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Do Not Miss the Elephant in the Room

Look at the Red Blood Cells

We read with great interest the paper by Silvain et al. (1) on the impact of red blood cell transfusion on platelet aggregation and inflammatory response in anemic coronary and noncoronary patients. The authors should be commended on a well-planned and well-conducted study regarding a somewhat neglected aspect of our therapeutic practice. We would like to point out, however, that much of the discussion surrounding this and other related reports on red blood cell transfusions in patients with heart disease is focused on how they affect platelet function and other aspects of the coagulation system. However, we should not miss the giant elephant in the room—the red blood cells themselves. By transfusing blood to patients, we administer some billions of red blood cells that have been submitted to a tedious procedure of collection, processing, and storage in packed red blood cell units. This process is known to produce alterations that lead to hemolysis and the formation of erythrocyte microparticles (2). Free hemoglobin is an extremely oxidative and vasospastic agent, and red blood cell microparticles have been shown to be associated with endothelial dysfunction and prothrombotic phenomena (3,4). As a result, red blood cells themselves (with no need to affect platelets in any significant way) may be a major determinant of transfusion adverse effects on cardiovascular outcomes. This may also explain, at least in part, why the authors found no connection between the storage duration of blood units with platelet aggregation parameters: storage affects red blood cells, which in turn may lead to the described unwanted cardiovascular effects, in a way virtually unrelated to platelet function.

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Reply

Do Not Miss the Elephant in the Room

Look at the Red Blood Cells

We thank Drs. Giannopoulos and Deftereos for their excellent comments on the potential role of red blood cells (RBCs) as an explanation for the excess of risk due to RBC transfusion.

We share their view on this point as data show an association between cell-free, hemoglobin-based blood substitutes and the risk of myocardial infarction and death (1) that is very similar to the one found in registries between RBC transfusion and poor outcomes in coronary patients. Unfortunately, we lack evidence on the impact of cell-free hemoglobin through endothelial dysfunction and prothrombotic effects in patients receiving a RBC transfusion.

We believe that activation of the P2Y purinergic receptors is one of the relevant mechanisms, as demonstrated in our previous in vitro study (2). Indeed, platelet reactivity was increased using different assays including light transmission aggregometry to adenosine diphosphate (ADP), collagen, and vasodilator-stimulated phosphoprotein phosphorylation platelet reactivity index (VASP-PRI), highly specific tests suggesting a partial activation of the $P2Y_{12}$ receptors. We concluded that the release of ADP from RBCs might be readily liberated in the context of blood storage, thus representing a potential stimulus for platelet activation and aggregation. The results of the TRANSFUSION-2 study (3) support this hypothesis as the impact on platelet reactivity was found only with tests exploring

the $P2Y_{12}$ receptor pathway and that a correlation between VASP-PRI increase and the duration of RBC storage was found only with this test.

Moreover, it cannot be excluded that there is an even bigger elephant in the room, as even with the best adjusting factors, the real effect of RBC transfusion on the outcomes of coronary patients might be confounded by cessation of life-saving medications. This is likely the case with antithrombotic agents in patients bearing both a high risk of bleeding and experiencing a highly thrombotic situation such as acute coronary syndromes.

At this stage, as suggested in the accompanying editorial of Rao et al. (4), only a well-sized randomized trial with specific data collection (e.g., withdrawal of medication, storage of red blood cells) could answer both important questions of the real clinical impact of red blood cell transfusion in coronary patients and the possible mechanistic explanations for it.

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Cardiac Positron Emission Tomography as a Prognostic Indicator of Cardiac Sarcoidosis

Cardiac positron emission tomography (PET) is now one of the most important diagnostic tools for the assessment of cardiac sarcoidosis (CS). The diagnostic accuracy of PET has been reported to exhibit 100% sensitivity and 80% to 90% specificity (1,2). In a recent issue of the *Journal*, Blankstein et al. (3) demonstrated that the presence of focal perfusion defect and F-18 fluorodeoxyglucose (FDG) uptake on cardiac PET identified patients at higher risk of death or ventricular tachycardia (VT). The focal FDG uptake in the right ventricle was also a very specific finding of CS. Although the results are interesting, there are several problems in the paper that should be acknowledged.

The first issue is the lack of an evaluation of treatment before and after the diagnosis of CS. With effective anti-inflammatory treatment, the FDG uptake on PET will be diminished, but if the extent of inflammation is advanced, only a partial effect can be obtained. The relationship between PET and treatment should thus be clarified.

The second issue relates to the Japanese Ministry of Health and Welfare guidelines. Reference 6 in the original article by Kida et al. 2013 is not appropriate as a reference for these guidelines; it is simply a small clinical study of cardiac magnetic resonance imaging. The quoted guideline is an older version of the guideline in reference (4) by Hiraga et al. 1993, which was revised in 2006, and the clinical diagnosis group was newly set as a diagnostic criterion (5). It would therefore be interesting to compare both clinical and histological diagnoses by using the 2006 Japanese guidelines.

Third, regarding the baseline characteristics of the patients (Table 1 [3]), 90% of the patients with adverse events had an implantable cardioverter-defibrillator (ICD) at baseline or on follow-up. Of 31 outcomes, there were 28 VT events. The reasons for the ICD implantations at baseline should be described because VT events tend to occur in patients with ICDs.

Fourth, the fasting time of 3 h is apparently insufficient to inhibit physiological uptake in nonaffected myocardium. We have recently reported that a long fasting time (>18 h) is necessary for the precise evaluation of cardiac PET (6).

Endomyocardial biopsy (EMBx) is usually performed because the diagnosis of CS is based principally on histology. However, the diagnostic rate achieved with EMBx has been reported to range from 20% to 30% (7). The paper by Blankstein et al. (3) reports very interesting findings about EMBx from the right ventricle. The overall diagnostic rate was 27%, but among the 20 patients with abnormal perfusion and FDG uptake, 45% had positive findings. These results indicate that a positive PET finding is useful not only for predicting outcomes but also for determining the indications for performing an EMBx. Further study is needed to resolve the issue of whether a positive PET finding of myocardium can improve the diagnostic rate of EMBx.