Effects of the new ultra-long-acting β_2-AR agonist indacaterol in chronic treatment alone or in combination with the β_1-AR blocker metoprolol on cardiac remodelling

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In advanced heart failure (HF), increased arterial elastance and arterio-ventricular uncoupling, as well as excessive sympathetic activation and extensive abnormalities in the β-adrenoceptors (β-ARs) signalling, contribute to cardiac remodelling, such as cardiac β-ARs desensitization and left ventricular dysfunction progression (1). In recent years, it has become clear that chronic treatment with β-blockers improves LV function failure, prevents or reverses progressive LV dilation, chamber sphericity and hypertrophy, and positively affects cardiac remodelling in HF patients (2). Although clinical trials have documented detrimental effects in HF patients treated with β_2-AR agonists long term, some β_2-AR agonists (clenbuterol, fenoterol) have recently been shown to attenuate ventricular remodelling in chronic ischemic HF experimental models. This effect was more pronounced when the β_2-AR agonist was combined with a β_1-AR blocker (3).
In the present study we have investigated the effects of chronic treatment with a new β_2-AR agonist, indacaterol, alone or in combination with metoprolol, a selective β_1-AR antagonist, on reversed ventricular remodelling in an experimental HF model.
HF was performed in male Wistar rats (225-250 g; n=50) by surgical occlusion of the left anterior descending coronary artery (LAD). The animals were randomized in five following experimental groups (n=10, each group): sham-operated rats (SHAM); heart failure rats (HF); rats treated with 100mg/kg/die metoprolol (M); rats treated with 0.3mg/Kg/die indacaterol (I); rats treated with metoprolol and indacaterol combined therapy (M+I). Treatment was started the day after the surgical procedure and continued for 15 weeks. Metoprolol and indacaterol were dissolved either independently, or in combination, in drinking water. Blood pressure measurements and echocardiography were taken four and fifteen weeks postoperatively.
Fifteen weeks after HF, echocardiographic data demonstrated a mean arterial pressure (MAP) and ejection fraction (EF) decrease, as well as increased heart rate (HR) and left ventricular diastolic diameter (LVID), compared to SHAM. Metoprolol and indacaterol treatments alone or in combination restored these cardiac hemodynamic changes. This data was confirmed by infarct size histological evaluation; indeed, after 15 weeks the infarct size was significantly larger in HF compared to the SHAM group (45.0±02.89 and 0.25±0.03%, respectively; $p<0.001$), but significantly reduced after metoprolol, indacaterol and combined treatment (8.50±0.87%; 12.50±1.44%; 4.33±1.20%, respectively; $p<0.001$).
Moreover, molecular data underlined a significant reduction in β_1 and β_2-AR-mRNA levels, as well as an increase in GRK2, ANP, BNP, collagen-I and plasmatic catecholamines levels in the HF group. Single and importantly, combination treatments, restored both the cardiac markers under study as well as plasma catecholamine.
This study underscored an additive interaction between indacaterol and metoprolol in normalizing and reversing cardiac remodelling in our experimental model. Translating these findings into clinical practice, whereby HF and COPD coexisting patients could benefit from combined treatment, should provide a safer and more effective approach compared to the currently administered single treatments.

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