Blood doping – a literature review*

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There is increasing evidence that the technique of reinfusing an athlete's stored blood prior to competition to improve performance has been used on many occasions. Although early experimental results were controversial and the precise mechanism by which the technique improves performance is still debated, there is now strong evidence that if the blood doping produces a sufficient rise in total red cell mass there are significant improvements in physiological variables such as maximum oxygen uptake, lactate buffering and thermoregulation. These physiological changes are matched by improvements in endurance performance. These may persist in diminishing degree for several weeks, but have to be weighed against the detaining effect produced by the repeated venesection required to obtain an adequate amount of stored blood for autologous reinfusion.

Experimental evidence suggests that the transient increase in blood volume and cardiac output following reinfusion is too short lived to be of any real importance and the major effect is related to the increase in total red cell mass and haemoglobin enabling an increased transport of oxygen and therefore a potentially greater reserve of blood which can be diverted to non-exercising tissues to improve thermoregulation. The increased red cell mass also improves lactate buffering. Although these benefits have been shown in several studies the increases in performance and measured physiological parameters do not bear a direct relationship to the changes in haematological variables.

Blood doping is of considerable importance, not only as an abuse of fair competition, but also because of the light it throws on the physiological limits to endurance performance. It has reawakened controversy as to whether oxygen transport is the limiting factor in endurance.

Definitions

Blood doping, blood boosting, blood packing or induced erythrocythaemia are terms used to describe the infusion of red blood cells to increase aerobic power.

Autologous blood doping refers to the infusion of the subject’s own stored blood.

Heterologous blood doping involves the infusion of blood from one or more cross-matched donors.

Techniques of blood doping

Heterologous blood doping

Use of a matched blood donor has the advantage that the athlete does not have to suffer the detaining effects of venesection. The blood can be used immediately and, if so, has not suffered any deleterious effects from storage. The disadvantages are the potential transfer of infection, such as hepatitis and AIDS, and possibilities of transfusion reactions. Heterologous blood transfusion or packing is also easier to detect with an appropriate blood sample.

Autologous blood doping

Autologous blood doping involves removing two units of the athlete's blood, storing the blood and then reinfusing it about seven days prior to the athletic contest. Venesection needs to be performed at least three weeks before reinfusion to allow the subject's haemoglobin to recover to normal levels. An interval of eight to twelve weeks is preferable in order to allow the athlete not only to regain his haemoglobin, but to get back to his previous level of fitness and overcome the detaining effect of blood donation.

The utility of autologous blood doping depends very much on how the blood is stored.

Conventional storage

In the conventional blood bank method, whole blood is citrated and refrigerated at 4°C. Despite the addition of preservatives and anticoagulants, the blood deteriorates steadily, the red cells becoming progressively less flexible and more fragile. There is an increase in blood viscosity resulting from this and increased brittleness of the red cells means that these cells can fragment on reinfusion. Six to seven percent of the stored red cells are lost each week and because of this steady deterioration blood is not transfused after three weeks of conventional storage in the United States of America and after four weeks in Scandinavia. By that time between 30 and 40 percent of the red blood cells may have been lost or be of no practical benefit when reinfused.

Conventional blood storage therefore is of minimal, if any, practical use for autologous blood doping, but
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could be used as a short term measure for heterologous blood transfusion. For autologous blood doping, the athlete is unlikely to have recovered fully from blood donation by the time the blood is transfused back and so although there may be some improvement above previous peak performance, the full potential advantage would not be gained.

High glycerol freezing

An elaborate technique can be used for almost indefinite storage of red cells. This technique is used routinely for rare blood types and is being increasingly used for autologous blood transfusion where patients are facing a major operation and only wish to receive their own blood. The blood is centrifuged and glycerol added to the high concentration of red cells which are then frozen at −80°C in liquid nitrogen. For reinfusion, the cells are carefully thawed and undergo a series of washes of increasing osmolality to remove the glycerol. They are then resuspended in normal saline and reinfused in a suspension with haematocrit of approximately 50 per cent.

The ageing of the red blood cells is suspended by freezing and there is a total loss of only 15 per cent of the red cells during the total handling process. Blood can be stored for up to ten years using this technique and the technique maximises the recovery of red blood cells and ensures that an adequate interval can be obtained between venesection and reinfusion of the blood for blood doping.

