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Title: Exercise ventilatory inefficiency is an independent predictor of mortality in patients with pulmonary arterial hypertension

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Body: Rationale: An excessive ventilatory ($V'E$) response to CO_2 output ($V'CO_2$) during incremental exercise is a strong prognosticator in cardiovascular diseases. The role of $\Delta V'E/\Delta V'CO_2$ to predict mortality in pulmonary arterial hypertension (PAH), however, remains to be demonstrated. Objective: To investigate the value of increased $\Delta V'E/\Delta V'CO_2$ as a negative prognostic marker in PAH. Methods: 80 patients with PAH who underwent a ramp-incremental cardiopulmonary exercise test (CPET) were followed-up for 5 yrs. $\Delta V'E/\Delta V'CO_2$ slope was calculated to the respiratory compensation point ($\Delta V'E/\Delta V'CO_{2(start\text{-}RCP)}$) or to peak exercise ($\Delta V'E/\Delta V'CO_{2(start\text{-}PEAK)}$). Results: 14 patients (17.5 %) died of PAH-related causes. Compared to survivors, deceased patients were younger and had lower peak O_2 uptake, O_2 pulse, and oxyhemoglobin saturation but, regardless the method of calculation, higher $\Delta V'E/\Delta V'CO_2$ ($p<0.05$). None of the other variables (including the six-minute walking distance) was related to mortality ($p>0.05$). The best cutoff to death prediction was higher for $\Delta V'E/\Delta V'CO_{2(start\text{-}PEAK)}$ (>55) than $\Delta V'E/\Delta V'CO_{2(start\text{-}RCP)}$ (>45). An univariate analysis revealed that the former variable was superior to the later on this regard ($p= 0.004$ vs. 0.02).In fact, a multiple regression analysis showed that resting heart rate (hazard ratio (95% CI)= 1.04 (1.00-1.08); $p=0.03$) and $\Delta V'E/\Delta V'CO_{2(start\text{-}PEAK)}$ (1.04 (1.01-1.07); $p= 0.006$) were the only independent predictors of mortality. Conclusions: A resting variable (heart rate) and an effort-independent marker of ventilatory inefficiency ($\Delta V'E/\Delta V'CO_{2(start\text{-}PEAK)}$) are clinically-useful markers of poor prognosis in patients with PAH.