Pirfenidone improves insulin sensitivity & cardiac function in high-fat diet-fed obese and insulin-resistant mice

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Background and Aims

Extracellular matrix (ECM) remodelling of metabolic tissues is closely linked to insulin resistance (IR). However, their role in the pathogenesis of cardiac IR and associated cardiac dysfunction is inadequately investigated. Pirfenidone is an anti-fibrotic medication used for idiopathic pulmonary fibrosis. This study investigated the effects of Pirfenidone on cardiac insulin sensitivity and cardiac function in high-fat (HF) diet-fed obese and insulin-resistant mice.

Materials and Methods

Male mice fed a high-fat (HF) diet for 12 weeks received twice-daily oral gavage of either vehicle (0.25% Carboxymethyl cellulose [CMC]) or Pirfenidone (125 mg/kg body weight) for 21 days. After the treatment, insulin sensitivity was measured by hyperinsulinaemic-euglycaemic clamp and left ventricular dynamics was determined by Pressure-Volume (PV) loop analysis (Transonic) using PV conductance catheter in closed-chest preparation. Immunohistochemical analysis was performed to assess changes in collagen expression in the left ventricle (LV) of the heart.

Results

Fig. 1: Pirfenidone treatment resulted in a 41% decrease in collagen expression in the LV. Collagen content in the left ventricle (LV) was quantified using Sirius red staining; representative image (20x magnification). Values are Mean ± SEM for n=6 for HF-Vehicle and HF-Pirfenidone mice. *P<0.05 compared with the HF-Vehicle group.

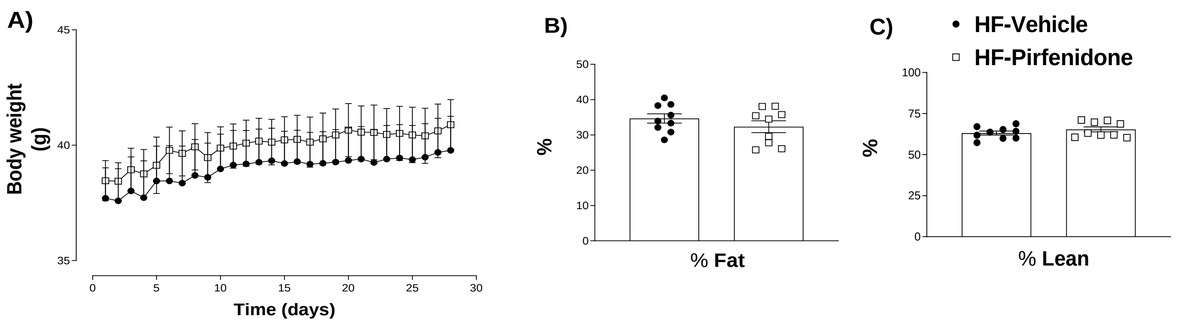


Fig. 2: Body weight & body composition remained unchanged by pirfenidone treatment. Body weight (A), percentage body fat mass (B) and percentage of lean mass (C) in high-fat (HF)-fed mice. Values are mean ± SEM for n=10 for HF-Vehicle and n=9 for HF-Pirfenidone mice.