Hypotheses and experimental basis of blood doping

Blood doping could be ergogenic through its effect on oxygen carriage by producing a polycythaemia and blood volume and cardiac output.

Oxygen carriage

Supporters of blood doping claim that it increases oxygen carriage by the blood. As each gram of haemoglobin if fully saturated carries 1.34 ml of oxygen, an increase of, say, 2 g of haemoglobin per 100 ml blood increases potential oxygen carriage per litre of blood by, say, 25 ml. Assuming a mixed venous saturation of fifty per cent, half of this would be available at the working muscle and at an exercise cardiac output of, say, 24 litres per minute 300 ml of extra oxygen could be delivered to the tissues.

Improved performance would only occur if exercise cardiac output was maintained and was unaffected by the increased blood viscosity implicit in raising the haematocrit or if the exercising muscles could use the additional oxygen and therefore work harder. The experimental evidence is described below.

Blood volume, stroke volume and cardiac output

Endurance exercise

Endurance athletes when compared with normal controls usually have an increased blood volume, with an above normal total red cell mass (up to 20 per cent increase), and plasma volume, the latter often increased to a greater degree. This often gives rise to a reduction in haemoglobin concentration and so called athletes anaemia or pseudoanaemia, which has been well documented. (See Review, pp 81.)

The increased blood volume of endurance athletes gives the heart a greater preload and thus improved stroke volume and maximum cardiac output. This, together with the improved vascularization of the muscle which results in greater oxygen extraction from the blood (lower mixed venous blood oxygen saturation), helps the athlete obtain very high levels of oxygen uptake and utilization for sustained periods of endurance work. The increased plasma volume also allows a greater blood flow to the skin to help dissipate heat and gives a greater latitude for dehydration. Since the endurance athlete often has a low haematocrit with a below normal blood viscosity, dehydration is potentially better tolerated since both hypovolaemia and a rise in blood viscosity to above normal levels would require a much greater fluid loss.

Blood transfusion

Blood transfusion does produce a transient increase in blood volume, stroke volume and cardiac output but work by Guyton and Richardson shows that this effect only lasts a few minutes in experimental animals since the increased capillary pressure causes plasma transudation and loss of blood plasma which buffers any attempt to increase blood volume artificially. Studies in man show most plasma shift has occurred within one hour of transfusion and whole blood transfusion has the same effect as giving packed cells in the normal subject, a normovolaemic polycythaemia. There is no measurable increase in blood volume 24 hours later, whether measured indirectly or using a labelled albumin method to confirm blood volume.

In a series of studies on five healthy young men, Kenstrup and Ekbloom showed that VO₂ max appeared to be directly related to the total red cell mass rather than the blood volume or the haemoglobin concentration. Blood withdrawal caused a fall in VO₂ max which was not increased by volume expansion. Volume expansion alone causing a drop in haemoglobin had no effect on VO₂ max whereas a reinfusion of red blood cells causing an elevated haemoglobin concentration and total red blood cell mass increased the VO₂ max. These findings reinforce the view that the endurance runner with a raised total red cell mass but a low normal haemoglobin (i.e. runners pseudoanaemia) is not at any physiological disadvantage compared with a runner with the same total red cell mass but a smaller plasma volume.

The other postulated benefits of blood doping with respect to endurance exercise performance are related to lactate buffering and thermoregulation.

Lactic acid buffering

The accumulation of lactic acid in exercising muscle limits contractile performance by direct inhibition of enzyme systems within the muscle. Reduction in lactate production or increased buffering of the lactate to maintain the muscle pH within more normal limits would act as a considerable ergogenic aid. One of the main acid/base buffering systems in the body is blood,
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and red blood cells are responsible for 70 per cent of the buffering capacity of blood. An increased total red cell mass therefore increases the buffering capacity for lactic acid and therefore allows a greater degree of anaerobic exercise before the muscles become inhibited by the acidity. In old fashioned terms, the athlete can achieve a greater ‘oxygen debt’. This effect is in addition to the greater aerobic power following blood doping.

