

levels were increased. Despite exposure to contrast medium, CVC and NCM groups did not differ in terms of histopathological findings from control group. In CV group, interstitial inflammation and other histopathological findings were remarkably lower compared to the C group. MDA levels were decreased and TAS levels were significantly increased in CVC and NCM compared to the CM group. Although not statistically significant, levels of SOD increased in both group compared to CM group.

Conclusion: This study demonstrated the protective role of carvedilol and nebivolol against CIN. Antioxidant properties of these drugs may have an effect in this.

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The role of brachial artery flow mediated dilation in diagnosis of reflex syncope

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Background: The aim of the study was to determine the role of endothelial function and inappropriate peripheral vasomotion in the pathogenesis of vasovagal syncope (VVS) in young patients.

Methods: We observed 50 pts (11 men, 39 women) aged 17-40 yrs (mean age 26.6 yrs) with suspected VVS referred to head-up tilt test (HUTT), without any concomitant disorders – group I, and 30 matched healthy subjects (7 men, 23 women) aged 17-40 yrs (mean age 28.7 yrs) – group II. In all subjects endothelium-dependent flow-mediated dilation (FMD) and endothelium-independent dilation (EID) were measured in the brachial artery by ultrasonography. A baseline rest image was acquired, and blood flow was estimated by pulsed Doppler velocity measurement, then a midartery pulsed Doppler signal was obtained upon immediate cuff release to assess hyperemic velocity. After 10 min of rest next image was acquired to reflect the reestablished baseline conditions. Then a single dose (0.4 mg) of nitroglycerin (NTG) was given s.l. to determine the maximum obtainable vasodilator response as a measure of EID. Brachial artery Gosling's Doppler Pulsatility Index (PI) and Puercelot's Resistance Index (RI) were also evaluated. We estimated the changes of PI (dPI) and RI (dRI) during reactive hyperemia and after NTG administration. Standard HUTT (acc. to Westminster protocol) was performed in all pts with suspected VVS.

Results: HUTT was positive in 48 pts (96%). Mean values of FMD ($18.77 \pm 6.20\%$ vs $8.31 \pm 2.87\%$; $p < 0.0000001$) and EID ($30.04 \pm 7.51\%$ vs $22.89 \pm 6.12\%$; $p = 0.000037$) were significantly higher in gr.I than in gr.II. Significant differences of FMD and EID was observed also in pts with positive and negative HUTT. There were no differences between pts with negative HUTT and healthy controls. PI was significantly higher in gr.I at rest (11.9 ± 9.25 vs 7.67 ± 6.86 ; $p = 0.00126$) and after NTG (15.5 ± 13.93 vs 11.99 ± 14.99 ; $p = 0.007126$) than in controls. Values of dPI were higher in gr.I, both during hyperemia (9.19 ± 9.12 vs 5.11 ± 6.89 ; $p = 0.002801$) and after NTG (85.32 ± 168.13 vs 26.13 ± 48.78 ; $p = 0.002619$) than in gr.II. Values of RI and dRI did not differ between studied groups.

Conclusions: The augmented endothelial function and inappropriate profound vasodilation of peripheral arteries play an important role in pathogenesis of VVS. Higher values of FMD and EID was observed in pts with VVS and positive result of HUTT compared to negative result of HUTT and healthy subjects. Measurements of FMD, EID, PI and changes of PI seem to be helpful in diagnosis of VVS in young people.

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Single housing reduces lung hemorrhages in male mice with tissue factor disulfide mutation and protects them from lethality

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Tissue factor (TF), the key initiator of coagulation, is expressed in sub-endothelial tissue, particularly in heart, lung and brain. The extracellular allosteric disulfide bond Cys186–Cys209 of human TF shows high evolutionary conservation. In vitro experiments suggest that TF pro-coagulant activity depends on the intact Cys186–Cys209 disulfide bond. To investigate the role of this allosteric disulfide bond in vivo, we generated a C213G mutant TF mouse by replacing Cys213 of the corresponding disulfide Cys190–Cys213 in murine TF.

