Editorials represent the opinions of the authors and The Journal and not those of the American Medical Association.

Do Transfusions Get to the Heart of the Matter?

Paul C. Hébert, MD, MHSc
Dean A. Fergusson, PhD

Over the last half-century, it has become well recognized that patients with cardiovascular diseases and, more specifically, ischemic heart disease may be adversely affected by anemia. This is because the myocardium consumes or extracts 60% to 75% of all oxygen delivered to the coronary circulation.1-3 Such an elevated extraction of oxygen, termed extraction ratio, is unique to the coronary circulation. As a result, oxygen delivery to the myocardium can be augmented only by increasing blood flow or oxygen content.1

Animal and human studies have investigated the effects of normovolemic anemia on coronary circulation.1,2,4-5 There appear to be minimal consequences from moderate levels of anemia with hemoglobin levels in the range of 7.0 g/dL if coronary circulation is normal.1,6-9 However, at comparable hemoglobin concentrations, myocardial dysfunction and ischemia occur earlier and are more pronounced in anemic animal models with moderate- to high-grade coronary stenoses.2,4,9,10 In humans, a retrospective study involving 1958 patients who declined a blood transfusion documented an increase in the risk of death with decreasing preoperative hemoglobin concentrations in patients with underlying cardiovascular disease compared with other patients.11 Despite consistent findings from physiological and observational studies regarding the risks of anemia in patients with ischemic heart disease, there remains limited clinical evidence that blood transfusions increase survival in this population following moderate levels of anemia.

In this issue of JAMA, Rao and colleagues12 report the results of their observational study examining the relationship among anemia, blood transfusion, and survival based on combined data from 3 large randomized trials involving 24,111 patients who had an acute myocardial infarction. The authors present a survival analysis using proportional hazards modeling demonstrating that the risk of death was estimated to be 3.94 times higher in patients who underwent transfusion compared with those who did not, adjusting for the influence of time, risk of bleeding, type of myocardial infarction, and procedures.

Prior to this study, conflicting results were reported in 2 other studies attempting to discern whether blood transfusions improve outcomes in patients with ischemic heart disease.13,14 One of the few large randomized trials evaluating transfusion practice, undertaken in 838 critically ill patients, concluded that a restrictive transfusion strategy was at least as good and possibly superior to a liberal transfusion strategy, given a trend toward improved 30-day mortality (23.3% vs 18.7%; \( P = .11 \)) and improved secondary outcomes.14 In a subgroup analysis of 327 patients with cardiac disease, there were no significant differences in primary or secondary outcomes in this high-risk subgroup. The authors acknowledged many of the limitations of this subgroup analysis, including the inability to detect clinically meaningful difference given the small sample size.15

Rao and colleagues based their evaluation on the second publication, which made use of 78,974 Medicare records. Wu et al15 retrospectively studied patients older than 65 years who were hospitalized with a primary diagnosis of acute myocardial infarction, and categorized patients according to their admission hematocrit level. Although anemia, defined in the study as a hematocrit level less than 39%, was present in nearly half the patients, only 3,680 patients (4.7%) received a red blood cell transfusion. The authors observed a reduction in 30-day mortality for patients who received at least 1 red blood cell transfusion if their admission hematocrit level was less than 33%, whereas red blood cell transfusion was associated with increased 30-day mortality for patients whose admitting hematocrit values were 36.1% or higher.

This study was among the first to demonstrate that red blood cell transfusion may be beneficial in patients with acute myocardial infarction. However, a number of potential biases limited any inferences made from this study. Specific concerns include a low rate of exposure to red blood cells, limited statistical adjustments made in the multivariable analysis, an analysis based on the admission hematocrit value rather than the value associated with the transfusion, no consideration for the time-dependent use of red blood cells, and

See also p 1555.
residual confounding because the use of red blood cells is intimately linked to hematocrit values (ie, confounding by indication). Moreover, the observed benefits of transfusion did not persist for patients with admission hematocrit levels between 30.1% and 33% in a secondary analysis that removed patients who died within 2 days of admission. Despite these limitations, the authors and an accompanying editorial16 stated that there was sufficient evidence from this publication to recommend red blood cell transfusion below a hematocrit level of 33% in elderly patients following an acute myocardial infarction.

The study by Rao et al12 attempted to overcome some of the limitations attributed to the study by Wu et al13 by using detailed and accurate prospectively collected data, by focusing on a patient population that required aggressive interventions and a greater exposure to blood products, and by using a number of multivariable statistical techniques that might better adjust for the influence of many baseline characteristics and time. In their analysis, the authors noted that transfusions were not associated with improved survival when nadir hematocrit values were in the range of 20% or 25% and were clearly associated with worsened outcomes when values were greater than 30%. Despite these rather sophisticated analytic methods, some limitations still remain. The study by Rao et al only had 2400 patients (10%) receiving transfusions, a small number of exposed individuals given an average mortality of 4%. Indeed, an overall mortality difference as large as 1% (25% relative risk reduction) could not have been detected, and larger differences certainly would have been missed in important subgroups, as suggested by the disproportionately high odds ratios at higher hematocrit levels.

