Revisiting the Role of sCD40L as an Inflammatory Biomarker in a Clinical Model of Acute Myocardial Infarction

To the Editor:
I read with great interest the recent article published by Liebetrau et al., which described the release kinetics of several inflammatory markers (C-reactive protein, interleukin 6, troponin T, and soluble CD40 ligand) over a time course after the transcoronary ablation of septal hypertrophy as a model of induced acute myocardial infarction in humans.

Two types of sample matrix were used in the study, namely serum (prepared using gel-filled tubes without additives) and plasma (EDTA tubes). The authors measured C-reactive protein and interleukin 6 in the serum samples, whereas soluble CD40 ligand (sCD40L) was measured using the EDTA plasma. This is an important preanalytic consideration, as platelets are the predominant source of sCD40L in circulation, and sCD40L is widely considered as a marker of acute platelet activation. Therefore, EDTA plasma was the appropriate sample matrix for the measurement of sCD40L.

In this study, the authors observed an acute reduction of sCD40L after transcoronary ablation of septal hypertrophy–induced acute myocardial infarction and proposed the potential immediate improvement in ventricular hemodynamics and reduction in acute platelet activation as the explanation for this finding. Another preanalytic factor which may confound sCD40L measurement in plasma was not accounted for by the published article. Specifically, the centrifugation parameters used for preparing plasma were not reported. Centrifugation of blood at suboptimal force and duration may lead to residual platelets in the resultant plasma sample. Given that platelets are the predominant source of sCD40L in plasma, incomplete removal of platelets can lead to artifactual levels of sCD40L measured in plasma, as freeze thawing of the prepared plasma leads to lysis of residual platelet during the assay steps.

Despite its proinflammatory and procoagulant properties, the reported associations between plasma sCD40L and cardiovascular risks have been inconsistent in literature. Two large, prospective studies (the CAPTURE [Chimeric Anti-Platelet Therapy in Unstable Angina Refractory to Standard Medical Therapy] trial and the Women’s Health Study) published in the noughties, reported the prognostic value of sCD40L as a biomarker for predicting subsequent cardiovascular risk both in patients with established coronary artery disease and otherwise healthy individuals. However, such observations were not replicated in other subsequent large prospective cohorts. For example, the Dallas Heart Study and the FATE (Firefighters And Their Endothelium) study both reported lack of association between plasma sCD40L and subsequent cardiovascular risks. The methods of plasma preparation have been poorly reported in these significant historic studies, thus posing a challenge in interpretation of their observations.

That such preanalytic issues are frequently overlooked is further evident by incidences where different plasma preparation protocols were reported for the same study during a period of time, such as the Dallas Heart Study, which reported different plasma preparation protocols in separate articles. In the study by Liebetrau et al., multiple time points of blood sampling were performed in close succession. It is crucial to report that the same plasma preparation protocol has been adhered to throughout the study to ensure the internal validity of the study findings.

Disclosures
None.

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References
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