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Title: Ventilatory inefficiency relative to oxygen uptake and carbon dioxide output are independent predictors of mortality in pulmonary arterial hypertension

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Body: Background: Exercise intolerance is a well-established prognostic marker in a number of cardiopulmonary diseases. In pulmonary arterial hypertension (PAH), excessive ventilatory (VE) response relative to metabolic demand associated with insufficient O_2 delivery are important factors impairing patients' exercise capacity. We therefore investigated whether the dynamic relationship between VE and both pulmonary carbon dioxide output (VCO_2) and O_2 uptake (VO_2) would constitute negative prognostic markers in this patient population. Methods: Eighty-one patients (36 idiopathic and 45 with associated conditions) were followed-up for up to 5 yrs. VE/VCO_2 slope (rest-to-peak data) and VO_2 efficiency slope (OUES) were calculated and analyzed in association with traditional cardiopulmonary exercise test (CPET)-based measurements. Results: Fourteen patients (17 %) died during the follow-up period. Resting variables were not related to prognosis ($p>0.05$). Univariate analysis indicated that peak VO_2, $\Delta VO_2/\Delta$ work rate, $\Delta V'E/\Delta V'CO_2$ and OUES were associated with lower survival ($p<0.05$). A multiple regression analysis of dichotomized data obtained after a ROC curve analysis showed that $\Delta V'E/\Delta V'CO_2 \geq 55$ [hazard ratio (HR) (95% CI)= 11.16 (1.4-86.6); p= 0.02] and OUES ≤ 0.56 [HR 11.24 (3.5-35.8); p= 0.02] were independent predictors of mortality. Association of these findings increased OR for mortality to 18.2 (5.8-57.3), p <0.01. Conclusion: Ventilatory inefficiency relative to pulmonary gas exchange during rapidly-incremental CPET is a marker of poor prognosis in patients with PAH.