Imeglimin opposes development of metabolic syndrome related diabetic cardiomyopathy

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Aim of study:

Imeglimin, a novel glucose lowering agent, targeting mitochondrial bioenergetics, decreases ROS overproduction and delays mPTP opening, preventing cell death during oxidative stress.

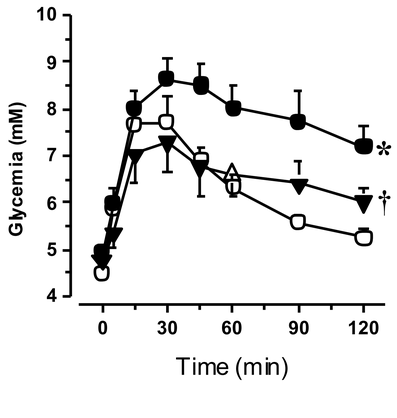
Whether Imeglimin could also exhibit protective effect on diabetic cardiomyopathy, i.e. left ventricular (LV) diastolic dysfunction (DF), is unknown.

Methods:

Animals and treatment.

Twelve weeks old Zucker fa/fa rats, a model of metabolic syndrome (MS) with demonstrated diastolic dysfunction, were treated during 9 days or 90 days with Imeglimin (150 mg/kg bid PO) to assess effects on left ventricular (LV) function and hemodynamics (echocardiography, MRI, LV catheterization).

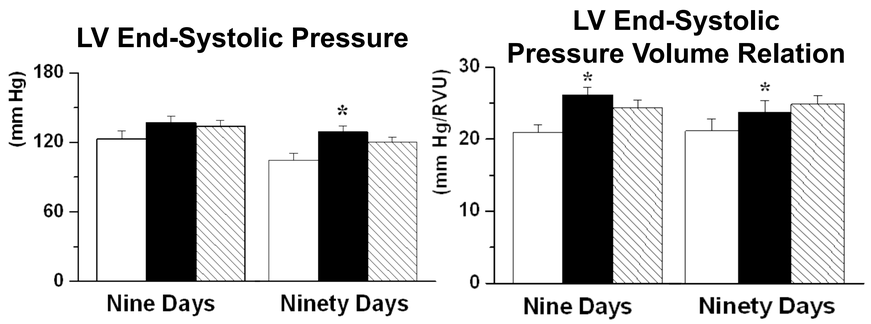
Oral glucose tolerance test



Compared to lean rats (○), Zucker fa/fa rats (●) are intolerant to glucose.
Imeglimin for 9 days (▼) normalizes glucose tolerance in Zucker fa/fa rats.

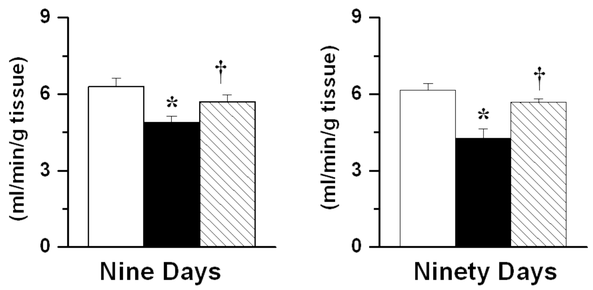
(*: p<0.05 vs. lean; †: p<0.05 vs. Zucker)

Left ventricular hemodynamics



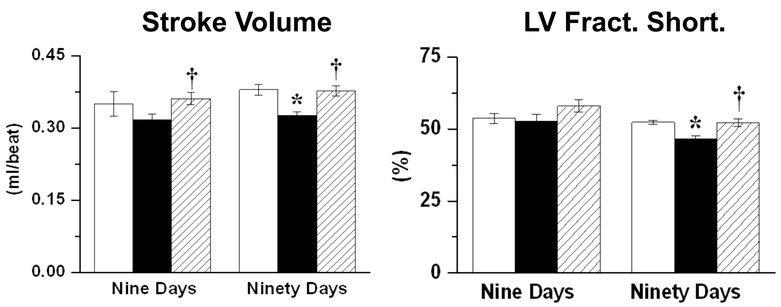
Compared to lean rats, both 13 and 24 weeks old Zucker fa/fa rats demonstrated an increase in cardiac contractility as seen by the increases in LVESPVR; Neither nine nor 90 days Imeglimin treatment modified cardiac contractility. (*: p<0.05 vs. lean)

