Chronic treatment with the direct AMP kinase activator PXL770 improves cardiac and renal function in diabetes related cardiorenal syndrome

Y Stephan[1], M Soulié[1], L. Nicol[1], P Gluais-Dagorn[2], S Hallakou-Bozec[2], V Richard[1], P Mulder[1]
(1) Normandie Univ, UNIROUEN, Inserm U1096, ENVI & FHU-REMOND-VHF, Rouen, France (2) POXEL SA, Lyon, France

Introduction

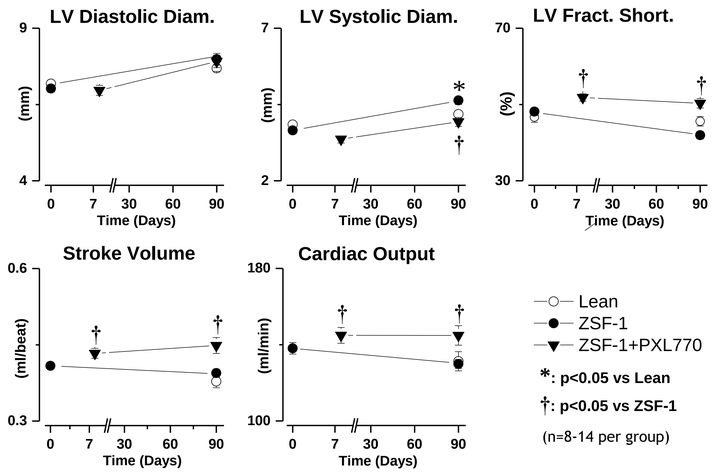
Adenosine monophosphate activated protein kinase (AMPK) activation has been suggested to be a prominent target for the treatment of diabetes/metabolic syndrome. In experimental animal models of diabetes, the direct AMPK activator PXL770 improves glycemic control and plasma lipids. However, whether these benefits of PXL770 are associated with improvements in diabetes-related cardiac and renal dysfunction is unknown. Thus, we used ZSF-1 rats, a model of cardio-renal syndrome, to investigate whether PXL770 exhibits protective effects on cardiac remodeling and function as well as on renal function.

Methods

ZSF-1 rats were either treated with vehicle or with the AMPK activator PXL770 (150 mg/kg per os, twice a day) for 90 days beginning at the age of 12 weeks. Cardiac remodeling/function, i.e. cardiac output, left ventricular (LV) systolic- and diastolic-diameters and fractional shortening were evaluated after 8 and 90 days by echocardiography. Furthermore, LV tissue perfusion (MRI) was evaluated after 90 days. LV hemodynamics, i.e. LV end-systolic and end-diastolic pressures, and LV end-systolic and end-diastolic pressure-volume relations (LV catheterization), glomerular filtration rate (transcutaneous glomerular filtration rate technique) as well as urinary albumin/creatinine excretion (Catalyst One, Idexx) were measured at day 8 and 90. Exercise capacity was determined using a treadmill.

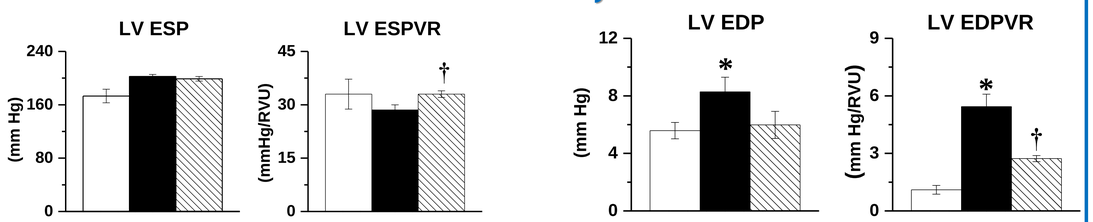
Results

LV remodeling and function



In untreated ZSF-1 rats, LV systolic diameter was significantly increased at day-90, but LV diastolic diameter was not modified, resulting in a (non-significant) reduction of LV fractional shortening. Moreover, neither stroke volume nor cardiac output were modified at day 90. After a 90-day treatment, PXL770 reduced LV systolic diameter, without modifying LV diastolic diameter, resulting in an increased LV fractional shortening. This was associated with an increase in stroke volume and cardiac output.

LV cardiac hemodynamics

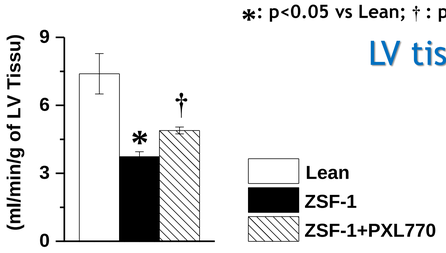


After 90 days, LV end-systolic pressure (LV ESP) as well as LV ESP-volume relation (LV ESPVR) were similar in lean and ZSF-1 rats. PXL770 did not modify LV ESP but significantly increased LV ESPVR.

After 90 days, LV end-diastolic pressure (LV EDP) as well as LV EDP-volume relation (LV EDPVR) were increased in ZSF-1 rats. PXL770 decreased LV EDP and significantly reduced LV EDPVR.