Homozygous C213G TF mice presented with a bleeding phenotype, affecting predominantly heart, lung, and brain. This resulted in a gender specific lethality with reduced survival especially in homozygous males. In brain and lung, the expression of C213G TF protein was about 10 fold lower, whereas expression was equal to the wildtype protein in heart. Procoagulant activity of C213G TF was reduced by about 100-fold in these organs. Between the genders, however, there was neither a difference in expression nor in activity. Homozygous female mice exhibited bleeding in lung less frequently, while bleeding in heart and brain occurred equally

frequent in males and females. At the molecular level, gene regulation patterns of C213G TF hearts and brains showed high homology between males and females, whereas patterns of gene regulation were very different in lungs of females compared to males. To test whether more aggressive behavior in male housing groups leads to higher incidence of lung bleeding we weaned 12 homozygous males to individual cages. After 100 days all males had survived and lung bleedings were reduced from 50% to 25%, suggesting fighting behavior might lead to exercise induced pulmonary hemorrhage.

These studies indicate that the allosteric Cys190–Cys213 disulfide bond is of crucial importance for proper in vivo expression and activity of murine TF. C213G TF mice suffer from a bleeding phenotype affecting heart, lung, and brain. Male mice further suffer from decreased survival and discriminate from females by a higher abundance of lung bleeding paralleled by a different pattern of pulmonary gene regulation. These findings suggest lung bleeding as the major reason for reduced survival in mice lacking the Cys190–Cys213 disulfide bond.

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Long-term treatment with melatonin may increase anticontractile activity of perivascular fat in obese mice

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Background: The anticontractile effect of perivascular adipose tissue (PVAT) is lost in obese patients due to adipocyte hypertrophy, leading to hypoxia, inflammation, and oxidative stress (Circulation 2009; 119(12):1661-1670). We recently demonstrated that the property of PVAT, partially maintained in an animal model of genetic obesity, seems to be related to the activity of BKCA channels, since is selectively blocked by iberiotoxin. We aimed to investigate functional responses of small mesenteric arteries in an animal model of genetic obesity after chronic treatment with melatonin, an endogenous hormone with antioxidant and vasculo-protective properties.

Methods: Obese mice (n=9) (B6.V-Lep ob/OlaHsd, Harlan Laboratories S.r.l.) (ob/ob) and control lean mice (n=8) (CLM) were treated with melatonin (MEL) 100 mg/kg per day for 8 weeks (from the 5th to the 13th week of age). Data were compared from untreated ob/ob (n=15) and CLM (n=10) animals. Mesenteric small resistance arteries were dissected and mounted on a wire myograph. Concentration-response to norepinephrine was evaluated in vessels with intact PVAT (WF) and in vessels in which PVAT was removed (NoF) under normoxic and hypoxic (30% 95% N2/5% CO2) conditions. Norepinephrine concentration-response curve was repeated with iberiotoxin (30' preincubation 100 nm/L).

Results: MEL significantly reduced the contractile response in NoF ob/ob and CLM vessels (ANOVA $P = 0.014$ and $p = 0.049$ respectively). The improvement after MEL was also seen in CLM NoF vessels during hypoxia (ANOVA $p < 0.05$) and following preincubation with iberiotoxin ($P < 0.05$), with no significant improvements in ob/ob. Increases in contractility following hypoxia and iberiotoxin treatment were restored by MEL in Ob/Ob WF vessels ($P = 0.013$ and $P = 0.036$ respectively), whereas MEL only rescued the effects of hypoxia ($P = 0.045$) in CLM WF arteries.

In conclusion, MEL exerts a protective effect in small vessels with and without PVAT from both ob/ob and CLM, counteracting the adverse effect of hypoxia and iberiotoxin in vessels with PVAT and in CLM vessels without PVAT. However, in Ob/Ob animals MEL rescues the effects only in the presence of PVAT indicating the importance of PVAT oxidative stress in vascular dysfunction observed in Ob/Ob animals.

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High levels of arginine, citrulline and ADMA are independent predictors of cardiovascular disease

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Purpose: Arginine is the sole nitrogen source for Nitric Oxide (NO) synthesis and citrulline is the major catabolic product of arginine. Arginine restores endothelial function in atherosclerotic patients, in whom there are elevated levels of Asymmetric Dimethylarginine (ADMA), an endogenous inhibitor of Nitric Oxide Synthase (NOS). In this study we investigated the relationships among plasma arginine levels, its catabolic end-product citrulline and the competitive inhibitor of NO biosynthesis (ADMA) and subclinical measures of atherosclerosis and as well incident Cardiovascular Disease (CVD).

Methods: We performed a matched case-control study derived from the population-based Malmö Diet and Cancer Cardiovascular Cohort (MDC-CC), all included subjects were without history of CVD at baseline. During 12 years of follow-up, 253 individuals had a CVD event and were matched for age, sex and