Editorial II

When should we transfuse critically ill and perioperative patients with known coronary artery disease?[†]

Red blood cell (RBC) transfusion is a life-saving therapy for major haemorrhage. However, many RBC transfusions prescribed for surgical patients or critically ill patients in the intensive care unit (ICU) are to increase haemoglobin concentration when clinically significant bleeding is not present or has stopped.[1–3] In these situations the potential benefits of RBC transfusion need to be balanced against the risks associated with it. Transmission of known viral infections by RBC transfusion is extremely rare and the much-debated importance of donor leucocytes is no longer relevant in the UK (and in an increasing number of other countries) because all blood components are leucodepleted before storage. However, other serious complications such as incompatible transfusion resulting from administration errors, and cases of transfusion-associated lung injury (TRALI) continue to occur and to cause significant morbidity and mortality.[4]

At present, most clinicians prescribing RBC transfusions make a risk/benefit assessment for individual patients based on their own experience and their interpretation of evidence-based guidelines, which are currently based largely on inadequate and poor-quality evidence. In the UK, we believe that this judgement is at present rarely influenced by the availability of RBCs in the blood bank, their cost or the possibility that unnecessary RBC use could deplete supplies for a patient with life-threatening haemorrhage.

This situation could change. If, or when, some form of additional donor screening for new-variant CJD is introduced, there could be a dramatic fall in blood supplies because potential donors may fear the implications of a positive test.[5 6] This very real possibility was recognized in the recent Health Service circular *Better Blood Transfusion*,[6] which also commented on the continued wide variation in blood use in surgery and surgical specialties.

One solution to this problem is to promote blood conservation strategies such as perioperative cell salvage. However, these are only suitable for some patients and even if implemented successfully, anaesthetists, surgeons and intensivists will still face decisions regarding the appropriate transfusion trigger for their anaemic patients. A second strategy is to avoid unnecessary RBC transfusions by developing and using a body of high-quality evidence to define essential indications for RBC transfusions, ensuring at the same time that patients are not exposed to dangerous levels of anaemia. Guidelines based on such evidence—and the clinicians using them—need to be clear how applicable their recommendations are. This is particularly true of the large, heterogeneous population of patients undergoing non-cardiac surgery.

Fortunately, we already have a high-quality randomized controlled trial—the Transfusion Requirements In Critical Care (TRICC) study[7]—and a Cochrane review[8] of this and other smaller randomized controlled trials to guide us. These conclude that, for *most* patients, RBC transfusion is not indicated unless the haemoglobin concentration decreases below 7–8 g dl^{-1}. These conclusions are reflected in the UK in the Association of Anaesthetists guideline,[9] the Scottish Intercollegiate Guideline Network (SIGN),[10] and the Handbook of Transfusion Medicine.[11] However, all these documents qualify their recommendations for patients with ischaemic heart disease. For example, the Cochrane systematic review found '… minimal evidence of the safety of conservative transfusion triggers in important subsets of patients, including those with severe cardiovascular disease…'.[8] In a recent international forum concerning perioperative triggers for red cell transfusion, all eight of the expert contributors said they modified their transfusion trigger in patients with coronary artery disease, to values ranging from 8 to 10 g dl^{-1}.[12]

There are sound reasons for these doubts, which arise from several areas of scientific research: first, our understanding of normal myocardial oxygen kinetics and how these change with coronary artery disease; second, the known changes in myocardial oxygen supply and demand associated with the physiological stress of the perioperative period and critical illness; third, animal studies that simulated coronary artery disease and anaemia; and fourth, clinical studies of patients suffering from coronary artery disease who subsequently underwent surgery or had a critical illness.

Normal myocardial oxygen kinetics

The resting oxygen extraction ratio of the heart is about 65%. It cannot increase significantly in response to

