Sickle cell anemia (SCA) is a genetic disease characterized by the presence of abnormal hemoglobin (HbS) that polymerizes under deoxygenated conditions causing a mechanical distortion of red blood cells (RBC). We recently investigated the contribution of blood rheology and vascular dysfunction in vaso-occlusive crises (VOC). Our findings demonstrated that SCA patients have blunted microvascular reactivity during local thermal heating tests compared to controls. In addition, increased blood viscosity and decreased microcirculatory oxygenation were independently associated with a higher risk to develop frequent VOC episodes. Several factors are involved in the vascular dysfunction of SCA, such as enhanced oxidative stress and reduced nitric oxide metabolism, but we recently observed that circulating exosomes, originating mainly from RBCs, were able to alter in vitro endothelial cells barrier permeability and the topographic distribution of the tight junction protein ZO-1 in a SCA severity-dependent manner compared to healthy children. In addition, SCA circulating exosomes promoted monocyte adhesion to endothelial cells, through increases in P-selectin expression. These new data suggest that exosomes originating from RBCs could be one of the sub-cellular elements involved in the endothelial dysfunction associated with SCA. In conclusion, vascular dysfunction and blood hyperviscosity emerge as key factors involved in the severity of SCA and the occurrence of frequent VOC events.