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Title: Circulating endothelial cell levels decrease after vasodilator therapy and are a biomarker of clinical worsening in refractory pulmonary hypertension in children

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Body: BACKGROUND: Pulmonary vasodilators in general and prostacyclin therapy in particular have improved the outcome of patients with pulmonary arterial hypertension (PAH). Endothelial dysfunction is a key feature of PAH and we previously described that circulating endothelial cells (CECs) could be used as a biomarker of endothelial dysfunction in PAH. We now hypothesized that PAH-specific vasodilator therapy might decrease CEC numbers. METHODS: CECs were quantified by immunomagnetic separation with mAb CD146-coated beads in peripheral blood from children with idiopathic PAH (iPAH, n =30) or PAH secondary to congenital heart disease (PAH-CHD, n =30): before, after treatment and during follow up. RESULTS: Oral treatment with endothelin antagonists and/or PDE5 inhibitors significantly reduced CEC counts in children. In 10 children with refractory PAH despite oral combination therapy, subcutaneous (SC) treprostinil was added and we observed a significant decrease in CEC counts during the first month of such treatment. CECs were quantified during a 6 to 36 month-follow-up after initiation of SC treprostinil and we found that CEC counts changed over time, with rising counts always preceding clinical deterioration. CONCLUSIONS: CECs might be useful as a biomarker during follow-up of PAH treatment in pediatric iPAH and PAH-CHD, to assess response to treatment and to anticipate clinical worsening.