

## Central hemodynamic effects in patients with chronic coronary syndrome after long-term ivabradine therapy

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**Objectives:** We sought to assess central hemodynamic effects in 23 patients (18 male, 5 female) with a resting heart rate (HR) of  $\geq 70$  beats per minute (bpm) and chronic coronary syndrome after long-term ivabradine therapy (6 months) by cardiac magnetic resonance (CMR).

**Methods and results:** In a cross-over design, all patients were treated with ivabradine (Iva, 7.5 mg bid) and placebo for 6 months each. CMR was performed three times (at baseline, after 6 and 12 months) to determine left ventricular (LV) function parameters, including end-diastolic and end-systolic volumes (EDVi, ESVi), stroke volume (SVi) and ejection fraction (EF) as well as volume-time curve (VTC) parameters, including peak ejection rate (PER), peak ejection time (PET), peak filling rate (PFR), peak filling time from ES (PFT), peak ejection rate normalized to EDV (PER/EDV) and peak filling rate normalized to EDV (PFR/EDV) for global LV function (systolic and diastolic) assessment. Flow measurements of the ascending aorta were performed with phase-contrast velocity imaging. Treatment with Iva led to a HR reduction of 11.4 bpm (Iva 58.8 $\pm$ 8.2 bpm vs placebo 70.2 $\pm$ 8.3 bpm,  $p < 0.0001$ ). There was no difference in LVEF (%) (Iva 57.4 $\pm$ 11.2 vs placebo 53.0 $\pm$ 10.9,  $p = 0.18$ ), EDVi or ESVi. SVi (ml/m<sup>2</sup>) remained comparatively unchanged after long-term treatment with

Iva (Iva 40.6 $\pm$ 9.6 vs placebo 35.7 $\pm$ 8.8,  $p = 0.08$ ). VTC parameters reflecting systolic LV function (PER, PET) were unaffected by Iva, while both PFR and PFR/EDV were significantly increased (PFR/EDV (s-1) Iva 2.4 $\pm$ 0.4 vs placebo 2.1 $\pm$ 0.4,  $p = 0.03$ ). There was a trend to longer PFT during treatment with Iva, though not reaching statistical significance. Medium and maximum aortic flow were not affected by treatment with Iva, while mean velocity (cm/s) was significantly reduced (Iva 6.7 $\pm$ 2.7 vs placebo 9.0 $\pm$ 3.4,  $p = 0.01$ ). Aortic flow parameters were correlated to aortic distensibility (AD), as surrogate parameter for arterial stiffness. AD was significantly correlated to both aortic flow and flow velocity, whereby mean velocity showed the strongest correlation to AD ( $r = 0.74$  [0.61 to 0.83],  $p < 0.0001$ ).

**Conclusion:** Systolic LV function was unaffected by treatment with Iva, while the filling during diastole was significantly improved. While medium and maximum aortic flow were not affected by Iva, mean velocity was significantly reduced. Aortic distensibility as surrogate parameter for arterial stiffness was significantly correlated to aortic mean velocity. This study confirms the underlying physiological principle of the If-current inhibitor Ivabradine.