*: p<0.05 vs Lean; †: p<0.05 vs. ZSF-1; (n=6-12 per group)

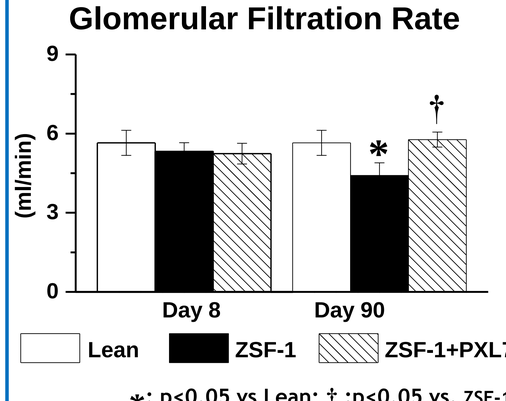
LV tissue perfusion



LV tissue perfusion was significantly decreased in ZSF-1 animals at Day 90. PXL770 treatment significantly increased basal perfusion after 90 days.

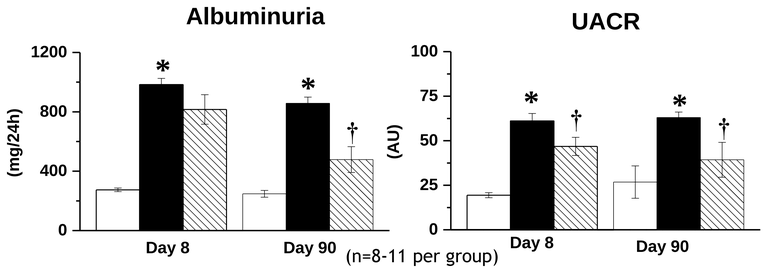
* : p<0.05 vs Lean ; † : p<0.05 vs ZSF-1; (n=5-6 per group)

Renal function



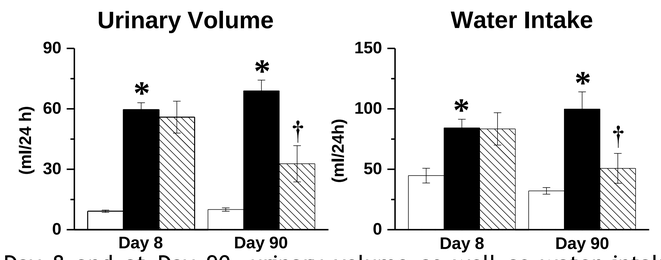
At Day 8, glomerular filtration rate was similar in all 3 groups. However, at Day 90, glomerular filtration rate was significantly decreased in untreated ZSF-1 rats, and 90-day treatment with PXL770 significantly increased glomerular filtration rate.

*: p<0.05 vs Lean; † :p<0.05 vs. ZSF-1(n=7-9 per group)



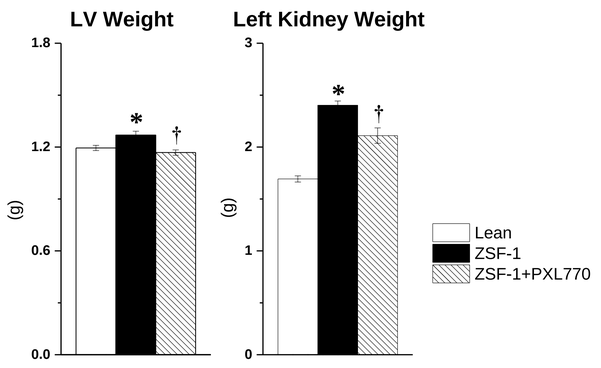
(n=8-11 per group)

At Day 8 and Day 90, albuminuria as well as UACR were significantly increased in untreated ZSF-1 rats. Albuminuria was only significantly decreased at day 90 in PXL770 treated rats. After 8-day and 90-day treatment with PXL770, UACR was significantly decreased.



At Day 8 and at Day 90, urinary volume as well as water intake were significantly increased in untreated ZSF-1. Only at Day 90, urinary volume and water intake were significantly decreased in PXL770 treated rats.

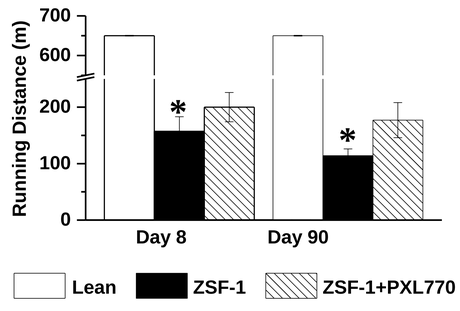
Organ weights



At Day 90, LV and kidney weights were significantly increased in ZSF-1 animals. 90-day treatment with PXL770 normalized LV weight and significantly decreased kidney-weight.

*: p<0.05 vs Lean; † : p<0.05 vs. ZSF-1; (n=11-17 per group)

Exercise Capacity



* : p<0.05 vs Lean (n=6-11 per group)

Maximum exercise capacity was significantly decreased in ZSF-1 rats at day 8 and 90. PXL770 improved this parameter without reaching statistical significance.

Conclusions

In ZSF1 rats, a model of diabetes related cardio-renal syndrome, long-term treatment with the direct AMPK activator PXL770 improves both LV diastolic and renal functions. These benefits were associated with reductions in ZSF-1 increased cardiac and renal weights. Whether PXL770, which is currently in clinical development for NASH, exerts similar effects in patients suffering from diabetic cardiomyopathy and/or nephropathy remains to be confirmed.