EFFECTS OF THE ANTIDIABETIC *IMEGLIMINE* IN HYPERGLYCEMIC MICE WITH SEPTIC SHOCK

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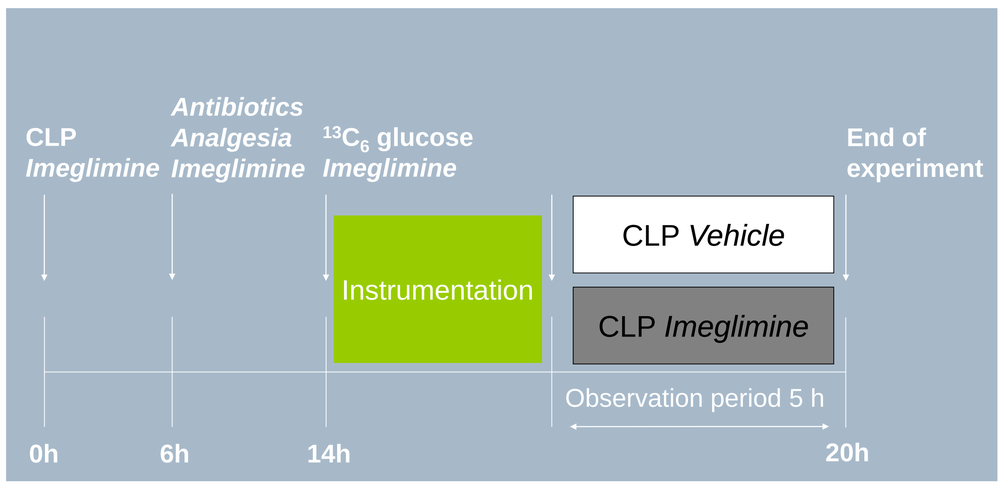
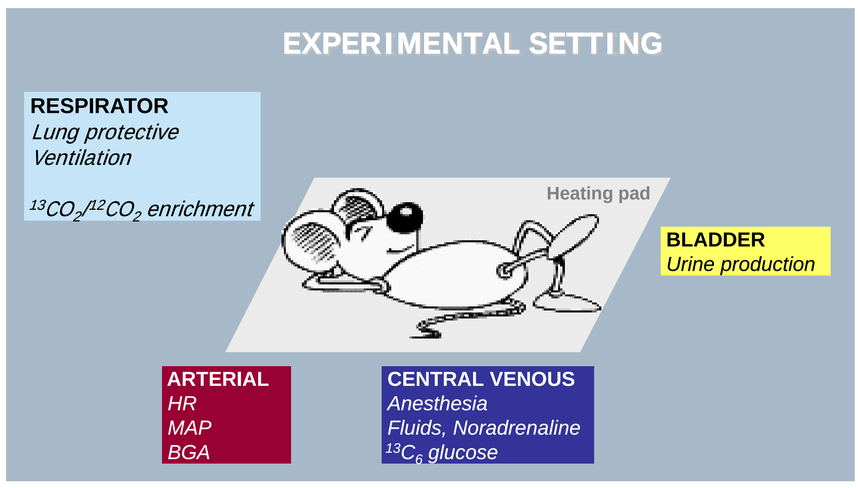
Introduction:

Shock-related hyperglycemia impairs mitochondrial function and integrity [1,2], ultimately leading to apoptosis and organ failure [2,3]. Imeglimin presents as a new antidiabetic drug with anti-hyperglycemic and anti-apoptotic properties [4].Therefore we investigated its effects in hyperglycemic mice with septic shock.





Methods:

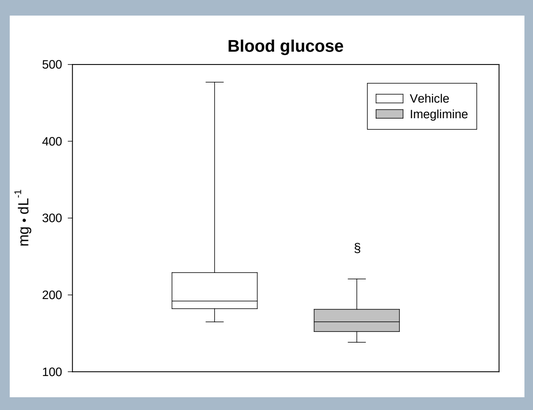
Immediately and 6 hours after cecal-ligation and puncture, mice randomly received s.c. *vehicle* (n=9) or *imeglimin* (n=10; 100 µg • g^{-1}). 14 hours later animals were anesthetized, mechanically ventilated and instrumented for a consecutive 5 h observation period. After a second imeglimin bolus, colloid fluid resuscitation was performed and continuous i.v. noradrenaline were titrated to maintain normotensive and hyperdynamic hemodynamics. 2 mg • g^{-1} • h^{-1} glucose were infused to induce hyperglycemia. Glucose oxidation and gluconeogenesis were derived from blood $^{13}C_6$-glucose and mixed expiratory $^{13}CO_2/^{12}CO_2$ isotope enrichment during continuous isotope infusion. Liver mitochondrial activity was assessed using high resolution respirometry [5-7]. Liver hemoxygenase-1 (HO-1), Bcl-2–associated X protein (Bax), cleaved caspase-3 and nuclear factor-κB (NF-κB) expression by immunoblotting and EMSA, respectively. All data are median (quartiles). Statistical significance was tested using Mann-Whitney Rank sum or if data were normally distributed by t- test.

