

Universitätsklinik für Viszerale Chirurgie und Medizin Hepatologie

#### Stiftungsratspräsidentin:

- Prof. Dr. med. Dr. phil. nat. Annalisa Berzigotti

#### Stiftungsrat:

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- Dr. med. Michael Schenk, Stiftungsrat



# **Research Progress Report**

Carvedilol decreases hepatic vascular resistance by reducing fibrogenesis, and reversing liver endothelial dysfunction in cirrhotic rats

Name of Grantee: Yeldos Nulan

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# Summary / Brief outline of topic

Carvedilol, a new non-selective  $\beta$ -blocker (NSBB) with anti- $\alpha$ 1-adrenergic activity, reduces portal pressure more than propranolol, likely decreasing intrahepatic vascular resistance. However, its intrahepatic effects remain largely unexplored. This study aims to clarify the intrahepatic effects of carvedilol and its relevance.

#### **Activities**

We combined in vitro and in vivo studies.

In vitro: Nitric Oxide (NO) release and oxidative stress were measured in primary liver sinusoidal endothelial cells (LSECs), as well as cell contraction and proliferation detection in primary hepatic stellate cells (HSCs).

In vivo: Cirrhotic rats (12-week thioacetamide (TAA)) were treated with vehicle, carvedilol (10mg/kg/day, 2-week), or propranolol (30mg/kg/day, 2-week) at early and advanced cirrhotic stages (9 and 12-week TAA). We measured hepatic hemodynamics, liver fibrosis, antioxidant activity, and Inflammatory biomarkers.

### **Results**

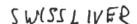
Carvedilol increased NO release in LSECs, while blunted HSCs cell contraction. Carvedilol reduced PP both in early and advanced cirrhosis (12w TAA: -22%; 9w TAA:-17%), liver fibrosis area (-26.8% Vs -23.1%) and  $\alpha$ SMA expression (-22.7% Vs -17.4%). Moreover, carvedilol improved endothelial dysfunction and reduced markers of oxidative stress and inflammation. Propranolol lacks these beneficial effects.

### **Discussion**

Administration: Lilian Smith

Murtenstrasse 35, 3008 Bern, Tel. +41 31 632 32 88

info@swissliver.ch www.swissliver.ch





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### STIFTUNG FÜR LEBERKRANKHEITEN

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The current study adds relevant information indicating that the beneficial effects of carvedilol over propranolol are not limited to a greater decrease in portal pressure due to a hemodynamic effect but involve a marked improvement in the main intrahepatic determinants of portal hypertension in cirrhosis, both structural and dynamic. Carvedilol achieved a marked reduction in liver fibrosis, associated with features of partial cirrhosis regression, and that were accompanied by marked improvement of hepatic endothelial dysfunction, moderate anti-inflammatory effects and of markers of liver dysfunction. The mechanism of these changes was substantiated by in vitro studies in HSCs and LSEC primary isolated from cirrhotic rats, and importantly, in human cells, underlining the translational potential of our findings. Future long-term longitudinal studies in human cirrhosis are encouraged to verify the extent of these benefits that may contribute not only to a greater effectivity of carvedilol over other drugs in preventing decompensation, complications of portal hypertension and enhance survival in advanced chronic liver disease, but also to contribute to accelerate cirrhosis regression when administered together with etiological therapy.

## **Achievements (Grants / Prizes / Publications)**

The study was presented at the European Association for the Study of the liver (EASL) in 2024.

The article is currently under review in Journal of Hepatology Reports.

### **Outlook / Next steps**

Our our group demonstrated in a recent study that simvastatin could increase NO in LSECs and decrease the activation of HSCs in cirrhosis. Currently, there is no study aimed at assessing the potential synergic effects of Carvedilol and Simvastatin in chronic liver disease. Therefore, investigating the effects of carvedilol and its synergic activity with Simvastatin on intrahepatic circulation in chronic liver disease, is our next step research priority.