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Title: Effects of ivabradine on exercise endurance and VO₂ kinetic in chronic ischemic heart disease

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Body: Background: Elevated heart rate (HR) represents an independent risk factor for morbidity and mortality in chronic ischemic heart disease (CIHD). Beta-blockers (β B) are considered the first choice medication to control HR in CIHD, however some patients have contraindications to their use. Ivabradine inhibits the I_f current of sinoatrial cells and controls HR avoiding β B collateral effects. Aim and Methods: We evaluated the short term effect of 5 mg of ivabradine b.i.d. on exercise endurance at cardiopulmonary exercise test (CPET), in 6 patients (age 59 \pm 12) with CIHD (NYHA I-II), sinus rhythm and contraindications to β B. Each patient performed an incremental workload test (IWT) and a constant workload test (CWT) at 85% of his maximal O₂ consumption (VO₂max) in two separate days, before and after 7 days of ivabradine. We analysed standard CPET variables at IWT. O₂ kinetic and Time to limitation (TLim) were evaluated at CWT. Results: Ivabradine induced a significant reduction in rest and maximal HR (83 \pm 12 vs 69 \pm 13 bpm, 123 \pm 9 vs 106 \pm 13 bpm; p<0.001 and p=0.03, respectively), with no difference in patient exercise tolerance at IWT. Furthermore, ivabradine led to a significant improvement in exercise endurance as shown by the TLim at CWT (266 \pm 79s vs 386 \pm 144s; p<0.008). No significant changes were observed in VO₂ kinetic (Tau). Conclusions: Seven days of ivabradine positively influenced baseline and maximal HR in CIHD patients. Furthermore, sub-maximal exercise tolerance was significantly improved, although no changes in VO₂max were observed at IWT.