Circulating microparticle levels in patients with coronary artery disease: a new indicator of vulnerability?

Nicolas Amabile1,2 and Chantal M. Boulanger1,3*

1INSERM U970, Paris Cardiovascular Research Center, Paris, France; 2Cardiology Department, Centre Marie Lannelongue, Le Plessis-Robinson, France; and 3University Paris Descartes, Paris, France

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This editorial refers to ‘Circulating CD31+/Annexin V+ microparticles correlate with cardiovascular outcomes’, by J.-M. Sinning et al., on page 2034

Despite significant advances in medical and interventional management during the past decades, coronary artery disease (CAD) and its consequences, which include myocardial infarction, sudden cardiac death, and chronic cardiac failure, remain a major contributor to mortality in western countries. Lifestyle modifications and secondary prevention medications, such as statins or angiotensin-converting enzyme (ACE) inhibitors, have improved outcome, but some patients still experience adverse cardiovascular events as a consequence of a particular atherosclerotic disease evolution. Identification of these high-risk, vulnerable patients remains a challenging issue.1 Atherosclerosis is a systemic disease characterized by endothelial dysfunction and by local and general inflammation. It is aggravated by platelet activation, and its ultimate evolution is plaque rupture and thrombosis.2 Identification of vulnerable plaques cannot be achieved by conventional angiography and requires sophisticated and invasive investigations such as intravascular ultrasound, optical coherence tomography, or magnetic resonance imaging.1 Moreover, there is no real consensus regarding a simple definition of vulnerable plaque. Risk stratification of patients based on measurement of circulating biomarkers [high sensitivity C-reactive protein, soluble lipoprotein phospholipase A2, B-type natriuretic peptide (BNP), etc.] or non-invasive evaluation of vascular structure or function (carotid intima-media thickness, flow-mediated dilatation, etc.) appear to be more efficient tools in many respects.1 However, none of the above-cited parameters appears to be perfectly appropriate in view of the required criteria (sensitivity, specificity, cost-effectiveness, and interobserver reproducibility),3 and the quest for new candidates is continuing.

Sinning and co-workers have now shown the prognostic value of baseline levels of circulating CD31+/Annexin V+ microparticle (MP) levels measured by flow cytometry in a cohort of n = 200 patients with stable and unstable CAD.4 They report that high values of this subset of plasma MPs are associated with a worse clinical outcome, including an increased incidence of adverse cardiovascular and cerebral events. MPs are submicron vesicles shed from the cellular membrane upon activation of apoptosis. Most cells, including platelets, leucocytes, and endothelial cells, are capable of releasing membrane MPs in the circulation. MPs are characterized by their size (diameter ranging from 0.1 to 1 μm), the presence of externalized phosphatidylserine at their surface, and a specific antigenic profile reflecting their cellular origin.5 Numerous reports have highlighted changes in circulating MP levels in association with cardiovascular diseases, including stable and unstable CAD, as evidence of ongoing thrombosis, inflammation, cell injury, or apoptosis.5

The relationship between MP plasma levels and clinical adverse events in CAD shown by Sinning is an important new finding, in line with previous observations from Nozaki et al. on a large group of patients with stable CAD and cardiovascular risk factors. In the Nozaki study, combining plasma levels of VE-cadherin+ endothelial MPs with other biomarker levels (BNP and high sensitivity C-reactive protein) and the Framingham risk score identified subjects with a higher risk of subsequent complications.6 Other studies have also shown associations between plasma endothelial MP levels and outcome in pulmonary hypertension7 or chronic renal failure patients.8