Thermoregulation
The transport functions of the blood during exercise are not only that of supplying active muscle with fuel and oxygen and carrying away the metabolic products of muscular activity, but also to transport heat away from the exercising muscle and to enable it to be dissipated without the core temperature of the athlete rising to dangerous levels. In many forms of endurance exercise, particularly in hot conditions, a significant part of the cardiac output is involved in heat dissipation with blood being shunted through the superficial layers of the skin to dissipate this heat. This part of the cardiac output is therefore not available for the transport of oxygen to the exercising muscle; thus, performance is limited. If, because of a raised haematocrit from blood doping, a smaller proportion of the total cardiac output can supply the same amount of oxygen to exercising muscle, this releases a larger component of the output for this secondary role of heat dissipation which can therefore be more efficient and will allow a higher work rate in unfavourable environmental conditions. Studies by Sawka et al. on exercise in a hot environment suggest that infusion of 900 ml of autologous freeze-preserved blood confers considerable advantages in terms of thermoregulation during endurance exercise.

Experimental evidence for beneficial effects of blood doping
A large number of studies have been performed on blood doping and the results of many of these are shown in Table 1. The evidence from those studies in which a significant rise in haemoglobin and haematocrit was achieved, is that the major effects of blood doping are through the effect on oxygen carriage. The effect on cardiac output and blood volume is transient and the increased endurance capacity seems therefore to be based on an increased red cell mass and haematocrit.

The first study by Pace et al. in 1947 showed that transfusion of 2000 ml of matched blood into recipients caused a considerable increase in haemoglobin and endurance time. Subsequent studies using refrigerated blood in smaller amounts have been much less spectacular and in some cases have shown changes which have been barely significant. The overwhelming impression from the studies shown in Table 1 is that if sufficient red cells are transfused a definite improvement can be obtained in endurance performance.

