

sion group. A new cancer-related diagnosis after surgery was not included in the model, yet there was a disproportionate number of subjects who died with a cancer-related diagnosis in the group not receiving transfusion compared with the transfused groups ( $P = 0.03$ ). If subjects who died from a cancer-related diagnosis are excluded from the analysis, mortality data from the three transfusion groups pooled, and the cumulative mortality rate recalculated to compare patients who received any transfusion with those who were not transfused, the mortality rate for transfused patients is more than twice that of patients who were not transfused (13.2% *vs.* 6.0%). This is a striking finding consistent with previous studies.

What should we tell our patients and how should we approach the transfusion decision in the setting of cardiothoracic surgery? First, as we demonstrated, the data presented in this study do not provide reassurance that patients who receive perioperative transfusion are unlikely to experience a reduction in long-term survival; this remains an open question, with current evidence favoring a restrictive transfusion strategy being associated with lower mortality. At a minimum, there seems to be no benefit to transfusion in the majority of patients. Transfusion is associated with substantial cost<sup>10</sup> and a host of well-documented risks, including disease transmission, hemolytic reactions, acute lung injury, and circulatory overload. Therefore, strategies to optimize hemoglobin and minimize bleeding and transfusion should be used.

Transfusion rates of greater than 50% in uncomplicated coronary artery bypass procedures should no longer be tolerated. A number of programs have demonstrated the ability to perform coronary artery bypass surgery with transfusion rates consistently less than 20%.<sup>11</sup> Transfusion in cardiac surgery should be an uncommon event. More data are needed, but until then, the decision to transfuse should continue to be viewed as one that carries substantial risk but no proven benefit in the hemodynamically stable patient.

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## Blood Transfusion and Survival in Cardiac Surgery

### To the Editor:

It is postulated that blood transfusion has been associated with cancer promotion because of the adverse effect of blood transfusion on the immune system. In contrast to a number of cited studies, Weightman *et al.* found no association between transfusion of up to six units of blood and long-term survival in cardiac surgery patients.<sup>1</sup> They attributed this discrepancy, at least in part, to their multivariate analysis that included anemia as a risk factor.

Because cardiopulmonary bypass (CPB) causes a state of temporary immunodeficiency, it has been suggested that CPB negatively affects the host defense against malignancy. Platell<sup>2</sup> found that the cancer-specific survival rates of patients with colon cancer were reduced after surgery with CPB. Thus, as an alternative explanation for their discrepancy, I hypothesize two related possibilities that will need to be tested. Perhaps, the incremental adverse effect of blood transfusion on the immune system in patients who have been on CPB is not enough to make a measurable effect on tumor promotion and long-term outcome until a sufficiently large number of packed erythrocytes have been transfused. Sec-

ond, if CPB and blood transfusion affect the immune system in a similar manner, there may be no incremental adverse effect on the immune system until a sufficiently large number of packed erythrocytes have been transfused. Consistent with the notion that an adverse effect on the immune system causes reduced long-term survival (although at odds with other studies that have compared long-term results of off-pump *vs.* CPB cardiac surgery), Weightman *et al.* reported a reduced hazards ratio of 0.63 for patients who were underwent off-pump surgery where, presumably, there is less immunosuppression, although this finding (possibly because of a small sample size) was not statistically significant.

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### In Reply:

Thank you for the opportunity to respond, and warm thanks to Drs. Gross, Shander, Waters, and Roth for their interest in our study<sup>1</sup> and their valuable comments. We emphasize that we did not study the short-term effects of blood transfusion and so are not able to respond to comments relating to short-term effects. We believe that it is important not to confuse short- and long-term effects.

It is an overstatement to suggest that all doses of blood, under all circumstances, have been consistently associated with long-term harm. It is contradicted by two of the references that Gross *et al.* provided.<sup>2,3</sup> The 2002 study by Engoren *et al.* was indeed a landmark, but it showed no relationship between total 5-yr mortality and intraoperative transfusion (relative risk, 1.2; 95% CIs, 0.6–1.7,  $P = 0.53$ ). It was only postoperative transfusion or a combination of intraoperative and postoperative transfusions that had a significant association. More recently, Engoren *et al.*<sup>4</sup> have studied 993 patients undergoing cardiac valve surgery and concluded that blood transfusion was not associated with reduced long-term survival. They also studied 2,213 intensive care patients<sup>5</sup> and found that blood transfusion was associated with improved late survival. Surgenor *et al.*<sup>3</sup> studied 3,254 cardiac surgery patients; between 6 months and 5 yr after surgery “there was no association between exposure to 1 or 2 units of blood and survival” (hazard ratio, 1.06; 95% CIs, 0.91–1.24,  $P = 0.431$ ).

We make no apologies for designing our study to investigate the dose-dependent effects of allogeneic transfusion on

life expectancy. We went into the study with an open mind. We observed that the transfusion of 1–2 units of allogeneic blood products was associated with a 1.00 relative risk of death, with 95% CIs between 0.7 and 1.4. The relative risk for patients who received 3–6 units was 0.98 (0.6–1.4). We concluded that there was not a strong association between moderate transfusion of blood or blood products and long-term mortality. It would be scientifically invalid to conclude otherwise.

To consider the power limitations of our study, it may be worthwhile to estimate the effect on absolute mortality that our data allow us to exclude. We observed an absolute mortality rate of 1.8% per year; our CIs allow us to exclude a 40% increase in relative risk or a 30% decrease in relative risk. Therefore, our study allows us to estimate that a 1- to 2-unit transfusion is associated with not more than a 0.7% increase, or 0.5% decrease, in the annual mortality rate.

Neither fresh frozen plasma nor platelets are truly acellular. We included them in our count of donor exposures because both products contain leukocytes, are allogeneic, and are associated with serious acute transfusion-related immune-mediated effects. Fresh frozen plasma is implicated in the pathogenesis of transfusion-related lung injury, the most common cause of transfusion-related death in the United States.<sup>6</sup> Presumably, Gross *et al.* are not suggesting that these products can be considered free of long-term risk. Nevertheless, it is a proper scientific scepticism to question this aspect of our study design. Consequently, we have further analyzed our data, counting only red cell containing transfusions: the relative risk of long-term mortality in patients receiving 1–2 units of red cells was 0.98 (95% CIs, 0.7–1.4).

Gross *et al.* may be underestimating the importance of anemia as a predictor of long-term survival. The Atherosclerosis Risk in Communities study<sup>7</sup> of 14,410 people between 45 and 64 yr old in the general United States population showed that anemia was associated with a 1.65 relative risk of mortality. This is a considerable risk factor; it is of similar magnitude to that associated with diabetes or heart failure. This magnitude of risk has been demonstrated in many other studies. van Straten *et al.*<sup>8</sup> studied 10,025 patients undergoing coronary artery graft surgery and demonstrated a relative risk for late mortality of 1.64 in patients with mild anemia. Riva *et al.*<sup>9</sup> studied 7,536 Europeans demonstrating an association between mild anemia and late mortality of 1.86. We suggest that any study of long-term survival that does not take baseline anemia into account may be flawed. We note that some studies on the association between long-term mortality risk and blood transfusion been published without taking preoperative anemia into account. We would be interested in seeing a reanalysis of their results after this factor has been included.

We thank Gross *et al.* for recognizing an error in our results. One hundred seventy-three patients, not 183, died who had been transfused and who did not have a history of cancer. This typographical error was the authors' responsibility not the publisher. Nevertheless, the preponderance of cancer-related deaths in the nontransfused group remains