Intraoperative conservation of red cell mass: controlled hypotension or haemodilution—
not necessarily mutually exclusive?

The amount of blood lost during operation is determined mainly by surgical technique and the methods used to secure haemostasis. However, it is also influenced profoundly by factors such as patient position on the operating table facilitating venous drainage away from the wound towards the heart, efficient respiratory gas exchange and, where appropriate, the use of a tourniquet. Implicit in the goal of modifying total blood loss is the ultimate aim of minimizing restorative blood transfusion. There is a variety of techniques which can reduce the need for transfusion of red cells; autotransfusion in the form of cell salvage, haemodilution and controlled hypotension. In this issue of the British Journal of Anaesthesia, Boldt and colleagues have compared the usefulness of controlled hypotension and acute normovolaemic haemodilution to reduce surgical blood loss during radical prostatectomy. Their aim was to reduce allogeneic blood transfusion for both medical and financial reasons. Previous studies have investigated the role of these techniques in isolation but this is the first purpose-designed, randomized, prospective study comparing the two techniques.

Controlled hypotension achieved popularity during the parallel emergence of ganglion blocking and neuromuscular blocking drugs, both of which have a quaternary ammonium ion moiety. The term ‘physiological trespass’ was coined which reflected the potential hazard of tending towards, among other things, conditions favouring stagnant hypoxia.

The concept of induced hypotension is to produce a reduction in peripheral vascular resistance and thus hydrostatic pressure while maintaining cardiac output. Some haemodilution is likely to occur and, depending on the extent of hypotension and the timing of infusion of clear fluids, this may be considerable and may induce a state of hypervolaemia, at least until operative blood loss and urine output compensate.

Deliberate acute preoperative haemodilution is usually performed with the aim of maintaining strict normovolaemia (ANH); indeed, maintenance of normovolaemia is critical, as the onset of sudden hypovolaemia in the presence of induced anaemia can be dangerous. Most of our knowledge of ANH is derived from experience with cardiac bypass, where the need to avoid pump-priming with blood inevitably produces haemodilution. The fact that these patients are protected against the potential adverse cardiac effects of haemodilution by revascularization does, however, mean that it is difficult to extrapolate from this situation to a more general population. Furthermore, cardiac bypass patients are monitored and managed after operation in intensive care units, and again this is not a level of care that is applicable universally to other specialties. We now know that in any adult surgical population there are individuals with unsuspected coronary disease and that silent myocardial ischaemia occurs in patients not considered to be at risk in the absence of formal assessment.

The technique of ANH is attractively simple and apparently inexpensive. A pre-determined number of units of whole blood are withdrawn in the immediate preoperative period and stored at room temperature until haemostasis has been secured (or until required, if blood loss is prolonged and continuous). In addition to offering the possibility of reducing allogeneic transfusion requirements, it has the additional theoretical benefits of increasing tissue oxygenation as a result of reduced viscosity and a possible beneficial effect on the coagulation mechanism because the transfused units of autologous blood contain normal levels of clotting factors and functioning platelets. These theoretical advantages have not, however, been convincingly shown to translate into clinical benefit.

It is becoming clear that it is important to distinguish between minimal ANH (target packed cell volume 25–30%, usually equating to 2 u. of autologous blood) and extreme ANH (target packed cell volume <20%). Advocates of minimal ANH acknowledge that the achievable reduction in allogeneic transfusion may be unimpressive, but the technique is probably safe and offers a form of autotransfusion to patients ineligible for predonation or intraoperative cell salvage. In contrast, extreme ANH can have a significant impact on allogeneic blood use, but the need for the patient to tolerate a very low packed cell volume means that its use is restricted to young, healthy patients undergoing elective surgery with an expected large blood loss.

The danger implicit in extending beyond minimal ANH
in older surgical patients has stimulated a renewed interest in hypervolaemic haemodilution (HH). Mathematical models demonstrating the limited effectiveness of minimal to moderate ANH\(^9\) can be used to show that HH may provide the benefits of extreme ANH with a greater margin of safety.\(^{10}\) The few clinical studies of HH suggest that it may indeed be as effective and safer than ANH.\(^{11,12}\) but in fact the final haemoglobin values achieved in some patients studied were surprisingly high and difficult to interpret. Smetanikov and Hopkins suggested that, on theoretical grounds, ANH may produce a greater final haemoglobin concentration than HH, but at the cost of a lower minimum packed cell volume during operation.\(^{13}\)

Various mathematical models have been used to describe the changing variables during blood loss and simultaneous fluid replacement. These can be used, for example to calculate total permissible volume of blood loss to achieve a pre-defined target packed cell volume or haemoglobin concentration. Alternatively, the final packed cell volume can be estimated from knowledge of the starting circulating volume and actual volume of blood loss.\(^{14}\) The relationship of blood loss and resulting packed cell volume is linear only where fluid replacement occurs after blood loss has ceased, which in practice is rarely the case; intraoperative i.v. infusion of fluid simultaneously with blood loss is more likely. The effect of the latter on packed cell volume (or haemoglobin concentration) is that of a kinetic first-order exponential decay\(^{13}\) where circulating volume (CV) is analogous to volume of distribution and rate of blood loss to clearance (Cl):

\[
T_{1/2} = 0.693 \times CV/Cl
\]

and

\[
Hb_{final} = Hb_{initial} \times e^{VL/CV}
\]

where \(VL\) = volume of blood lost.

