Polymorphisms of Inflammatory Markers/Mediators and Arterial Stiffness

To the Editor:

We read with interest the article by Schumacher et al., which sheds new light into the still-controversial issue of the contribution of C-reactive protein (CRP) in the pathogenesis of cardiovascular disease. To this end, the authors tested the causality of CRP in arterial stiffness using genetically elevated CRP levels. However, such a causal relationship, through the mendelian randomization assumption, could not be established. Although CRP levels were associated with CRP genes and aortic pulse wave velocity (aPWV), none of the CRP genetic variants were associated individually or in combination with aPWV.

These findings are supported by our previous study that has established a causal relationship between acute inflammation and arterial stiffness. Although there was an overall positive correlation between CRP and aPWV, we showed that there was time dissociation in their response. CRP was elevated after 8 hours but reached its peak at 32 hours (increase by 1.77 mg/L), whereas aPWV reached its peak at 8 hours (increased by 0.43 m/s) and returned to baseline levels after 32 hours. Also, bearing in mind that arterial stiffness is determined by endothelial function, further corroboration to the noncausal association between CRP and arterial stiffening is provided by the study of Clapp et al., which showed normalization of endothelial dysfunction several hours after typhoid vaccination in spite of increased CRP levels. However, it should be noted that the CRP gene is highly polymorphic, and, accordingly, it would be interesting to investigate additional polymorphisms of CRP and their relation with aPWV and cardiovascular events in large cohort studies.

Polymorphisms of other mediators that are involved in the inflammatory cascade and arterial homeostasis may impact on arterial stiffness. We have studied the relationship between the polymorphism (−174G>C) in the promoter region of interleukin 6 (a strong predictor of clinically evident cardiovascular disease) and arterial function (using pulse wave analysis by SphygmCor, AtCor Medical) in 241 healthy/general-population individuals (mean age: 41±8 years; 161 men). Both wave reflections assessed by augmentation index and arterial stiffness assessed by transit time correlated with the −174G>C polymorphism. In detail, 124 subjects (51.45%) carried the GG genotype, 13 (5.4%) the CC genotype, and 104 (43.15%) the GC genotype. Augmentation index was 18.7±12%, 20±12.8%, and 22.1±12.2%, respectively. Transit time was 152.3±15.9, 145.6±16.3 and 149.3±15.2 ms, respectively. In multiple regression analysis (controlling for age, sex, height, heart rate, systolic blood pressure, cholesterol, and CRP levels), the −174G>C polymorphism correlated with augmentation index and transit time (adjusted R²=0.571, β=1.05, P=0.015 and adjusted R²=0.422, β=−0.098, P=0.05, respectively), indicating increased wave reflections and arterial stiffness in the presence of the C allele.

Nevertheless, as also stated by the authors, their study does not diminish the validity of CRP as a risk marker of atherosclerotic disease. A recent example is the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin, which provided evidence for the potential clinical usefulness of CRP. However, it seems that the relation between CRP and arterial stiffness is more likely explained by residual confounding, reverse causality, or both.

Disclosures

None.

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