PPAR alpha-agonist treatment prevents the development of cardiac hypertrophy in a rat model of renovascular hypertension

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Introduction and Aim. Cardiac hypertrophy is induced by prolonged abnormal physiological and pathophysiological conditions, including those arising from hypertension, hemodynamic stress, myocardial infarction and valvular heart disease. Peroxisome proliferator-activated receptor-alpha agonists are reported as cardioprotective agents in various models of cardiac dysfunction; however whether fenofibrate improves cardiac remodeling in a model of renal-induced hypertension is currently unknown.

Methods. A two-Kidney One-Clip (2K1C) model was applied to seven weeks old Wistar Kyoto rats by placing a silver clip, with an internal diameter of 0.2 mm, on the right renal artery (n=20); sham operated rats were used as controls (2K0C, n=4). Four weeks after clipping, 2K1C animals were randomized to receive fenofibrate (150 mg/kg/d by gavage, n=8) or vehicle (n=12), for eight weeks. Systolic pressure was measured in conscious rats before surgery and then every 4 weeks, using the tail-cuff apparatus. At the same time points, cardiac and renal Magnetic Resonance Imaging (MRI) was performed to evaluate functional and morphological parameters. Plasma renin activity (PRA) was measured at 4 and 12 weeks. Histological analyses were performed on hearts collected at 12 weeks.
Data are expressed as means ± SEM.

Results. Compared to sham operated, 2K1C rats developed hypertension over 12 weeks after artery clipping (168 ± 13 vs 247 ± 9 mmHg; $p<0.01$) which was not affected by pharmacological treatment with fenofibrate (245 ± 27 mmHg). In the vehicle-treated 2K1C rats, PRA dramatically increased from 5.17 ± 0.83 ng/ml/h at 4 weeks to 10.33 ± 2.54 at 12 weeks. This increase was prevented (7.95 ± 2.41 ng/ml/h at 12 weeks) by fenofibrate.
At the 12 weeks follow-up, cardiac MRI analysis of the vehicle-treated 2K1C rats revealed an increase of left ventricular (LV) wall thickness (diastolic: 2.09 ± 0.11 vs 1.75 ± 0.02 mm, $p<0.05$ vs sham; systolic: 3.52 ± 0.14 vs 2.95 ± 0.06 mm, $p<0.01$ vs sham) and mass (780.2 ± 42.7 vs 608.9 ± 11.2 mg, $p<0.01$ vs sham) compared with sham operated animals, with no effect on relative wall thickness, indicating the development of eccentric cardiac hypertrophy. Chronic treatment with fenofibrate was able to significantly modulate such cardiac hypertrophy (mass: $p<0.01$; thickness: $p<0.05$ vs vehicle).
At 12 weeks, MRI analysis showed renal volume alterations induced by arterial stenosis in clipped (1.06 ± 0.16 vs 1.70 ± 0.02 cm^3) and non-clipped (2.79 ± 0.15 vs 1.80 ± 0.03 cm^3 $p<0.01$) kidneys of vehicle-treated 2K1C compared with 2K0C rats. These alterations paralleled with an increase of 24-h proteinuria. Renal morphological alterations and proteinuria development were prevented by fenofibrate.
Histological evaluations of the ventricular wall showed a medial thickening of intramyocardial arteries and perivascular collagen deposition in vehicle compared with 2K0C rats. Fenofibrate treatment completely prevented media thickening ($p < 0.01$ vs vehicle) and attenuated collagen accumulation ($p < 0.01$ vs vehicle).

Conclusions.
Fenofibrate improved renal stenosis-induced LV hypertrophy and cardiac vascular alterations, independently of an effect on blood pressure. These cardiac effects may be mediated by PRA decrease and, indirectly, by renal protection.