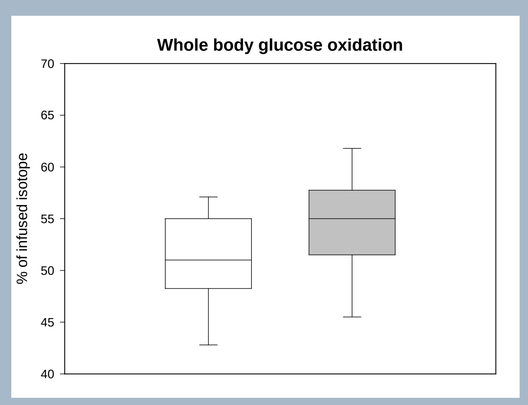
Results:

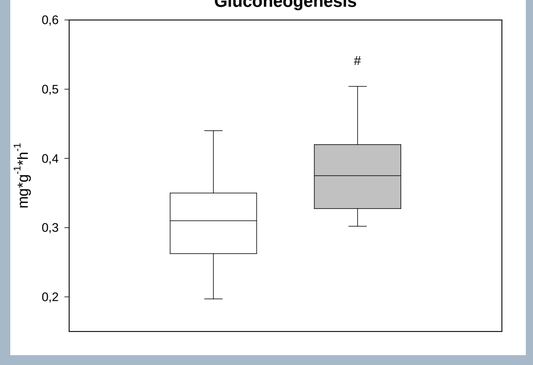
Imeglimin did neither affect noradrenaline requirements (0.15 (0.10;0.98) vs 0.13 (0.06;0.56) µg•g^{-1}, p=0.23) needed to achieve target hemodynamics nor liver macrocirculation. It decreased blood glucose levels by increasing whole body glucose oxidation, which coincided with partial restoration of gluconeogenesis. Regarding liver mitochondrial activity oxidative phosphorylation as well as maximal oxidative capacity were increased in the imeglimine group. Whereas liver HO-1 was upregulated, NF-κB as well as Bax and cleaved Caspase-3 expression were attenuated in the imeglimine treated animals.

	Vehicle		Imeglimine		intergroup
	Baseline	*5 h*	*Baseline*	*5 h*	
Heart rate [min^{-1}]	**490 (375;513)**	**476 (450;489)**	**435 (395;485)**	**410 (401;432)**	*n.s.*
MAP [mmHg]	**64 (61;72)**	**56 (52;58)**	**65 (65;68)**	**52 (51;56)**	*n.s.*
Flow V. portae [mL • min^{-1}]	**8 (5.9;8.4)**	**6.2 (3.3;7.3)**	**7 (6.2;7.3)**	**5 (4.5;6.1)**	*n.s.*
Liver $S0_2$ [%]	**67 (64;70)**	**65 (59;67)**	**70 (68;71) §**	**68(62;70)**	*§ p=0.03 vs Vehicle baseline*
pH	**7.34 (7.30;7.34)**	**7.30 (7.27;7.28)**	**7.32 (7.29;7.37)**	**7.20 (7.02;7.26)**	*n.s.*
P_aCO_2 [mmHg]	**32 (30;34)**	**35 (34;41)**	**31 (29;34)**	**38 (35;43)**	*n.s.*
P_aO_2 [mmHg]	**337 (312;366)**	**314 (292;347)**	**349 (347;357)**	**347 (336;354)**	*n.s.*
Blood lactate [mmol • L^{-1}]		**3.2 (2.5;3.5)**		**3.7 (3.1;4.7)**	*n.s.*

