if, by not using drugs, we are assured that athletes are not being harmed. Performance enhancement is not against the spirit of sport; it is the spirit of sport. To choose to be better is to be human. Athletes should be the given this choice. Their welfare should be paramount. But taking drugs is not necessarily cheating. The legalisation of drugs in sport may be fairer and safer.

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**LEADER**

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Sudden death risk in older athletes: increasing the denominator

D S Tunstall Pedoe

Excluding the older athlete should be a last resort

Publicity and campaigning surrounding the tragedy of sudden death in young athletes (incidence 1 in 200 000 young athletes per year) has rather overshadowed the mortality risk of older competitors aged >30.

Population studies show that death rates during sports participation increase dramatically with age as the incidence of coronary heart disease increases. Is this just coincidental, or is the sport triggering the deaths? The highest overall mortality (numbers dying —“the numerator”) is in recreational sports favoured by the middle aged and elderly, such as fishing and lawn bowls. This is because of the large numbers of participants and their lengthy exposure (time spent participating in the sport) (“the denominator”) in assessing comparative risk. The latter will vary with different populations of participants.

Sport exposure risk =
\[
\frac{\text{Number of deaths (Numerator)}}{\text{Number of participants} \times \text{Time of exposure to risk (Denominator)}}
\]

Lack of information about the denominator means that in most sports and recreational activity the exposure risk cannot be calculated and so compared. Collecting the death statistics without the denominator is almost meaningless, and can lead to illogical deductions, for instance that recreational fishing is more dangerous than hang gliding.

"His death had seriously held up play, and the ambulance had damaged the grass."

Many sports have their share of older coronary prone participants. I recall visiting a golf club many years ago the day after a sudden coronary death on the 12th fairway. Members felt that it was very inconsiderate of the deceased, who had had previous cardiac events. His death had seriously held up play, and the ambulance had damaged the grass. He should not have played.

To predict the risk for any particular event such as the London Marathon with its 32 000 participants you would need to know:

- the age and sex distribution of the competitors
- the incidence of coronary disease in the various population subgroups entering the marathon
- the duration of exposure to risk
- the intensity of exercise and its accompanying increased risk.

This list contains a lot of unknowns, but there are more.

Is the risk linear with time spent running in the marathon? Probably not, but data recording reduced risk from road races of shorter distance suggest that time of exposure is important rather than just peak intensity of exercise, which would be higher in shorter distance races and would give the opposite effect.

Calculations are complicated by the fact that marathon runners are not a randomly selected subgroup of the population. Some older athletes take up exercise as a lifestyle change. They aim to reduce their known high risk of coronary events and may believe the claims of the now discredited 1970s running "gurus" James Fixx (author of The complete book of running) and Dr Tom Bassler, that if they take enough exercise they are immune from, or can even reverse, coronary artery disease.

"I had coronary artery surgery 15 years ago and have cured my heart disease by running marathons," says a runner raising money for the British Heart Foundation, in a report from an East Anglian newspaper. Such naivety is not uncommon and may lead to a dangerous denial of symptoms.

The distribution of coronary risk may therefore be distorted by these factors, making prediction difficult. What are the measured risks? Road running is one of the few sports with large numbers of participants and measured exposure.8 9 Associated with 580 000 runs in the London Marathon since 1981, there have been eight deaths. One was from subarachnoid haemorrhage, two from hypertrophic cardiomyopathy, and five from coronary heart disease. (There have also been five successful cardiac resuscitations, all with coronary heart disease.) Counting all the eight deaths (including the 22 year old runner with subarachnoid haemorrhage) and postulating the average time of exposure as 4.5 hours, this gives the following statistics on the exposure death risk of the various population subgroups entering the marathon (table 1).

The death rate normalised for “time of exposure” can be compared with day
to day risks of road vehicular transport in Europe and is less than that for motorcycles (two thirds), but four times that of riding a bicycle for the same length of time. The transport figures are from the European Transport Safety Council and have been updated since those used in earlier publications. In the last few years, the death risk of European travel has become safer with a larger denominator (number of people travelling on the roads).

