**EDITORIAL COMMENT**

**There Will Be Blood***

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Bleeding in patients with coronary artery disease has attracted increasing interest because it has been found to have major implications. Outcomes following acute coronary syndromes and percutaneous coronary intervention are much worse among those patients who experience major bleeding (1,2). What continues to be unclear is whether bleeding identifies a high-risk group by virtue of the hemorrhage itself, by virtue of comorbid illness, or by some other mechanism. Recently, suspicion has focused on potentially harmful effects of red blood transfusion.

In this issue of *JACC: Cardiovascular Interventions*, Shishehbor et al. (3) have compared the outcomes of patients who did or did not require blood transfusion during hospitalization with ST-segment elevation myocardial infarction (STEMI). The patient cohort is derived from the GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries) IIb trial that compared hirudin with heparin in patients with acute coronary syndromes and percutaneous coronary intervention. A total of 3,575 patients who had presented with ST-segment elevation were eligible for analysis, of whom 307 (8.6%) required a blood transfusion. The investigators found that blood transfusion was associated with increased short- and long-term mortality in the setting of STEMI.

Patients who needed a blood transfusion were older and sicker than those who did not require transfusion. The study design was nonrandomized. In an attempt to overcome these limitations, the investigators used multiple statistical methods including use of Cox proportional hazards survival models with transfusion as a time-dependent covariate for whole and propensity-matched groups and sensitivity analyses to assess the magnitude of potential hidden bias. The investigators are to be commended for this probing analysis of the data, wherein blood transfusion remained a strong predictor of death in the setting of STEMI even after such adjustment. Although not proof of a cause-and-effect relationship, the findings are in agreement with recent data highlighting potentially significant risk associated with blood transfusion among patients with non-STEMI and patients undergoing percutaneous or surgical revascularization.

What does this mean? Could blood transfusions really be killing patients? The hypothesis that transfusion may in certain circumstances do more harm than good is neither new nor surprising. Growing concern, however, reaches beyond the familiar hazards of microbial transmission and acute antigen-antibody reactions, with particular focus on the potential for transfused blood to impair tissue oxygenation. It is well established that stored red blood cells are low in 2,3-diphosphoglyceric acid resulting in high oxygen affinity (i.e., the hemoglobin will tend not to release oxygen to the tissues). However, experimental studies now indicate that the physiologic impact of 2,3-diphosphoglyceric acid depletion may have been overstated and that other structural and biochemical changes that occur in blood during storage may have greater impact on their function in vivo—and may explain the paradox whereby increasing hemoglobin by transfusion may raise calculated oxygen delivery but measures of tissue oxygenation either decrease or do not change (4).

Normally, erythrocytes have a flexible membrane and can reversibly alter their biconcave, discoid shape, thus allowing them to pass through capillaries smaller in diameter (2 to 6 μm) than red blood cells (±8 μm). During storage, there is a significant decrease in the deformability of red blood cells. Other hemorheologic alterations have also been documented, such as changes in red blood cell shape, decreased surface/volume ratio, increased mean hemoglobin concentration and osmotic fragility, increased aggregability and intracellular viscosity (5). Together, these factors may predispose to “plugging” of transfused cells at the microvascular level, leading to tissue ischemia. It is reasonable to assume that vascular beds already compromised by microvascular dysfunction or obstruction (such as acutely infarcted myocardium) may be particularly vulnerable in this respect.

Attention has also focused on the transport of nitric oxide (NO) by red blood cells. Nitric oxide produced by vascular endothelium may be bound by erythrocytes in protected form as an S-nitrosothiol. Upon release of oxygen, S-nitrosothiol hemoglobin may dispense NO bioactivity to microvascular cells, physiologically coupling hemoglobin deoxygenation to vasodilation (6). This elegant mechanism facilitates increases in regional blood flow in zones of hypoxia and, intriguingly, may enable NO-bioactivity to be imported from a healthy vascular bed to one that is compromised by endothelial dysfunction (as would pertain in the coronary circulation of patients with STEMI). Recent data indicate that this biochemical function is significantly disrupted by storage of erythrocytes (7). Other adverse effects of red blood cell transfusion may include prothrombotic effects, pro-inflammatory, and immunosup-

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pressive effects of cytokines and other infused bioactive substances that accumulate in stored blood.

The study by Shishehbor et al. (3) has a number of limitations. No information was available regarding associated transfusions that may have been administered in addition to the packed red cell units (such as fresh frozen plasma or platelets). Such data would be important to help determine the specific role of red blood cell transfusion versus the effects of severe hemorrhage and/or associated coagulopathy. The age of stored units was not included in the GUSTO IIb database but is another important variable that may influence the risk associated with transfusion. Older units exhibit progressive decline in erythrocyte function and higher levels of potentially harmful cytokines and cellular breakdown products. The clinical significance of these in vitro findings are uncertain, although recent data from patients undergoing cardiac surgery suggest that transfusion of older rather than fresh blood may indeed be associated with increased risk of adverse events, including excess mortality (8). In this context, data regarding the urgency of transfusion in the study by Shishehbor et al. (3) adds to a growing literature that prompts us to think twice before deciding “there will be blood.”

Shishehbor et al. (3) suggest a randomized trial should be performed to define the optimal use of blood transfusion in patients with STEMI. Designing such a trial would be difficult. Many would consider it unethical to withhold transfusion from an anemic patient who (despite successful revascularization) exhibits clear evidence of ongoing cardiac ischemia, although a study of fresh versus older blood in this setting would certainly appear reasonable. A study of blood transfusion versus no blood transfusion for asymptomatic anemia following STEMI would also be of tremendous interest, although perhaps more as a means to confirm the putative adverse effects of transfusion. It is difficult to believe that a beneficial effect of transfusion would be observed in anemic patients with STEMI who have already received prompt revascularization and who have no evidence of ongoing ischemia, although this remains an open question. Asymptomatic patients who have received incomplete revascularization might conceivably benefit in the presence of silent ischemia, particularly in watershed areas of acute infarction. Such factors would need to be considered in the design and analysis of any future randomized trial.

It is important to emphasize that concerns about possible adverse effects of transfusion should not lead doctors to withhold blood when it is clearly indicated. Patients who show symptoms or signs of ischemia are most likely to derive a net benefit from transfusion, particularly those who exhibit evidence of oxygen-supply dependency. For asymptomatic patients, it would seem prudent to avoid the use of arbitrary cutoffs (such as a hemoglobin <8 g/dl) to trigger transfusion. With minimal potential gain to offset any adverse effects, transfusion could in theory be more likely to cause harm in these circumstances. One exception may be transfusion of an asymptomatic patient who has anemia caused by major bleeding and who remains at high risk for further bleeding. Greater reserve of red cell mass might lessen the chance that such a re-bleed would be a fatal event. For the majority of asymptomatic patients, however, this important study by Shishehbor et al. (3) adds to a growing literature that prompts us to think twice before deciding “there will be blood.”

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