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increased oxygen demand. As a result, it is normal for the coronary sinus P_{O_2} to be very low (about 3 kPa). Coronary flow is tightly autoregulated by processes that ensure close matching of oxygen supply and demand. Significant left ventricular coronary flow occurs only during diastole, and the subendocardial region is particularly at risk of ischaemia because of the high pressure in the left ventricle. Normal resting adult coronary blood flow is about 250 ml min^{-1}. If the haemoglobin concentration is normal (13.5 g dl^{-1}), this produces a coronary oxygen delivery (D_{O_2}) of 40 ml min^{-1}, which meets resting myocardial demands of about 25 ml min^{-1}. If this demand remains constant and the patient is euvolaemic, but haemoglobin concentration is allowed to fall to 8 g dl^{-1} before transfusion, myocardial oxygen delivery decreases to 25 ml min^{-1}. As oxygen extraction cannot increase further, this level of D_{O_2} could not match demand unless coronary flow increases. Provided circulating volume is maintained, reduced blood viscosity and coronary vasodilatation normally result in increased flow to meet demand. The haemoglobin level at which reduced oxygen carriage is optimally balanced by the flow improvement associated with reduced blood viscosity is uncertain, and is likely to be specific to individual patients and patterns of coronary disease. Animal studies suggest that the normal coronary vascular resistance can decrease by up to fivefold, and studies of normovolaemic haemodilution in healthy young human volunteers found that evidence of myocardial ischaemia was extremely unusual, even with haemoglobin concentrations of 5 g dl^{-1}.[13] However, it is clear that coronary lesions are potential risk factors for ischaemia in the presence of anaemia.

Myocardial oxygen demand

Myocardial oxygen demand correlates closely with the product of pressure and flow. It has long been recognized that the additional work done by the heart to generate greater pressure at a constant flow requires more oxygen than is required to increase flow at constant pressure. In practice, this means that the vasodilated normotensive patient with an elevated cardiac output is at lower risk of excessive myocardial oxygen demand than is the vasoconstricted hypertensive patient with normal cardiac output. Inotropic agents such as epinephrine also increase myocardial oxygen demand by direct effects on heart rate and contractility, and via a vasoconstriction-induced increase in afterload. These factors mean that at any time a patient's risk from anaemia depends not only on the extent of preexisting coronary artery disease, but also on their current cardiovascular status and treatment. For example, a patient with sepsis might tolerate anaemia during the hyperdynamic early phase, but go on to develop myocardial ischaemia associated with the increased sympathetic activation associated with difficult weaning from the ventilator.[14]

Animal studies

Several animal studies in the literature have investigated the relationship between isovolaemic haemodilution and various types of coronary artery stenosis.[15–17] These confirm that coronary artery narrowing decreases the tolerance of the heart to anaemia, with exact values of haemoglobin depending on the model used. For example, Spahn and colleagues[17] studied dogs with critical stenosis of the left anterior descending coronary artery and found that myocardial dysfunction occurred at a haemoglobin level <7.5 g dl^{-1}, which was reversible by blood transfusion. However, it is questionable whether these studies help with the clinical dilemma being discussed. Most of these models were not subject to major fluctuations in myocardial work, usually examined single coronary artery lesions rather than potentially diffuse disease, and were not carried out in humans. Most investigators were interested in tolerance of acute normovolaemic haemodilution for coronary artery bypass surgery, where the extent of coronary artery disease is known in detail from preoperative angiography. This is rarely the case for patients presenting for non-cardiac surgery or intensive care.

Clinical studies

Several large studies have confirmed the association between anaemia and cardiac morbidity in patients with coronary artery disease. Carson and colleagues[18] retrospectively studied 1958 patients who refused blood transfusion during major surgery. For patients with known cardiovascular disease, but not for those without, there was an interaction between the presence of preoperative anaemia and increased risk of death, which increased progressively from a haemoglobin value of 10 g dl^{-1} downwards. Another analysis of 4470 critically ill patients in Canadian ICUs found that in patients with cardiac disease there was a trend toward an increased mortality when haemoglobin values were <9.5 g dl^{-1} compared with anaemic patients with other diagnoses.[19] It is difficult to exclude the effect of confounding variables in these cohort studies, but their conclusions are supported by a prospective case-controlled study in 27 patients undergoing peripheral vascular surgery.[20] The authors examined the relation between postoperative ischaemic cardiac complications and anaemia and found that a haematocrit of 0.28 (haemoglobin concentration about 9 g dl^{-1}) best predicted the chance of complications. These studies all suggest that a transfusion trigger of 9–10 g dl^{-1} is more appropriate than lower haemoglobin concentrations in patients with coronary artery disease. However, these studies represent, at best, level-3 evidence and do not exclude the possibility that higher or lower haemoglobin values are optimal in specific patient subgroups.