In the latter two studies, no significant relationship was reported for platelet MP levels.7,8 The results from these previous studies suggest that measurement of circulating MPs of endothelial origin represents a surrogate biomarker of endothelial function with potential prognostic value. However, whether or not the study of Sinning targets MPs of similar cellular origins is not yet known. Indeed, the CD31+/AnnexinV+ MP subpopulation measured in their study is characterized by externalized phosphatidylserine...
(i.e. the MPs are Annexin V positive) and the presence of platelet/endothelial cell adhesion molecule 1 (PECAM-1; CD31 positive). This MP subpopulation might derive from three different cell types, as PECAM-1 is expressed by endothelial cells, activated platelets, and some leucocyte subsets (Figure 1). Endothelial and platelet MPs have different antigenic compositions and biological properties. They may therefore have different prognostic implications, depending on their mode of generation and the clinical situation. Despite the uncertainty regarding the cellular origin of CD31+/Annexin V+ MPs, the interest in their measurement in CAD patients is highlighted by Sinning et al. in their analysis.4 The authors showed that the addition of MP levels to a statistical model including traditional risk factors improved predictions of a major adverse cardiovascular and cerebral event (MACCE), allowing a better identification of high-risk patients.

Taking a wider view, whether or not plasma MPs are the chicken or the egg is not known. In view of the available literature, plausible evidence for both could be presented. First, the release of circulating MPs within the vascular compartment is a function of the pathological process affecting parental cells. The stimuli involved in cell blebbing include variations in shear stress, inflammation, oxidative stress, and smoking components.5 The increase in CD31+/AnnexinV+ MP levels reflects activation and/or apoptosis of platelets and endothelial cells (Figure 1). Sinning’s group previously observed that levels of this particular MP subgroup were correlated with the degree of endothelial dysfunction.9 Thus, CD31+/AnnexinV+ MP levels might simply represent evidence of endothelial dysfunction and platelet activation, that happen to be associated with enhanced cardiovascular complications in patients with CAD.10,11 However, it is also known that circulating MPs are more than just simple ‘cellular dust’. They display various bioactive substances and receptors on their surface and harbour a concentrated set of cytokines, signalling proteins, lipids, and nucleic acids. Increasing experimental evidence points to MPs as pivotal actors during the development of cardiovascular diseases (Figure 1). MPs also interfere with the other protagonists of disrupted vascular homeostasis at each step of the development of atherosclerosis, from early vascular wall injury and endothelial dysfunction to plaque rupture and thrombus formation.5 In vitro and in vivo generated MPs can promote inflammation within the vascular wall by enhancing pro-inflammatory cytokine release [interleukin-6 (IL-6) and IL-8] or by increasing expression of endothelial cell adhesion molecules, therefore promoting leucocyte adhesion and migration towards early atherosclerotic lesions. Furthermore, circulating MPs isolated from patients with myocardial infarction reduce endothelium-dependent relaxation by inhibiting the nitric oxide synthase pathway12 (Figure 1). The subsequent decrease in nitric oxide production causes vascular resistance and spasms, and favours smooth muscle cell proliferation and platelet aggregation.

Moreover, MPs accumulating in advanced atherosclerotic lesions stimulate in vivo neovascularization following CD40 ligation, and are likely to favour vasorum proliferation and plaque vulnerability.5 Further, externalization of phosphatidylserine at the surface of MPs makes them highly pro-thrombogenic, as they can...
bind to clotting enzyme complexes and augment thrombin generation (Figure 1). Some MPs may also expose tissue factor. In light of these data, increased circulating MP levels in some CAD patients might also explain why these patients are more prone to adverse events: enhanced levels of CD31+/AnnexinV+ MPs might amplify an ongoing pathological process involved in the development of athero-thrombotic complications and may help identify a biological phenotype of ‘vulnerable’ patients (Figure 1).

In conclusion, circulating MPs represent an intriguing avenue for improving cardiovascular risk stratification and prognosis. Translating their measurement into practical tools in clinical settings will require standardization and optimization of current methods for their identification and quantification. The past few years have seen unprecedented improvement in their analysis and detection thresholds; growing interest in their potential will probably sustain the quest to better exploit this new plasma biomarker.

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