The lack of randomized trials and the apparent contradictory results from both observational studies certainly may leave physicians with more questions than answers. How might the results of these studies be reconciled? First, both studies consistently demonstrate that patients who receive red blood cells at a higher hematocrit level appear to be harmed by transfusions. At hematocrit levels less than 30%, it is possible that the interpretation given by the authors represents aspects of the true effects, especially since there are many differences between studies. Wu et al derived observations from a wide population of elderly patients who had acute myocardial infarction, whereas Rao et al only included younger individuals who required aggressive interventional management. It is plausible that a higher transfusion threshold would benefit elderly patients because of the greater degree of diffuse vascular disease, the presence of additional comorbid illnesses, and the inability to augment cardiac output as a means of compensation for anemia. Younger patients may derive less benefit from transfusions because of widespread use of aggressive revascularization procedures, statins, new antiplatelet agents, and other therapies that have been shown to save lives. In addition to more elaborate treatment for the primary lesion, collateral blood flow is either adequate or treated as part of cardiovascular management strategy. It is also possible that younger patients can better adapt to anemia. If this interpretation holds, physicians should adopt a transfusion strategy based on a higher hematocrit level in elderly patients while allowing younger patients who are aggressively treated for their acute coronary syndromes to be treated according to a more restrictive approach to transfusion.

It is also plausible that there is limited incremental benefit of transfusion following myocardial infarction with hematocrit in excess of 21% or hemoglobin concentration exceeding 7.0 g/dL, as suggested by the findings of Rao et al. In a systematic review17 of studies evaluating transfusion triggers, a total of 1780 patients from 10 clinical trials were identified. From this total, 892 patients (50%) had cardiovascular disease. Using meta-analytic techniques, there were no differences in the combined odds of death or cardiac events using restrictive strategies compared with more liberal approaches.

Based on existing literature, the evidence is sufficient to state that transfusions are rarely beneficial when hemoglobin level exceeds 10 g/dL (hematocrit >30%) in the absence of acute blood loss. It is also reasonable to conclude that the benefits of transfusion exceed the risks when hemoglobin concentrations fall below 7.0 g/dL. Between hemoglobin concentrations of 8.0 to 10.0 g/dL, controversy still remains given the conflicting evidence from 2 major observational studies, laboratory studies, and a systematic review.

Rather than primarily focusing on transfusions in acute coronary syndromes, physicians should first administer all therapies that have been shown to be effective to reduce mortality and limit infarct size, such as aggressive revascularization18 and newer antiplatelet agents.19,20 In the absence of clinical trial evidence related to transfusion triggers, it appears that red blood cells may potentially be beneficial when hemoglobin concentration falls below 8.0 g/dL. Given that multiple transfusions represent a significant increase in effective circulating blood volume in patients with impairments in left ventricular filling or pulmonary edema, physicians should administer only 1 unit of blood at a time, measure hemoglobin concentration following each transfusion in the acute setting, and accept a concentration in the range of 9.0 g/dL. Physicians ordering red blood cells should also consider that transfusions may have a number of unanticipated consequences, such as stimulation of inflammatory pathways,21,22 or result in increased rates of infection because of immune suppression.23

Observational studies such as the reports by Rao et al and Wu et al do not provide unbiased estimates of the benefits of therapy when the degree of anemia is directly related to the administration of red blood cells. Given the complex interplay between the risks and benefits of anemia and transfusion in patients with ischemic heart disease, it is time to undertake randomized controlled clinical trials in different populations of patients with ischemic heart disease.
REFERENCES

See also p 1563.

Measuring Race and Ethnicity: Why and How?
Margaret A. Winker, MD

RACE AND ETHNICITY ARE CONSTANTLY EVOLVING CONCEPTS, deceptively easy to measure and used ubiquitously in the biomedical literature, yet slippery to pinpoint as definitive individual characteristics. A current dictionary definition of race is “a family, tribe, people, or nation belonging to the same common stock, or a class or kind of people unified by shared interests, habits, or characteristics.”1 For 154 years, the US government has defined race for its census takers, and for many years census takers then defined it for US residents. The terms used reflect the nation’s changing demographics and increasing recognition of human diversity. The 1850 enumerators used a form that assumed a default race of white, with a checkmark indicating nonwhites as black or mulatto, with additional indications for free or slave.2 Indian was added as a category in 1860. Since 1960, individuals have been able to specify their own race and ethnicity, and by 2000 the census enumerated 126 racial and ethnic categories.3

Medical definitions of race have lagged behind, although thankfully the former Medical Subject Headings (MeSH) terms such as Caucasoid, Mongoloid, Negroid, and Australoid rarely appear in biomedical literature.4 Given that the connotations and definitions of race and ethnicity are constantly evolving, the use of the terms and concepts of race and ethnicity in the biomedical literature deserves examination.

Study results that associate characteristic and outcomes with race, often defined by an investigator as skin color, are largely a function of other less easily measured variables. From the “experiments” chronicled in The Mismeasure of Man5 to the (mis)interpretations in The Bell Curve,6 outcomes more directly linked to socioeconomic status and deprivation and poorer health and health care have been attributed to race. Such attribution can be a convenient explanation to avoid disrupting the status quo. If racial handicap is believed to equate to genetic defect, and if genetics implies that the resulting characteristics are predestined, societal interventions for individuals with smaller skulls (and worse nutrition)5 or worse