Increasing participation of older athletes (denominator), with all the health benefits for the vast majority, will probably result in an increase in the total number of sports deaths. However, this should be more than balanced by a decrease in the overall risk of death in those taking regular exercise.

Dying on the golf course, although unfortunate, should become more socially acceptable as the benefits of exercise even for the coronary prone are more generally appreciated.

Excluding the older athlete should be a last resort.

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**Table 1 London Marathon deaths over 24 years compared with European Transport Safety Council travel risks 2001–2002 (>580 000 marathons, 25 million km, eight deaths)**

<table>
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<th>Mode of transport</th>
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**Tendinopathy**

**Reactive oxygen species and tendinopathy: do they matter?**

C S Bestwick, N Maffulli

Reactive oxygen species are probably involved in tendinopathy

We propose that a molecular link between the exaggerated dysfunctional repair response in overuse tendinopathies and the subsequent orchestration of effective tendon healing is the control of the production and persistence of reactive oxygen species within the intracellular and extracellular milieu of the tendon tissue. Reactive oxygen production and the ensuing cellular response can be strongly influenced by lifestyle factors such as the intensity and frequency of exercise.

“Reactive oxygen species” (ROS; also referred to as active oxygen species, AOS; reactive oxygen intermediates, ROI) is a collective term for both radical and non-radical but reactive species derived from oxygen. A free radical, is “any species capable of independent existence that contains one or more unpaired electrons”.1 The presence of such unpaired electron(s) often imparts considerable reactivity. Commonly detected and potentially physiologically relevant ROS include the superoxide anion, hydrogen peroxide (H$_2$O$_2$), the hydroxyl radical, singlet oxygen, and peroxyl radicals. A further and interrelated group are the reactive nitrogen species (RNS)—for example, peroxynitrite.1

ROS are continually produced during normal cell metabolism. The mitochondrial respiratory chain, NADPH-cytochrome P$_{450}$ enzymes in the endoplasmic reticulum, phagocytic cells, lipoxygenase, and cyclo-oxygenase are also sources of basal ROS production.1 Trauma and environmental and physiological stimuli may enhance ROS production.1

Traditionally, ROS are viewed as imposing cellular/tissue damage through lipid peroxidation, protein modification, DNA strand cleavage, and oxidative base modification, although the relative reactivity and susceptibility of the molecular targets vary. Thus, ROS production is implicated in numerous aspects of pathophysiology including tumorigenesis, coronary heart disease, autoimmune disease, overuse exercise related damage to muscle, and impairment of fracture healing.1 2

This association with cellular damage and pathology has predisposed much of the literature to consider decreased ROS production de facto a universally desirable phenomenon. This, however, belies the complexity of ROS action, in which subtle changes in ROS type and concentration may exert profound effects on cell metabolism and development including proliferation, differentiation, and adaptive responses. At higher levels, ROS may initiate and/or execute the demise of the cell. The ability of H$_2$O$_2$ to diffuse across membranes imparts potential to exert effects at sites distant...
from its production. Thus ROS changes may have widespread consequences for cell function as well as integrity and viability.7 4

**POTENTIAL SOURCES OF ROS PRODUCTION IN TENDINOPATHY**

To our knowledge, there is a paucity of studies on ROS participation in clinically relevant models of tendinopathy. However, recent investigations show increased expression of peroxiredoxin 5, a thioredoxin peroxidase with antioxidant properties, in tendinopathic tendon, suggesting that oxidative stress may be involved in the pathogenesis of tendon degeneration.7 Raised ROS concentrations are proposed to contribute to the development of tendinopathy as a side effect of fluoroquinolone antibiotic use.6

What is the potential source(s) of ROS production in the tendon or its immediate vicinity? During cyclical loading of the tendon, the period of maximum tensile load is associated with ischemia,7 and subsequent restoration of normal tissue oxygenation may enhance ROS production. Hyperthermia in the exercising tendon may stimulate ROS production, probably from the mitochondria.7 Fibroblasts also specifically generate ROS, through an NADPH oxidase complex, in response to cytokines and growth factors, the production and release of which are stimulated after tendon injury.8 9