Support for a haemoglobin transfusion threshold nearer 10 g dl^{-1} for patients with severe coronary disease comes from a recent large retrospective cohort study in 79 000 patients aged >65 yr with acute myocardial infarction.[21] The authors found an association between RBC transfusion and lower 30-day mortality for patients with an admission haematocrit <0.33 (about 11 g dl^{-1}), but not above this level. Anaemia is an independent risk factor for reduced survival in patients with cardiac failure, and in a small randomized controlled trial in 32 patients with severe congestive cardiac failure, correction of mild anaemia (haemoglobin 10–11.5 g dl^{-1}) with erythropoietin improved functional status and resulted in a non-significant reduction in mortality.[22] It makes medical sense that 'not all patients with ischaemic heart disease are the same', and those with severe disease may need to be treated differently from those in whom disease is mild or stable. At present there are no simple criteria, other than regular clinical assessment, that reliably identify patients with differing levels of tolerance of anaemia.

The only large randomized study that has considered transfusion triggers for a non-cardiac surgery population of perioperative or critically ill patients with coronary artery disease was a retrospective subgroup analysis of the TRICC randomized controlled trial dataset, in which the transfusion trigger was either <7 g dl^{-1} or <10 g dl^{-1}.[23] The authors identified 357 patients who had 'cardiovascular disease' as a primary or secondary ICU admission diagnosis and found no difference in outcome [difference in 30-day mortality 0.3%; confidence interval (CI) –8.4% to 9.1%]. However, the authors also examined the 257 patients who were known to have ischaemic heart disease from ICU admission diagnoses and listed comorbidity. For these patients, the difference in 30-day mortality was –4.9% (95% CI –15.3% to 5.6%), with a non-significant trend towards better outcome in patients whose haemoglobin concentration was kept above 10 g dl^{-1} (P=0.3). This subgroup analysis should be interpreted cautiously, however. It suggests that large differences in 30-day mortality did not occur between the transfusion strategies, but does not exclude clinically important differences. There is also no information about the severity of the cardiac disease. To complicate matters further, it is important to remember that patients in the TRICC study received non-leucodepleted RBCs. Results might be different with the current RBC product, because the infusion of donor leucocytes with the red cells, or the infusion of RBCs modified by storage in the presence of leucocytes, may have adverse effects on outcome.[2,24–26] It is also not known if the TRICC data are applicable to perioperative patients with less severe or no organ failure, or if specific subgroups of patients with ischaemic heart disease behave differently.

We therefore need trials addressing transfusion triggers for patients with coronary artery disease. These will be difficult to design, expensive to carry out, and will need large research networks to be successful. A particular problem is stratification of the severity of the disease, as it seems likely that the safe haemoglobin concentration depends in part on the pattern and severity of coronary disease. Despite these problems, potential RBC shortages and the continuing concerns about blood safety should make this issue a research priority. Many patients undergoing major surgery or suffering from critical illness have known ischaemic heart disease. An increasing number of patients are also elderly and may have undiagnosed coronary artery disease.

In the absence of adequately powered data from randomized controlled trials, what does the available evidence suggest we should currently do for this large patient group? The grey area seems to lie between haemoglobin values of 7 and 10 g dl^{-1}. Patients with stable or mild coronary artery disease can probably be managed with transfusion triggers of 7–8 g dl^{-1} unless they have evidence of worsening ischaemia or infarction. Patients with severe, symptomatic disease should probably have a transfusion trigger nearer 9–10 g dl^{-1}, which should probably be close to 10 g dl^{-1} if there is evidence of ischaemia, recent infarction, or acute cardiac dysfunction. In addition to these general principles, clinicians should regularly reassess the likely myocardial oxygen supply/demand balance of their patients, bearing in mind that this may change during the illness, and modify their transfusion decisions based on this information. Until we have more high-quality evidence regarding transfusion triggers, it is important that we do not over-interpret the results of one excellent randomized controlled trial (the TRICC study) by applying them to a large population of patients for whom we do not yet have clear answers.