Table 1. Summary of experimental studies of blood doping

<table>
<thead>
<tr>
<th>Authors</th>
<th>Date</th>
<th>Number of subjects</th>
<th>Storage technique</th>
<th>Volume infused of whole blood or equivalent whole blood (ml)</th>
<th>Time of reinfusion post phlebotomy (weeks)</th>
<th>Hct/Hb</th>
<th>% increase vs control</th>
<th>VO2max</th>
<th>Endurance</th>
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<tr>
<td>Pace et al.</td>
<td>1947</td>
<td>12</td>
<td>fresh</td>
<td>2000</td>
<td>1</td>
<td>26(a)</td>
<td>NR</td>
<td>12.9</td>
<td>34.7(a)</td>
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<tr>
<td>Gullbring et al.</td>
<td>1960</td>
<td>6</td>
<td>reinf</td>
<td>610</td>
<td>1</td>
<td>0.7</td>
<td>NR</td>
<td>3.4</td>
<td>3</td>
</tr>
<tr>
<td>Robinson et al.</td>
<td>1966</td>
<td>7</td>
<td>reinf</td>
<td>1000</td>
<td>2</td>
<td>7</td>
<td>NR</td>
<td>4.8</td>
<td>1.4</td>
</tr>
<tr>
<td>Ekblom et al.</td>
<td>1972</td>
<td>7</td>
<td>reinf</td>
<td>800</td>
<td>2</td>
<td>4.3</td>
<td>NR</td>
<td>5.3</td>
<td>1.3</td>
</tr>
<tr>
<td>Von Rost et al.</td>
<td>1975</td>
<td>9</td>
<td>reinf</td>
<td>1200</td>
<td>2</td>
<td>1.3</td>
<td>NR</td>
<td>4.2</td>
<td>37(b)</td>
</tr>
<tr>
<td>Bell et al.</td>
<td>1976</td>
<td>7</td>
<td>reinf</td>
<td>900</td>
<td>3</td>
<td>2.7</td>
<td>NR</td>
<td>4.3</td>
<td>7(b)</td>
</tr>
<tr>
<td>Ekblom et al.</td>
<td>1976</td>
<td>5</td>
<td>reinf</td>
<td>500</td>
<td>1</td>
<td>1.1</td>
<td>NR</td>
<td>5.6</td>
<td>7.5</td>
</tr>
<tr>
<td>Videman and</td>
<td>1977</td>
<td>10</td>
<td>reinf</td>
<td>2000</td>
<td>5</td>
<td>4.5(b)</td>
<td>NR</td>
<td>8.0</td>
<td>NR</td>
</tr>
<tr>
<td>Rytopsaq</td>
<td>1977</td>
<td>16</td>
<td>reinf</td>
<td>500</td>
<td>2.5</td>
<td>NR</td>
<td>0</td>
<td>NR</td>
<td>15.8(a)</td>
</tr>
<tr>
<td>Frye and Ruhling</td>
<td>1978</td>
<td>16</td>
<td>frozen</td>
<td>1800</td>
<td>16</td>
<td>NR</td>
<td>12.8(a)</td>
<td>NR</td>
<td>15.8(a)</td>
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<td>Williams et al.</td>
<td>1978</td>
<td>16</td>
<td>fresh</td>
<td>460</td>
<td>3</td>
<td>3.3</td>
<td>NR</td>
<td>4.1</td>
<td>NR</td>
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<tr>
<td>Cottrell</td>
<td>1979</td>
<td>9</td>
<td>frozen</td>
<td>405</td>
<td>9</td>
<td>NR</td>
<td>2</td>
<td>NR</td>
<td>2</td>
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<tr>
<td>Robertson et al.</td>
<td>1979</td>
<td>7</td>
<td>reinf</td>
<td>800</td>
<td>3</td>
<td>0.4</td>
<td>NR</td>
<td>0.5</td>
<td>14.3(a)</td>
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<tr>
<td>Pat et al.</td>
<td>1979</td>
<td>7</td>
<td>reinf</td>
<td>450</td>
<td>3</td>
<td>0.35</td>
<td>NR</td>
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<td>13.1(a)</td>
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<td>Buick et al.</td>
<td>1980</td>
<td>11</td>
<td>frozen</td>
<td>900</td>
<td>7</td>
<td>11.5(a)</td>
<td>NR</td>
<td>5(a)</td>
<td>13.1(a)</td>
</tr>
<tr>
<td>Spriet et al.</td>
<td>1980</td>
<td>4</td>
<td>frozen</td>
<td>800</td>
<td>11</td>
<td>7.9(a)</td>
<td>3.9(a)</td>
<td>NR</td>
<td>2.5(a)</td>
</tr>
<tr>
<td>Williams et al.</td>
<td>1981</td>
<td>12</td>
<td>frozen</td>
<td>920</td>
<td>7</td>
<td>7.9(a)</td>
<td>NR</td>
<td>2.5(a)</td>
<td>11</td>
</tr>
<tr>
<td>G dof et al.</td>
<td>1982</td>
<td>6</td>
<td>reinf</td>
<td>760</td>
<td>4</td>
<td>4.6</td>
<td>NR</td>
<td>1.1(b)</td>
<td>NR</td>
</tr>
<tr>
<td>Thomson et al.</td>
<td>1982</td>
<td>4</td>
<td>frozen</td>
<td>1000</td>
<td>12</td>
<td>3.5(b)</td>
<td>inc.</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Konstrup and</td>
<td>1983</td>
<td>5</td>
<td>reinf</td>
<td>900</td>
<td>5</td>
<td>2(a)</td>
<td>NR</td>
<td>7(a)</td>
<td>24(a)</td>
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<tr>
<td>Ekblom</td>
<td>1984</td>
<td>9</td>
<td>frozen</td>
<td>900</td>
<td>16</td>
<td>18(a)</td>
<td>NR</td>
<td>10(a)</td>
<td>22(a)</td>
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<td>Berglund et al.</td>
<td>1986</td>
<td>6</td>
<td>reinf</td>
<td>1350</td>
<td>4</td>
<td>7.9(a)</td>
<td>NR</td>
<td>11(a)</td>
<td>NR</td>
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<td>Sawka et al.</td>
<td>1987</td>
<td>6</td>
<td>frozen</td>
<td>900</td>
<td>20</td>
<td>inc.</td>
<td>11(a)</td>
<td>NR</td>
<td>improved</td>
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<tr>
<td>Brien et al.</td>
<td>1987</td>
<td>6</td>
<td>frozen</td>
<td>900</td>
<td>11</td>
<td>5(a)</td>
<td>NR</td>
<td>5(a)</td>
<td>NR</td>
</tr>
</tbody>
</table>

Key: (a) Statistically significant, (b) No statistical analysis reported, NR Not reported, inc. increased
The improvement in performance is often much less than would be predicted from the increased haemoglobin and there is considerable doubt as to the exact mechanism by which the increased endurance capacity is achieved.