A further possibility is that tendons are indirectly influenced by changes in ROS metabolism in other tissues and cells such as in exercising muscle. Resting muscles generate both intracellular and extracellular superoxide, the production of both being enhanced during contraction. In addition, although the extent of enhancement is contested,10 exhaustive exercise increases ROS generation by activated phagocytes. Although surgery is a late event in the management of tendinopathy, and cyclic stretching of human tenocytes increases the production of inflammatory mediators,12 Detection of ROS production and changes in ROS concentrations would, however, only represent a start in dissecting their role in tendinopathy, as any changes may be as much a part of healing as of tissue disruption. Studies on avian fibroblasts suggest that, during tendon healing, mechanical load and growth factors—for example, platelet derived growth factor (PDGF) and insulin-like growth factor I—operate in concert to stimulate tenocyte cell division.11 Interestingly, PDGF stimulation of rat vascular smooth muscle cells transiently increases intracellular H2O2 concentration, and H2O2 is required for PDGF signal transduction.12 Thus, in tendons, the pro-proliferative action of growth factors and mechanical load may be mediated through H2O2 production. Chemotaxis of cells in the wounded tendon (micro-tear) may also be influenced by ROS/RNS generation. Proliferation and migration of vascular smooth muscle cells is inhibited by the H2O2 scavenger, catalase.14 However, balance and control of ROS exposure is critical to the final cell response. Heightened concentrations of H2O2 retard both proliferation and restitution in the gastric mucosa,16 and equine tenocytes show a decrease in proliferation when subjected to 10–100 μM H2O2.7

A recent intriguing observation is that extracorporeal shock wave therapy, which is reported to promote tendon repair and bone growth, induces increased production of superoxide anion, which mediates extracellular signal regulated kinase signal transduction during osteogenesis.17 Differentiation was not influenced by inhibition of H2O2, peroxynitrile, or nitric oxide production, suggesting the specific involvement of superoxide.18

Tenocyte numbers are increased in tendinopathic tendons, and this may be a factor in degeneration and also a prerequisite to healing.11 ROS may not only induce cell death, but also determine the mechanistic form of death, such as apoptosis or oncosis.19 Apoptosis is a highly regulated programme of cellular suicide, which is of critical importance to the regulation of cell number and genomic integrity. Evidence for the involvement of apoptosis in tendon pathology is gradually emerging. Degenerative joint disease of the knee, an age related condition, is associated with higher susceptibility of periarticular tenocytes to Fas ligand induced apoptosis.14 These changes may contribute to decreased cellularity in degenerative tendons and promote their rupturing. Apoptosis has also been detected in human tendinopathic tendons,17 and the increased number of apoptotic tendon cells in degenerative tendon tissue may affect the rate of collagen synthesis and repair.17

**DOES THE TENDON ADAPT TO VARYING ROS EXPOSURE? A HYPOTHESIS**

Continued sublethal ROS exposure will not occur in a metabolically or genomics static system, and ROS exposure may induce an adaptive response in tissues.10 20 21 In the organism, adaptation seems to be cell type, and possibly antioxidative specific and age related effects on the development and composition of the antioxidative system will also need to be considered.2 It may be simplistic to extrapolate skeletal muscle adaptation to tendons. However, the effects of adaptation induced by ROS may result in changes in tenocyte ability to transpend physiological/environmental signals and resist stress arising from musculature, phagocyte, and endogenously derived ROS. Could a failure to have experienced enhanced ROS generation, possibly through avoidance of repetitive exercise/training, and hence an absence of adaptation, predispose tendons of the occasional exerciser to ROS damage during sudden exercise? Similarly, does excessive or unusual exercise by the trained athlete cause ROS exposure that evades the protective effect of any adaptive response achieved through training?

**CONCLUSION**

Tendinopathies have a complex aetiology, and we have not attempted, indeed with the current level of information we are not able, to specifically cite participation of ROS in tendon degeneration, failure, or healing. Nevertheless, recent research1 19 has provided intriguing glimpses of ROS participation in tendon pathology, and the possibility that such species influence the propensity for tendinopathic development and repair is surely one that merits further investigation.

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