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Title: Oxygen pulse slope analysis during exercise testing identifies patients with systemic sclerosis at a possible risk for developing pulmonary vasculopathy

Mr. Maarten 28719 Ninaber m.k.ninaber@lumc.nl MD ¹, Mr. Willem 28720 Hamersma w.b.g.j.hamersma@lumc.nl MD ¹, Dr. Annemie 28749 Schuerwegh a.j.m.schuerwegh@lumc.nl MD ², Dr. Gabor 28721 Kovacs gabor.kovacs@klinikum-graz.at MD ³, Prof. Dr Horst 28722 Olschewski horst.olschewski@klinikum-graz.at MD ³ and Dr. Jan 28723 Stolk j.stolk@lumc.nl MD ¹. ¹ Pulmonology, Leiden University Medical Center, Leiden, Netherlands ; ² Rheumatology, Leiden University Medical Center, Leiden, Netherlands and ³ Pulmonology, Medical University Graz, Graz, Austria .

Body: Background: Patients with systemic sclerosis (SSc) are at risk for developing obliteration of microvascular structures leading to pulmonary hypertension (PH) which warrants early detection. Methods: In an observational, prospective design, we studied 121 eligible patients with SSc in an assessment program including non-invasive CPET to analyse an abnormal V'O₂/HR slope represented by a breakpoint in the slope. To study the pathophysiologic meaning of such a breakpoint we applied our method to a published data set of a similar population in which CPET and pulmonary arterial pressures were measured simultaneously. Results: A pathological V'O₂/HR slope was observed in 41 of 121 (34%) patients. Their mean V'O₂/HR slope was 6 ± 2 ml, of whom 27 patients (66%) had a normal echocardiographic pulmonary arterial systolic pressures (PASP) at rest. In a historic CPET data set we calculated a breakpoint in both the V'O₂/HR slope and V' O₂/mPAP slope in 16 of 45 SSc patients (36%). For each patient we calculated the difference in V'O₂ between the two breakpoints. Mean difference in V'O₂ was $127 \text{ ml} \pm 63 \text{ ml}$. In 15 patients, a breakpoint in the V'O₂/mPAP slope occurred at a lower V'O₂ than in the V'O₂/HR slope. Conclusions: The oxygen pulse breakpoint analysis in non-invasive CPET is a mathematical tool to detect abnormal cardiopulmonary vascular responses to exercise. The breakpoint in the V'O₂/mPAP slope occurred at a slightly lower V'O₂, suggesting that a sudden increase in pulmonary arterial pressures results in a disproportional increase in heart rate during CPET.