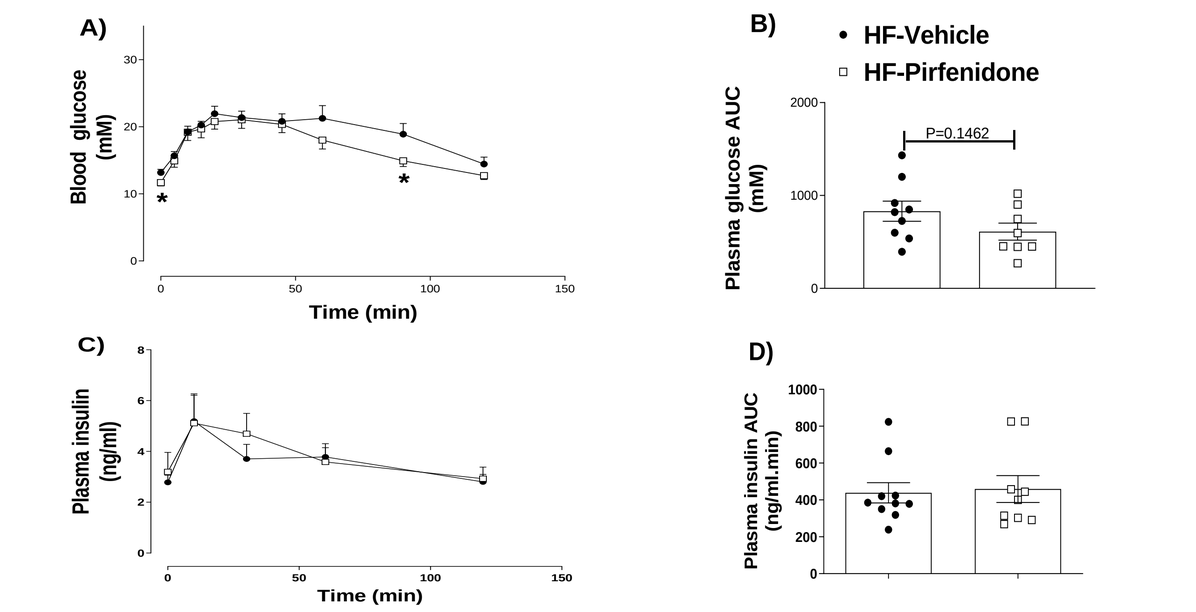


Fig. 3: Pirfenidone treated HF-fed mice displayed decreased fasting blood glucose without appreciably altered fasting insulin. Pirfenidone treated mice also showed improved glucose tolerance, while the insulin level remained unchanged. Plasma glucose and insulin concentrations were measured prior to and after oral administration of glucose (2gm/kg) to high-fat (HF)-fed mice pre-treated with twice-daily oral gavage of either vehicle or pirfenidone (125 mg/kg bw) for 21 days. Values are mean ± SEM for n=10 for HF-Vehicle and n=9 for HF-Pirfenidone mice. *P<0.05 compared with HF-Vehicle.

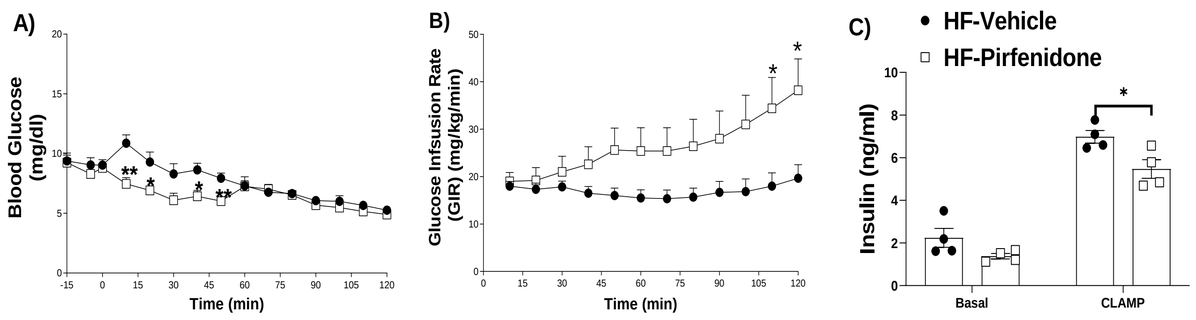


Fig. 4: During the hyperinsulinaemic-euglycaemic (ICv) clamp, Pirfenidone treated HF-fed mice displayed a higher glucose infusion rate (GIR) than vehicle controls, suggesting improved insulin sensitivity. Blood glucose level was maintained at 6.5 mmoL/l over the course of steady-state of the ICv clamp (n=4-5) (A), Glucose Infusion Rate (GIR); euglycemia was maintained throughout the ICv by infusing 50% glucose (n=5) (B), Insulin levels were measured in HF-Vehicle and HF-Pirfenidone mice at basal (-5 min) and during the ICv clamp (100 and 120 min) (n=4) (C). All of the data are presented by mean ± SEM with significance. *P<0.05, **P<0.01 compared with HF-Vehicle group.

