Short- and long-term imeglimin treatment reduces metabolic syndrome-related diabetic cardiomyopathy

Marianne Lachaux[1], Lionel Nicol[1], Mouad Hamzaoui[1], Isabelle Rémy-Jouet[1], Pascale Fouqueray[2], Sébastien Bolze[2], Sophie Hallakou-Bozec[2], Vincent Richard[1], Paul Mulder[1]

[1] INSERM U1096, 22 Boulevard Gambetta, 76183 Rouen, France; [2] Poxel SA, 259/261 avenue Jean Jaurès, 69007 Lyon, France

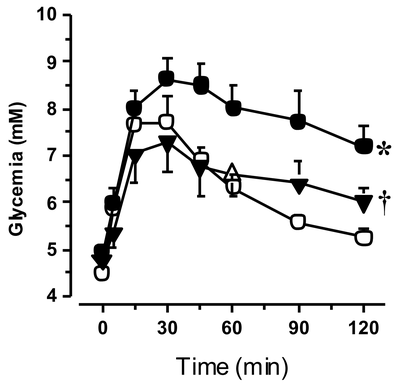
Inserm — Institut national de la santé et de la recherche médicale

marianne.lachaux@gmail.com

Aim of study. Imeglimin, a novel glucose lowering agent, targeting mitochondrial bioenergetics, decreases reactive oxygen species (ROS) overproduction and delays mPTP opening, preventing cell death during oxidative stress. Whether Imeglimin could also exhibit protective effects on diabetic cardiomyopathy, i.e. left ventricular (LV) diastolic and endothelial vascular dysfunctions, is unknown.

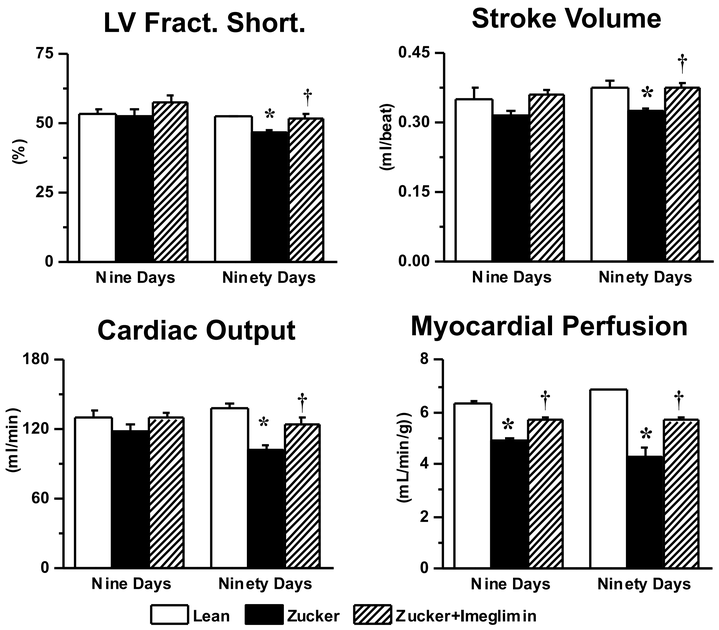
Methods. Twelve weeks old Zucker fa/fa rats, a model of metabolic syndrome (MS) with demonstrated diastolic dysfunction, were treated during 9 days or 90 days with Imeglimin (150 mg/kg bid PO) to assess effects on left ventricular (LV) function, hemodynamics (echocardiography, MRI, LV catheterization) as well as vascular endothelial function (Mulvany's myograph, Halpern's arteriograph).

Oral Glucose Tolerance Test



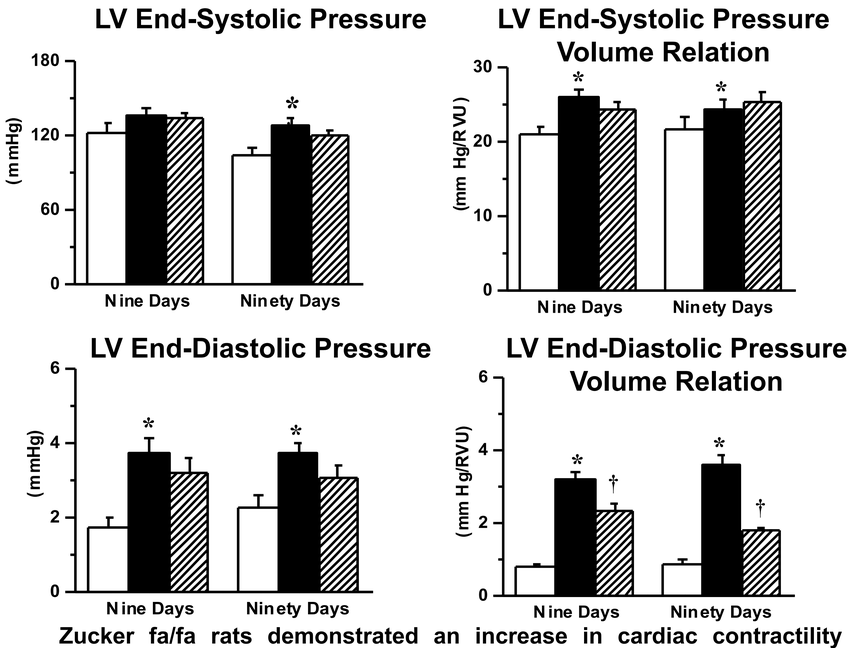
Compared to lean rats (○), 13 weeks old Zucker fa/fa rats (●) are intolerant to glucose.
Imeglimin for 9 days (▼) normalizes glucose tolerance in Zucker fa/fa rats.
(*: p<0.05 vs. lean; †: p<0.05 vs. Zucker)

