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

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Abstract:
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. This study examined the role of ECM deposition on cardiac IR and cardiac function in high-fat (HF) diet-fed obese and insulin-resistant mice. Pirfenidone is an anti-fibrotic medication used for idiopathic pulmonary fibrosis. Male c57BL/6 mice fed on 60% HF-diet for 12-week were treated with either vehicle or pirfenidone (125mg/kg body-weight) for 21-days. Insulin sensitivity was measured by the hyperinsulinemic-euglycemic clamp (ICv), and cardiac function was measured by Pressure-Volume (PV) loop analysis. In HF-fed mice, pirfenidone reduced non-fasting blood glucose and improved glycemic response to an oral glucose load. Pirfenidone ameliorated HF-diet induced IR evidenced by increasing glucose infusion rate, glucose disappearance rate, and percent suppression of endogenous glucose appearance rate when compared to vehicle treatment. Pulse pressure and the minimum rate of pressure change (dp/dtmin) were also decreased by pirfenidone, an indication of improved cardiac function. These beneficial effects of pirfenidone were accompanied by decreased collagen deposition in the left ventricle of the heart. Our finding suggests that anti-fibrotic drugs have the potential to reverse obesity-associated IR and cardiac dysfunction.