The final haemoglobin concentration assumes steady state after loss of a given volume of blood during which normovolaemia has been maintained by simultaneous infusion of non-haemoglobin fluids.

Similarly, the volume of blood lost (VL) to give a target final haemoglobin concentration can be calculated from:

\[
VL = CV \times \ln(Hb_{initial}/Hb_{final})
\]

where \(\ln\) = natural or Napierian logarithm.\(^{15}\)

Using this decay exponential model, it can be shown that after 50% loss of circulating volume during which normovolaemia has been maintained, the final haemoglobin concentration is 61% of the initial value; in a linear relationship the final haemoglobin concentration would be 50% of the initial value. Extending this concept, if 100% circulating volume was lost during maintenance of normovolaemia by infusing non-haemoglobin fluids, then the final haemoglobin concentration would be 36% of the initial value. There would of course be zero haemoglobin where a non-haemoglobin infusion followed total exsanguination; this is the extreme limit of the linear relationship.

The study of Boldt and colleagues in this issue does not directly address itself to a comparison of normovolaemic and hypervolaemic haemodilution. Instead, the authors compared a variety of outcomes in three groups of patients undergoing radical prostatectomy. Patients were allocated randomly to receive standard anaesthetic techniques, controlled hypotension or ANH. However, analysis of their data showed that patients treated by controlled hypotension had lower ‘baseline’ values for clotting factors and platelets than controls, suggesting a degree of haemodilution before commencement of blood loss. The finding that blood loss and transfusion requirements were lowest in the controlled hypotension group, with rather disappointing results in the ANH group as predicted by mathematical models, suggests that the combination of controlled hypotension with hypervolaemic haemodilution might be the most effective blood conservation option for such patients.

The effectiveness of this regimen would clearly require careful clinical study. As always in the assessment of blood conservation techniques, however, there are major difficulties in establishing safety, given that the adverse effects of allogeneic transfusion are now so rare that valid statistical comparisons are all but impossible. Nevertheless, the fact that the minimum intraoperative haemoglobin concentration in hypervolaemic haemodilution is likely to remain higher than with ANH is reassuring, especially because the initial hypervolaemia may protect against sudden subsequent hypovolaemia, which could exacerbate hypoxia in the presence of a low packed cell volume. Clearly, it would be the responsibility of the anaesthetist to choose acceptable lower limits of haemoglobin or packed cell volume and arterial pressure for any individual patient, although it would be helpful if nomograms could be derived from controlled clinical studies. There is some reassuring evidence that the initial hypervolaemia is well tolerated in patients without heart disease even in the absence of induced hypotension,\(^{16}\) and it would seem reasonable to suppose that reduction in systemic vascular resistance would help protect against cardiac failure in the unrecognized susceptible patient.

Further prospective, randomized studies are required to assess the safety of the combination of hypotension and haemodilution and to establish safe combined lower limits of packed cell volume and arterial pressure.\(^{17}\) If these techniques can reliably preserve red cell mass, the requirement of allogeneic transfusion will decrease. To achieve this, however, a radical shift in attitudes to intraoperative blood replacement is necessary, with reconsideration of blood loss, as currently measured, as the main indicator of the need for blood replacement. The transfusion trigger should not be a single measurement index; rather it should be a composite of variables specific for an individual patient.\(^{18}\) Accurate assessment of intraoperative blood loss requires measurement of packed cell volume (and haemo-
globin concentration) in addition to the simplistic traditional measurement of blood in the suction reservoir and weight of swabs.

Many questions remain to be answered, but it is likely that use of a structured approach to conserve red cell mass during operation will reduce requirements for allogeneic transfusion without the compromise in safety inherent in acute normovolaemic haemodilution. In 1995 at a consensus conference, it was concluded that there was insufficient evidence of efficacy and safety in the use of ANH and it seems that this is still the case.

I. D. Levack
Department of Anaesthetics
Western General Hospital
Crewe Road
Edinburgh EH4 2XL, UK

J. Gillon
Edinburgh and South East Scotland Blood Transfusion Service
Royal Infirmary
Edinburgh, UK

References
2 Enderby GEH. Controlled circulation with hypotensive drugs and posture to reduce bleeding in surgery. Preliminary results with pentamethonium iodide. Lancet 1950; i: 1145–7
4 Paton WDM, Zaimis EJ. Clinical potentialities of certain bisquaternary salts causing neuromuscular and ganglionic blockade. Nature 1948; 162: 810
8 Rotman G, Ness PM. Acute normovolemic hemodilution is a legitimate alternative to allogeneic blood transfusion. Transfusion 1998; 38: 477–80
9 Brecher ME, Rosenfield M. Mathematical and computer modeling of acute normovolemic hemodilution. Transfusion 1994; 34: 176–9
17 Drobin D, Hahn RG. Time course of increased haemodilution in hypotension induced by extradural anaesthesia. Br J Anaesth 1996; 77: 223–6