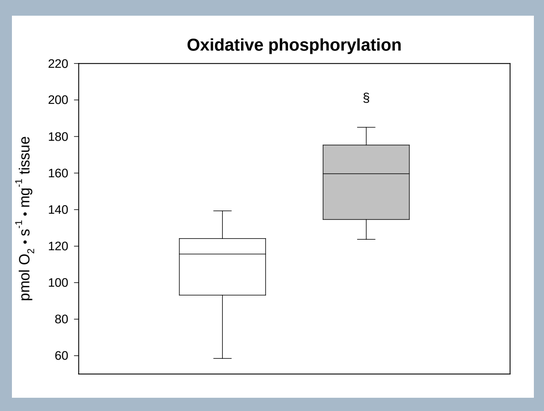
GLUCOSE METABOLISM

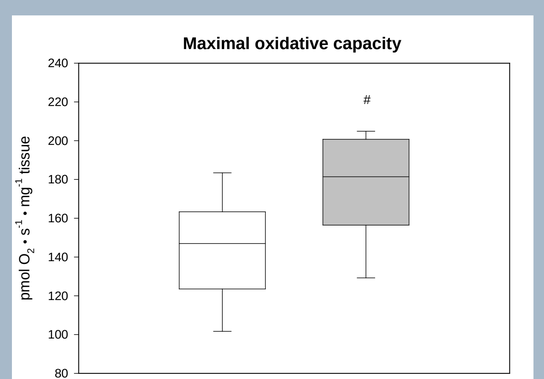






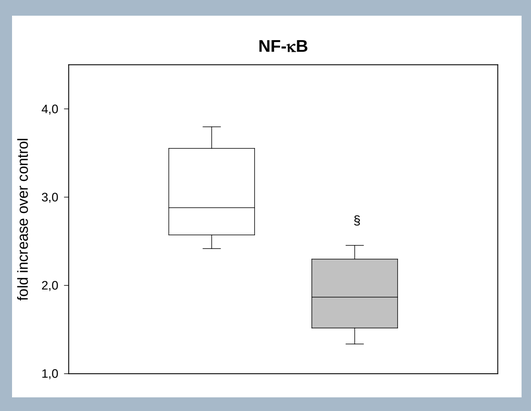
LIVER MITOCHONDRIAL ACTIVITY

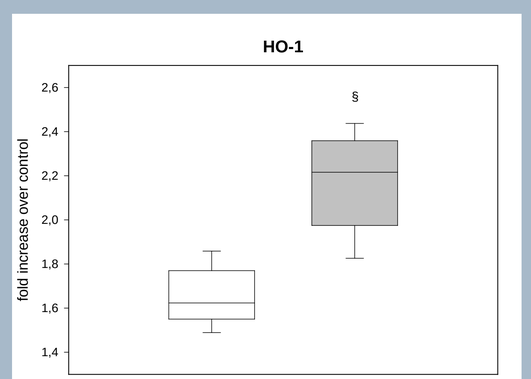




§ p=0.018 vs Vehiucle # p<0.001 vs Vehicle

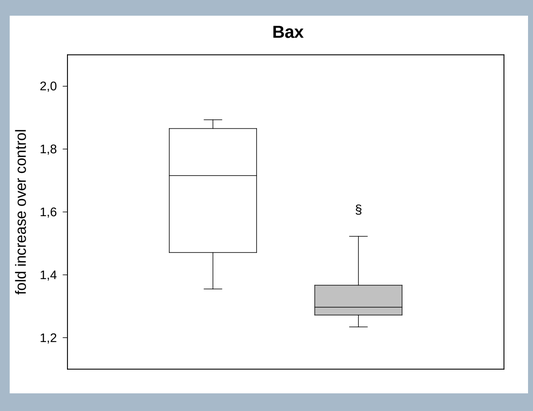
LIVER SIGNAL TRANSDUCTION

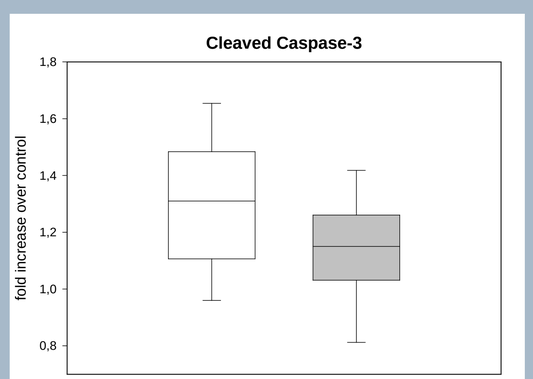




§ p<0.001 vs Vehicle

LIVER APOPTOSIS





§ p=0.001 vs Vehicle

Conclusions:

Imeglimin improved liver mitochondrial activity as well as whole body glucose utilization and gluconeogenesis, a well-established marker of liver metabolic capacity [5,6]. This was coincided with attenuated organ injury, at least in part due to diminished NF-κB activation and inhibition of the mitochondrial apoptosis pathway.

Acknowledgements:

In memoriam of ***Xavier Leverve*** who initiated this project.
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References:

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