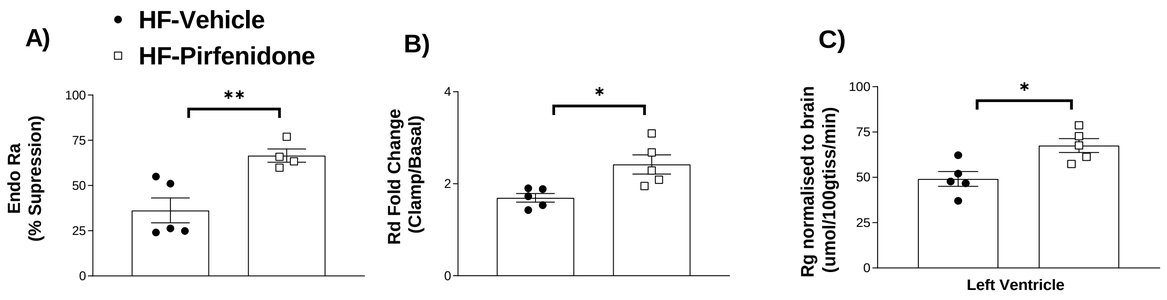


Fig. 5: Whole-body insulin sensitivity measured by percent suppression of hepatic glucose production and fold change in glucose disappearance rate (Rd) [ratio of clamp Rd vs basal Rd] was increased in pirfenidone treated mice compared to vehicle treated mice. Pirfenidone treated mice also displayed higher left ventricle Rg [umol/100g/min (normalised to the brain)] than vehicle-treated HF-fed mice, suggesting ameliorated cardiac IR. The percent suppression of endogenous glucose appearance (EndoRa) in HF-Vehicle and HF-Pirfenidone mice (A), the fold change in glucose disappearance rate (Rd) [ratio of clamp Rd vs basal Rd] in all mice groups (B), Glucose metabolic index (Rg) in left ventricle normalized to the brain (C). Values are means ± S.E.M. (n =4-5). *P<0.05, **P<0.01 compared with HF-Vehicle group.

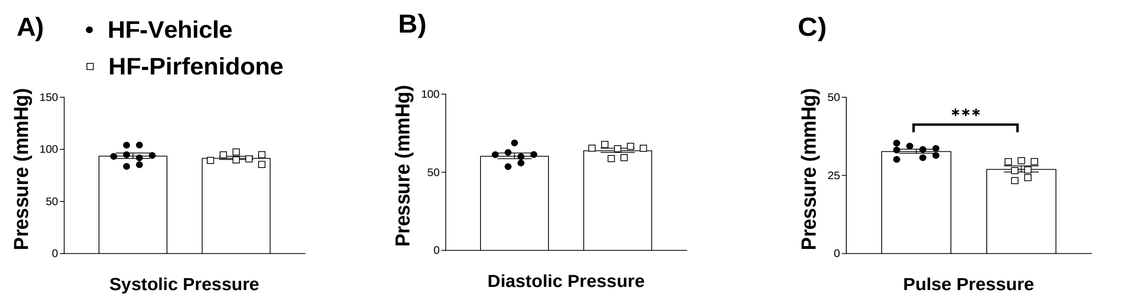


Fig. 6: PV loop analysis revealed a significant decrease in pulse pressure by the pirfenidone treatment, suggesting improved vascular compliance. Comparison of the systolic pressure (A), diastolic pressure (B) and pulse pressure (C) in HF-Vehicle and HF-Pirfenidone mice. Values are Mean ± SEM for n=10 for HF-Vehicle and n= 9 for HF-Pirfenidone mice. ***P<0.001 compared with HF-Vehicle group.

