Endothelial cell-derived extracellular vesicles released upon stimulation with antiphospholipid antibodies: A genuine direct procoagulant mechanism or a new factor in the lupus anticoagulant paradox?

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Background: Antiphospholipid antibodies (aPL) are a heterogeneous group of autoantibodies that lead to thrombosis and pregnancy morbidity. Paradoxically, the capacity of some of these autoantibodies to inhibit coagulation pathways in vitro relates to their capacity to trigger thrombosis in vivo. While the exact mechanism(s) by which aPL dampen clotting in vitro remains to be demonstrated, it is known that aPL activate endothelial cells thus triggering the production of presumably procoagulant extracellular vesicles (EVs). **Aim:** To assess the procoagulant activity of endothelial cell-derived extracellular vesicles released by aPL stimulus. **Results:** IgG from patients with primary vascular and obstetric APS who manifest refractoriness to treatment, lead to a prolongation in lag time and a decrease in overall coagulation potential related to EV-rich supernatant of endothelial cells. This effect is abrogated by co-stimulation of endothelial cells with β2GPI, cannot be explained by changes in the number of EVs, and is not shared with IgG from patients with obstetric or vascular clinical manifestations alone, IgG from non-refractory patients even with both clinical conditions or IgG from patients with aPL-non-related clinical manifestations. **Conclusions:** According to our knowledge, for the first time we are describing that anticoagulant effects of some aPL are reflected in the endothelial cell-derived EVs for which the same autoantibodies perform as triggers. Our findings suggest that EVs do not constitute a direct procoagulant mechanism. Further analysis is required to establish how this phenomenon relates to lupus anticoagulant and whether aPL from patients with the worst clinical features make up immunocomplexes with EVs.