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References

1 Rao MP, Boralessa H, Morgan C, *et al.* Blood component use in critically ill patients. *Anaesthesia* 2002; **57**: 530–4
2 Vincent JL, Baron JF, Reinhart K, *et al.* Anemia and blood transfusion in critically ill patients. *JAMA* 2002; **288**: 1499–507
3 Garrioch M, Walsh TS, Maciver C, Lee R, McClelland DBL, for the

ATICS study group. Red blood cell use in Intensive Care in Scotland (the ATICS study). *Transfusion Med* 2002; **12** (suppl. 1): 6
4 Love EM, Jones H, Williamson LM, *et al*. *Serious Hazards Of Transfusion Annual Report 1999/2000*. Manchester: SHOT Steering Group, 2000. www.shot.demon.co.uk
5 Mortimer PP. Making blood safer. *Br Med J* 2002; **325**: 400–1
6 Better Blood Transfusion: appropriate use of blood. HSC 2002/009. www.doh.gov.uk/publications/coinh.html
7 Hebert PC, Wells GF, Blajchman MA, *et al*. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med* 1999; **340**: 409–17
8 Hill SR, Carless PA, Henry DA, *et al*. Transfusion thresholds and other strategies for guiding allogeneic red blood cell tansfusions (Cochrane review). In: *The Cochrane Library*, Issue 2. Oxford: Update Software, 2002
9 Blood Transfusion and the Anaesthesist. www.aagbi.org/guidelines.html
10 Perioperative Blood Transfusion for Elective Surgery: a National Clinical Guideline. www.sign.ac.uk
11 Handbook of Transfusion Medicine. www.transfusionguidelines.org.uk
12 Engelfriet CP, Reesink HW, McCullough J, *et al*. Perioperative triggering for red cell transfusions. *Vox Sang* 2002; **82**: 215–26
13 Leung JM, Weiskopf RB, Feiner J, *et al*. Electrocardiographic ST-segment changes during acute, severe isovolemic hemodilution in humans. *Anesthesiology* 2000; **93**: 1004–10
14 Srivastava S, Chatila W, Amoateng-Adjepong Y, *et al*. Myocardial ischemia and weaning failure in patients with coronary artery disease: an update. *Crit Care Med* 1999; **27**: 2109–12
15 Geha AS, Baue AE. Graded coronary stenosis and coronary flow during acute normovolemic anemia. *World J Surg* 1978; **2**: 645–52
16 Most AS, Ruocco NA, Gewirtz H. Effect of a reduction in blood viscosity on maximal myocardial oxygen delivery distal to a moderate coronary stenosis. *Circulation* 1986; **74**: 1085–92
17 Spahn DR, Smith LR, Veronee C, *et al*. Acute isovolemic hemodilution and blood transfusion: Effects on regional function and metabolism in myocardium with compromised coronary blood flow. *J Thorac Cardiovasc Surg* 1993; **105**: 694–704
18 Carson JL, Duff A, Poses RM, *et al*. Effect of anaemia and cardiovascular disease on surgical mortality and morbidity. *Lancet* 1996; **348**: 1055–60
19 Hebert PC, Wells G, Tweeddale M, *et al*. Does transfusion practice affect mortality in critically ill patients? *Am J Respir Crit Care Med* 1997; **155**: 1618–23
20 Nelson AH, Fleisher LA, Rosenbaum SH. Relationship between postoperative anemia and cardiac morbidity in high-risk vascular patients in the intensive care unit. *Crit Care Med* 1993; **21**: 860–6
21 Wu WC, Rathore SS, Wang Y, Radford MJ, Krumholz HM. Blood transfusion in elderly patients with acute myocardial infarction. *N Engl J Med* 2001; **345**: 1230–6
22 Silverberg DS, Wexler D, Sheps D, *et al*. The effect of correction of mild anemia in severe, resistant congestive heart failure using subcutaneous erythropoietin and intravenous iron: a randomised controlled study. *J Am Coll Cardiol* 2001; **37**: 1775–80
23 Hebert PC, Yeltsir E, Martin C, *et al*. Is a low transfusion threshold safe in critically ill patients with cardiovascular disease? *Crit Care Med* 2001; **29**: 227–34
24 Brand A, van de Watering LM, Claas FH. Clinical significance of leukoreduction of blood components. *Vox Sang* 2000; **78** (suppl. 2): 227–9
25 McLellan SA, Walsh TS, McClelland DB. Should we demand fresh red blood cells for perioperative and critically ill patients? *Br J Anaesth* 2002; **89**: 537–40
26 Hebert PC, Fergusson DA. Red blood cell transfusions in critically ill patients. *JAMA* 2002; **288**: 1525–6

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