UNIVERSITÄT LEIPZIG

Medizinische Fakultät

HERZZENTRUM LEIPZIG

The Heart and The Gut – Examining the microbiome, intestinal permeability and TMAO under HFpEF in the ZSF1 rat animal model

Salmina Guivala, Sandra Erbs[I], Holger Thiele[I], Petra Büttner[I]

[1] Heart Center Leipzig at University Leipzig, Department of Cardiology, Leipzig, Germany

Background

Elevated Trimethylamine-N-Oxide (TMAO) is associated with cardiovascular diseases, specifically Heart Failure With Preserved Ejection Fraction (HFpEF) [1].

The precursor Trimethylamine (TMA) is synthesized by the gut microbiome, passes into circulation and is metabolized to TMAO[2]. Elevated plasma levels of TMAO therefore could be caused by a microbiotic shift and an increased intestinal permeability. Obese ZSF1 rats develop hypertension and metabolic syndrome, culminating in HFpEF. In this study we examined the gut microbiome and gut wall permeability in ZSF1 rats.

Methods

TMAO was measured using Tandem-mass-spectroscopy in plasma samples of lean / healthy (n=12) and obese (n=11) rats. Microbiome was characterized by identifying bacteria by DNA sequencing from stool samples. Morphology of the intestinal barrier was assessed by visualizing intercellular contacts histochemically while functionality was determined using impedance based barrier tests on in vitro colon cells.

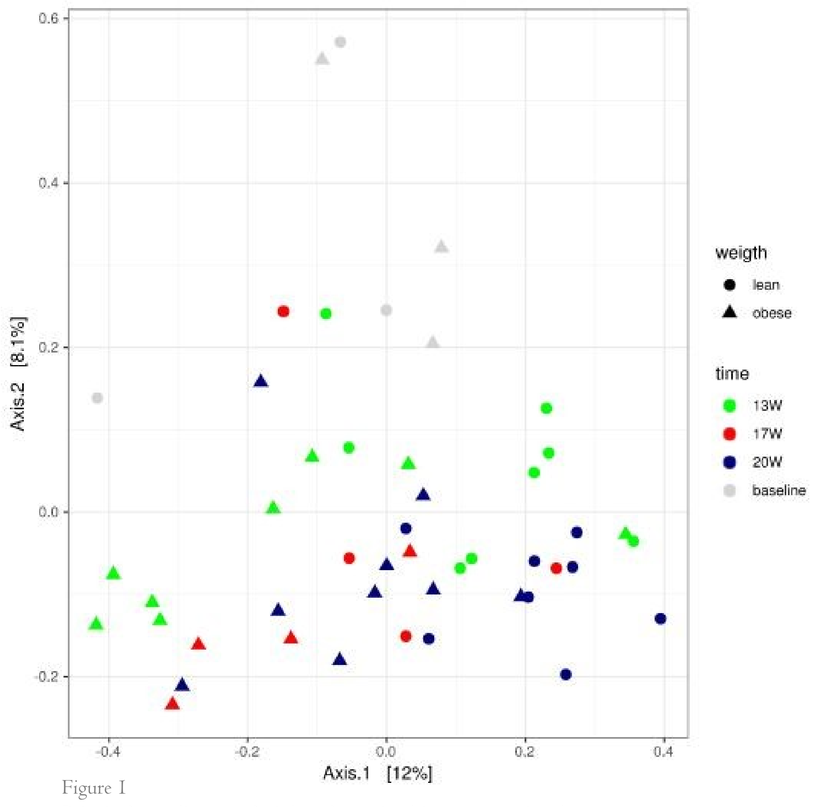

Figure I
Principal coordinate analysis based on microbiome sequencing data

Results

TMAO plasma levels were on average 86% higher in obese rats ($p<0,05$). The decrease in barrier function was significantly ($p<0,05$) smaller in obese rats. Using the relative changes in microbiome composition over time as a preliminary indicator, differences in the phyla Deferribacteres (271% vs. -56%) and Verrucomicrobia (25 % vs. -68%) between obese and lean rats were striking. The principal coordinate analysis based on microbiome sequencing data also indicated differences in diversity between the two experimental groups.

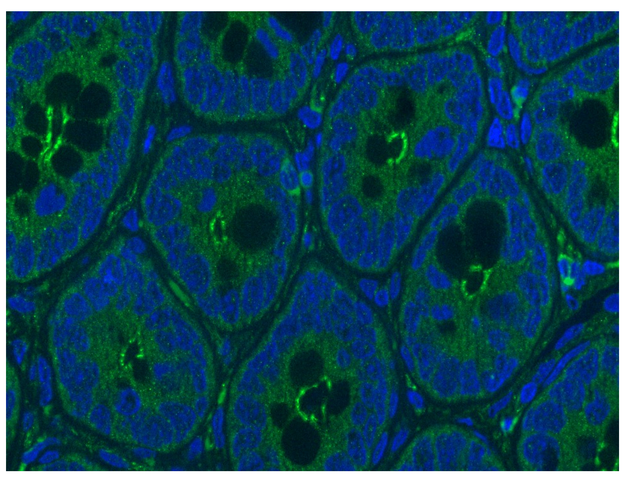

Image I
Fluorescence microscopy image of tight junction (Zonula Occludens I protein) in small Intestine sample from obese ZSF1 Rat; (Nuclei staining via Hoechst)