Left Ventricular Function and Perfusion



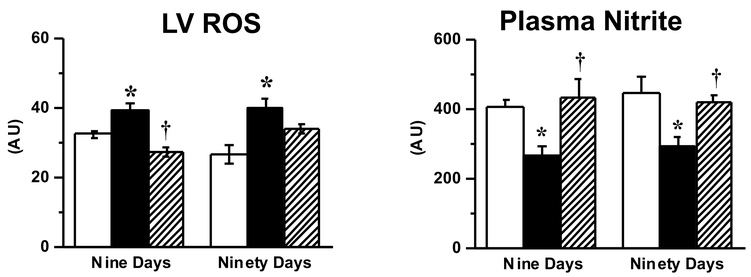
At the end of the study both LV fractional shortening (Fract. Short.), stroke volume, cardiac output as well as myocardial perfusion were reduced in Zucker fa/fa rats.
Both 9 and 90 days Imeglimin treatment significantly increases myocardial perfusion, while 90 days Imeglimin treatment improved LV Fract. Short., stroke volume and cardiac output.
(*: p<0.05 vs. lean; †: p<0.05 vs. Zucker)

Left Ventricular Hemodynamics



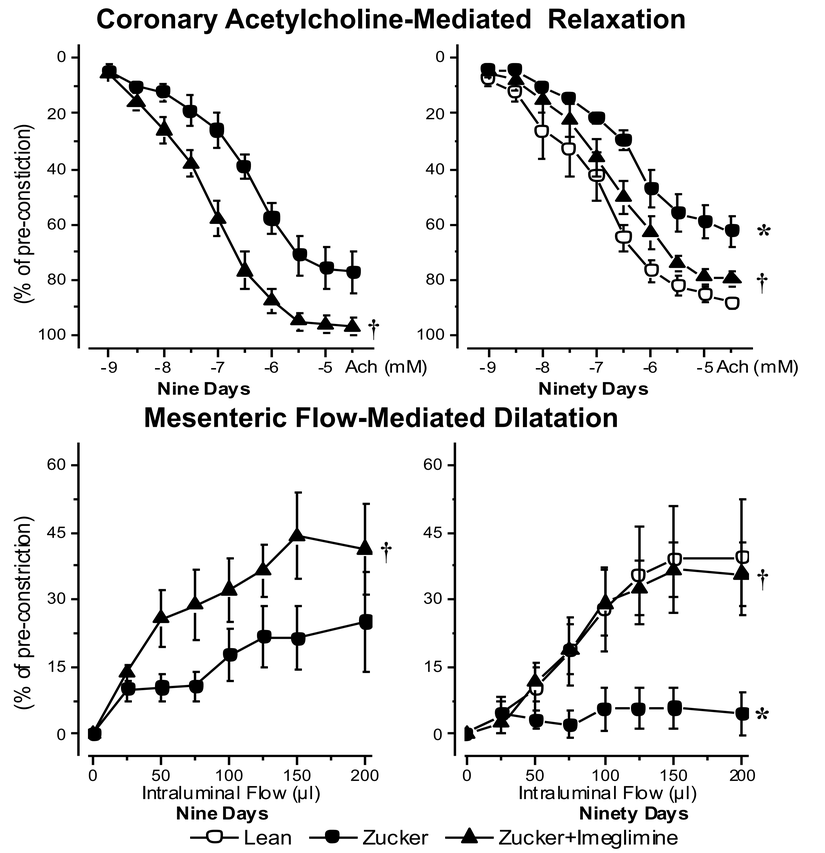
Zucker fa/fa rats demonstrated an increase in cardiac contractility (increases in LVESPVR in 13 and 24 weeks old rats); neither 9 nor 90 days Imeglimin treatment modified cardiac contractility.
Zucker fa/fa rats demonstrated an impairment of diastolic LV function (increases in LVEDP and LVEDPVR). Nine and 90 days Imeglimin treatment decreases LVEDP and LVEDPVR, demonstrating a better diastolic function. (*: p<0.05 vs. lean; †: p<0.05 vs. Zucker)

Oxidative Stress



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

Vascular Function



Compared to lean rats, 24 weeks old Zucker fa/fa rats have a reduced LV coronary acetylcholine-mediated relaxation. Both 9 and 90 days Imeglimin treatment improved coronary relaxation.
Coronary dysfunction in Zucker fa/fa rats was associated with an impairment of mesenteric flow- mediated dilatation, which was prevented by both 9 and 90 days of Imeglimin treatment. (*: 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 both short- and long-term Imeglimin treatment improves LV diastolic dysfunction, myocardial perfusion as well as coronary and peripheral vascular dysfunctions. The cardiac and vascular improvements probably involve reduced oxidative stress and increased NO-bioavailability.
These results suggest that Imeglimin may exert protective effects on diabetic cardiomyopathy characterized by ~~a~~ diastolic and vascular dysfunctions present at least in half of type-2 diabetic patients.