Fibrinogen, genes, and arterial stiffness

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The levels of fibrinogen, one of the major coagulation proteins and an acute-phase protein, increase with age and represent a cardiovascular risk factor. Meta-analyses have shown that the plasma level of fibrinogen is associated with coronary heart disease mortality in the long-term in men but not in women, although mean fibrinogen levels in women are higher than those in men [1]. Similar associations have been reported with ischemic stroke with a lower degree of significance than for coronary heart disease. All these studies suggested that the impact of fibrinogen on cardiovascular disease should be analysed taking into account other biomarkers such as interleukin-6, C-reactive-protein, white blood cells count in multivariate analysis. Importantly, an increase in fibrinogene of 1 g/l causes a two times greater relative risk of cardiovascular events or mortality.

The Rotterdam Study has already demonstrated that fibrinogen is a risk factor of cardiovascular mortality in patients with preserved sinus rhythm but not in atrial fibrillation, suggesting an association with mechanical factors such as shear stress. Previous studies have already reported significant associations between fibrinogen level and arterial stiffness. In the Framingham Heart Study, fibrinogen was associated with central blood pressure but this association was no longer significant using a multimarker approach [2].

Although the association of plasma fibrinogen level with cardiovascular risk factors and distinct biomarkers is well established, determinants of fibrinogen level remains to be elucidated, in particular the influence of genetic variants. In this issue of the journal, Sie *et al.* [3] investigated the association of fibrinogen level, genotype and haplotypes with arterial stiffness. Fibrinogen genes have not yet been identified in genetic studies of arterial stiffness using genome-wide linkage studies and candidate genes polymorphisms [4]. However, the authors confirmed that fibrinogen level was associated with aortic stiffness in women. In addition, they identified three polymorphisms in fibrinogen α and γ associated with the fibrinogen level and distinct haplotypes associated with fibrinogen level (FGA haplotype 4) and arterial stiffness (FGA haplotype 3 and FGG haplotype 2). The role of fibrinogen haplotypes but not those of single nucleotide polymorphisms has been previously reported in the occurrence of myocardial infarction. In the present study, the authors suggest that the effect on arterial stiffness is related to the function of fibrinogen independently of its circulating level.

In this study, arterial stiffness was measured using three different parameters: aortic pulse wave velocity, brachial pulse pressure (PP), and carotid stiffness measured from vessel wall motion and brachial PP. Aortic pulse wave velocity and echotracking do not cause any methodological problem but the use of brachial PP in place of carotid PP raises several questions. The phenotype of hypertension is commonly derived from peak-systolic blood pressure and end-diastolic blood pressure. The validity of this phenotype may be discussed. A pulsatile phenomenon as blood pressure cannot be represented only by two points as systolic blood pressure and diastolic blood pressure, which correspond only to a single straight line. Other possibilities may be proposed such as the use of mean and pulse pressure or even the decomposition of the pressure curve into a foreward and a reflected wave [5]. Furthermore, PP level is critically influenced by the site of measurement. The difference between brachial and carotid PP approximates 12 mmHg for the same mean arterial pressure, and this value is highly influenced by age and heart rate [5]. Genetic results on metalloproteinases have been obtained using only central arterial parameters as the impedance spectrum [4]. On the basis of invasive and noninvasive studies, central (carotid) PP has been shown to predict much better cardiovascular and coronary mortality than brachial PP [5].

The findings of this study raise interesting questions about the mechanism linked to theses different fibrinogen variants. The various functions of fibrinogen in blood clotting, fibrinolysis, cellular and matrix interactions, and inflammatory response are dependent on interactive sites on the molecule. Fibrinogen is constituted of two sets of three chains Aα, Bβ, and γ joined together by five disulfide bridges in the N-terminal E domain [6]. The mutations described in the present paper are not localized in the sequences of the molecule known to mediate cell-matrix interactions and cell adhesion. This suggests that the sites of fibrinogen participating in the function of arterial stiffness involve other molecular and cellular interactions of fibrinogen with circulating cells or vascular

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cells. Along the same lines, another question arises regarding the importance of these associations particularly in women. Understanding better how genotypes correlate with arterial stiffness and other distensibility measurements of major quality is an important step to identify new targets to reduce the rigidity of the arterial wall.

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