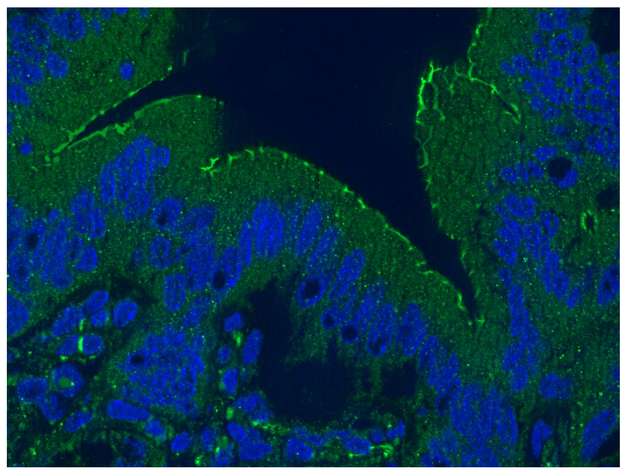

Image 2
Fluorescence microscopy image of tight junction (Zonula Occludens I protein) in colon sample from lean ZSF1 Rat; (Nuclei staining via Hoechst)

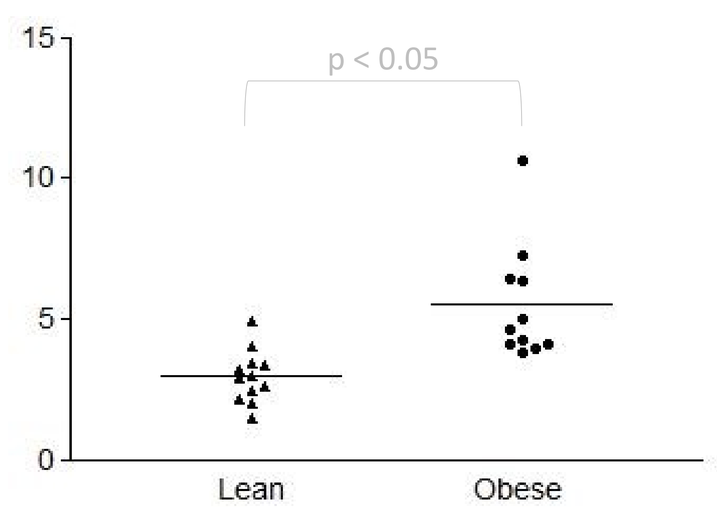

Figure 2:
TMAO Plasma-Levels in lean and obese ZSF1-Rats

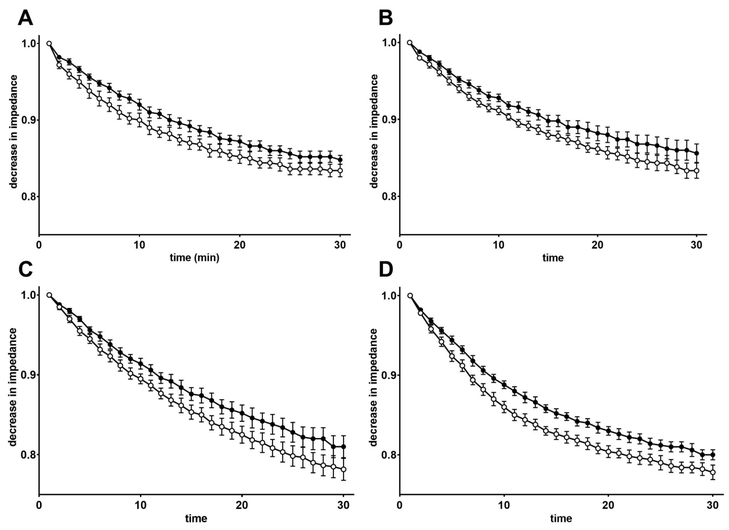

Figure 3
Impedance based barrier tests on colon cells using A: Histamin 100µM, B: TRAP 50µM, C: TRAP 50µM and Y-27632 10µM and D: Ethanol 1%. Black circles indicate obese ZSF1 rats, white circles indicate lean ZSF1 rats.

Conclusion

Our data shows a microbiome shift as well as an increase in plasma TMAO levels in rats with HFpEF.

Epithelial cells of obese rats appear to be less sensitive, which could be attributed to a decrease in cell reactivity and may be regarded as epithelial dysfunction.

Contact

Petra Büttner
Herzzentrum Leipzig, Forschungslabor Kardiologie
Petra.Buettner@medizin.uni-leipzig.de
+49 341 865-252605

References

[1]Zeisel SH, Warrier M. Trimethylamine N-Oxide, the Microbiome, and Heart and Kidney Disease. Annu Rev Nutr 2017;37:157–81. DOI: 10.1146/annurev-nutr-071816-064732

[2] Al-Rubaye H, Perfetti G, Kaski J-C. The Role of Microbiota in Cardiovascular Risk: Focus on Trimethylamine Oxide. Curr Probl Cardiol 2018:1–14. DOI: 10.1016/j.cpcardiol.2018.06.005