Anti-PF4/heparin antibodies from patients with heparin-induced thrombocytopenia provoke direct activation of small vessel endothelial cells

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Heparin-induced thrombocytopenia (HIT) is a serious complication that occurs in approximately 1-5% of patients treated with heparin and may be associated with severe thrombotic events which occur both in large vessels (arteries and veins) and capillaries (skin, "white clot syndrome"). Therapy includes immediate cessation of heparin and the administration of either danaparoid sodium (Orgaran) or hirudin (Lepirudin). Our group has also reported the beneficial effect of intravenous IgG. HIT is mediated by antibodies (Abs) directed mostly to epitope(s) formed by complexes between heparin or other anionic mucopolysaccharides and platelet factor 4 (PF4). Anti-PF4/heparin IgG Abs from six patients with HIT were affinity purified and assessed for interaction with human microvascular and large vessel EC endothelial cells (EC). The Abs activated human bone-marrow small vessel EC(TrHBMEC), only in the presence of PF4, but did not activate large vessel EC human umbilical vein EC (HUVEC) under same conditions. These Abs were found to bind to TrHBMEC through the $F(ab)_2$ portion of the anti-PF4/heparin IgG. TrHBMEC activation was characterized by an augmented release of IL-6, von Willebrand factor, soluble thrombomodulin and by an elevated expression of the adhesion molecules P-selectin, E-selectin and VCAM-I to different degrees. Enhanced monocyte adhesion to PF4/heparin Ab-treated TrHBMEC (33-72% adhesion) was also observed. None of these effects occurred with unstimulated HUVEC. Our findings indicate that anti-PF4/heparin Abs directly activate small vessel EC while interaction with large vessel EC requires pre-activation with TNFα. These results may explain some of the specific clinical manifestations in HIT.