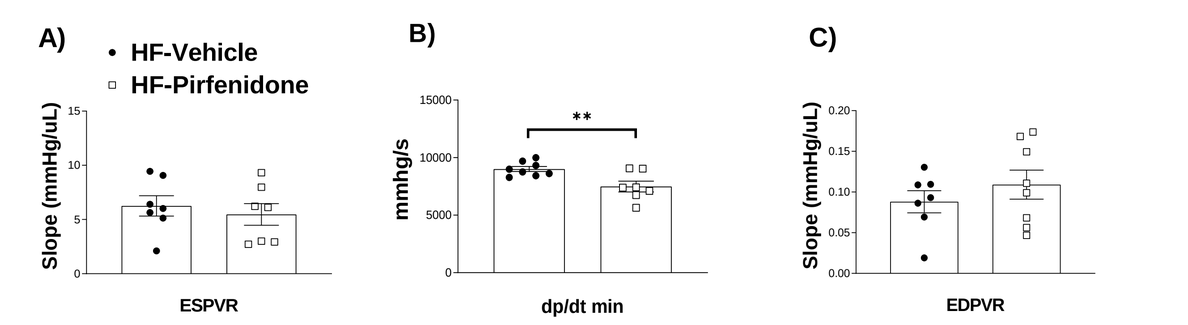
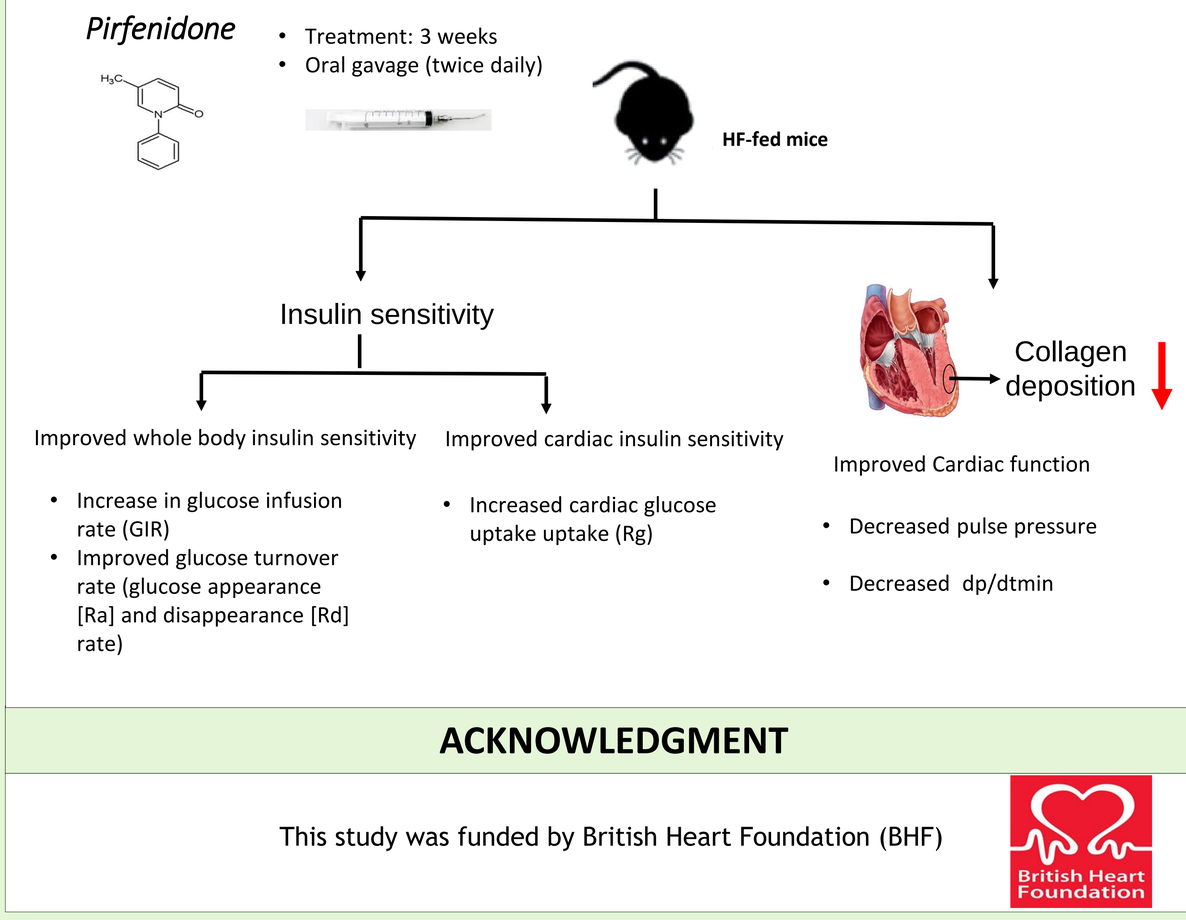


Fig. 7: Pirfenidone also reversed HF-diet induced an increase in the absolute value of the minimum rate of pressure change (dp/dtmin) in the LV. In contrast, other systolic and diastolic parameters, including end-systolic pressure-volume relationship (ESPVR) and end-diastolic pressure-volume relationship (EDPVR), were not different among the groups. The mean slope of the end-systolic pressure-volume relationship (ESPVR) (A), the minimum rate of pressure change (dp/dtmin) (B) and end-diastolic pressure-volume relationship (EDPVR) (C) (n = 7-9 for HF-Vehicle and HF-Pirfenidone mice). All data are expressed as the mean ± SEM . **P<0.01 compare with HF-Vehicle group.

SUMMARY



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