Early studies used small numbers of volunteers without any control subjects and without a double blind crossover of the procedures used. More recent studies such as those of Buick et al., Williams et al., Robertson et al.13, and Brien and Simon9 had much better experimental design, used the high glycerol freezing technique and all show a significant improvement in endurance performance with blood doping. However, the individual variations in improvement remain unexplained even when adequate time (a week) between the reinfusion and the testing is allowed. Reinfused blood takes a finite time to overcome the effects of storage. In particular, the concentration of certain enzymes such as 2,3-DPG falls in conventionally stored blood and takes 24 hours or more to achieve normal levels. However, this effect is said to be less marked in glycerol frozen blood.

The discrepancies between the rise in haematocrit, the increase in maximum oxygen uptake and improvement in aerobic performances which show an unpredictable relationship to each other do raise questions on the exact nature of the ergogenic effects of blood doping as well as questioning what limits maximal aerobic performance.

The centralist theory is that the oxygen transport by the cardiovascular systems and lungs and its carriage in the blood is the limiting factor is favoured by the proven benefits of blood doping. The lack of a predictable response to improvements in haematocrit and total red cell mass suggest that there may be limitations at the muscle level which are also of considerable importance.

**Adverse effects of blood doping**

The demonstrated benefits of blood doping might give the impression that it is a totally safe procedure. Apart from the theoretical risks of transmissible infectious disease such as AIDS and hepatitis, if heterologous transfusion is used, any intravenous infusion carries risks such as venous thrombosis, phlebitis and sepsis, particularly if the transfusion is given in less than adequately sterile circumstances. The raised haematocrit, increased viscosity and hypercoagulability of blood following transfusion may well be compounded by an athlete spending many hours relatively immobile, travelling to the sporting venue and running a high risk of venous thrombosis, even pulmonary embolism.

For autologous blood doping, venesection of 500 ml of blood on one or more occasions has a marked detraining effect, and will limit the amount and quality of the training in the run up to competition.

A possibly anecdotal disadvantage is that the removed blood may contain damning evidence of a banned substance such as an anabolic steroid, taken in training but stopped well before competition, but then reintroduced in the stored blood and giving a positive in the urine, when tested at competition for banned substances.

**The detection of blood doping**

Blood doping is banned by IOC doping regulations. It is generally recognised as a form of cheating. However, there is no easy way of detecting blood doping. It is easy therefore both for an athlete to cheat and get away without being detected, and also for an athlete to be accused unfairly of blood doping and not be able to vindicate himself. It is the only doping ban that cannot presently be supported by testing.

The International Olympic Committee has funded Berglund to try to find a method of detecting blood doping but so far methods of detection have been disappointing. Infusion of conventionally refrigerated blood does produce a rapid increase in serum iron and bilirubin and a drop in serum erythropoietin. Unfortunately, serum erythropoietin is suppressed by physical exercise so low levels after competition are not diagnostic. Berglund has produced an algorithm to detect blood doping based on his studies5-20, but this has limited sensitivity. So far his studies have used conventionally refrigerated, rather than glycerol-deep-frozen, blood in athletes living and training at sea level.

Heterologous transfusion could be detected by showing red cells carrying foreign non-ABO blood groups, since a complete match of all groups would be statistically a remote possibility (unless the runner had a twin).

It has been suggested that one of the best methods of detecting blood transfusion would be by showing a non-uniform distribution in the red cell size (which is influenced by the age of the red blood cells), but this technique is not yet practical16.

All techniques of detection require at least one blood sample, and most require several for definite evidence of blood doping to be proven. At the moment, athletes are subjected to urine, but not blood sampling and the detection of blood doping therefore remains a major problem for the athletic authorities.

Since trace substances in infused blood are detectable, possibly the only practical way of detecting autologous blood doping might be to insist that athletes in training take some regular form of marking substance that shows in the urine, and discontinue it a few days before competition. However, this would be an infringement of their rights, and it seems unlikely that any acceptable method of detection will be developed in the near future.

Perhaps the discovery and isolation of erythropoietin will make blood doping irrelevant. Erythropoietin is a direct stimulus to further red cell production and is a potentially cleaner method of achieving the same effects. Erythropoietin is not currently a banned substance and the potential for it being used to confer an unfair disadvantage is considerable.

We hope that the ethics of sport, particularly Olympic sport, will return to earlier idealistic levels so that winning at any medical price, with consequent costly and constant policing and dope testing become superceded. The 1988 Olympics were nicknamed the ‘Anabolic Olympics’. Let us hope the Barcelona Olympics do not become the ‘Haematocrit Olympics’.
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