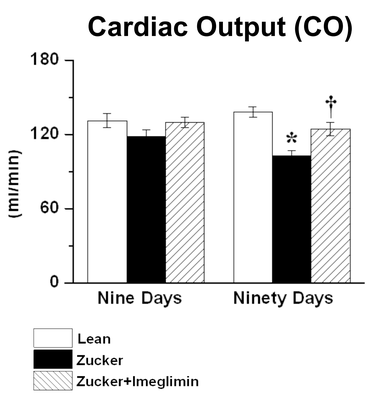
LV tissue perfusion



Compared to lean rats, both 13 and 24 weeks old Zucker fa/fa rats had a reduction in LV tissue perfusion which was prevented by both short- (9 days) and long-term (90 days) Imeglimin treatment. (*: p<0.05 vs. lean; †: p<0.05 vs. Zucker)

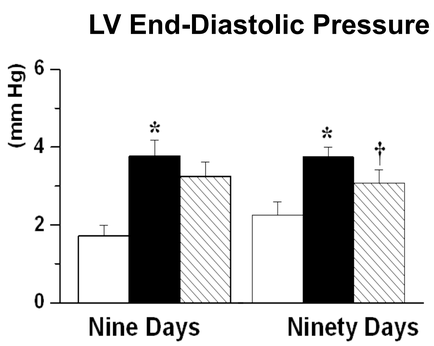
Left ventricular function

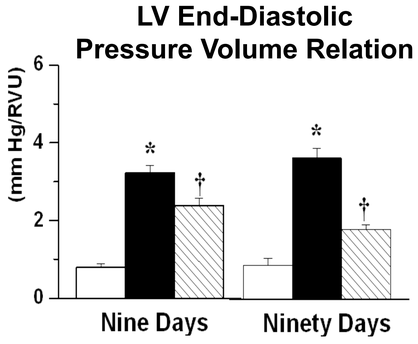




Compared to lean rats, 24 weeks old Zucker fa/fa rats have a significant reduction in both LV fractional shortening (Fract. Short.) and stroke volume associated with a decrease in cardiac output. Long-term (90 days) Imeglimin treatment significantly increases stroke volume, LV Fract. Short. and cardiac output.

(*: p<0.05 vs. lean; †: p<0.05 vs. Zucker)

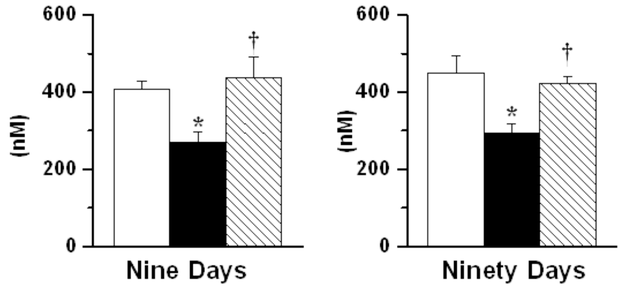




Compared to lean rats, both 13 and 24 weeks old Zucker fa/fa rats demonstrated an impairment of diastolic function as seen by the increases in LVEDPVR and Tau. Imeglimin significantly decreases these parameters demonstrating a better diastolic function.

(*: p<0.05 vs. lean; †: p<0.05 vs. Zucker)

Plasma nitrite



Compared to lean rats, both 13 and 24 weeks old Zucker fa/fa rats have reduced plasma nitrite levels. Both 9 and 90 days Imeglimin increased plasma nitrite level suggesting an increase in NO bioavailability. (*: p<0.05 vs. lean; †: p<0.05 vs. Zucker)

Conclusion:

In a relevant rat model of metabolic syndrome which exhibits diabetic cardiomyopathy characteristics, Imeglimin normalizes glucose tolerance, while short- as well as long-term treatment improves LV function, i.e. LV diastolic dysfunction. These results are associated with a higher myocardial perfusion and an increase in nitrite plasma levels.

These results suggest that Imeglimin may exert protective effects on diabetic cardiomyopathy characterized by a diastolic dysfunction present in half of T2D patients.