cell lines, as well as from controls. So far, we could not observe any obvious differences between the cardiomyocytes of the three cell lines. Current efforts are directed at analyzing changes in the protein quality control system by performing biochemical and immunofluorescence analyses and to apply mechanical stress by electrostimulation. In addition, we will also focus on the integrity of sarcomeres and Z-disks after pharmacological inhibition of autophagy or the proteasome. Thus, we hope that the hiPSC lines will provide better insight into the disease pathomechanisms and hence enable to design strategies for the development of new experimental therapies for BAG3^{P209L}-related myofibrillar myopathy.

B 08-42

Heterogeneity of aortic endothelial cells in healthy C57BL/6 mice

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The author has objected to a publication of the abstract.

B 08-43

Alteration of MiRNAs profiling on experimental model of chronic anthracycline-induced cardiomyopathy

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Introduction

MicroRNAs are small, non-coding RNA molecules involved in regulation and fine-tuning of gene expression. The present study aims to determine changes in miRNAs on the well-established experimental model of chronic anthracycline (ANT) cardiotoxicity at two distinct stages of cardiotoxicity development.

Methods

Cardiotoxicity was induced in rabbits treated with daunorubicin (DAU, 3 mg/kg, weekly; for 5 and 10 weeks) and compared with the control (saline in the same schedule). The 1st analysis was done after the five DAU cycles (cumulative dose ~250 mg/m^2) when we found first signs of cardiotoxicity, i.e., significantly increased levels of plasma cardiac troponin T (cTnT 0.018±0.003 µg/L vs. 0.006±0.001 µg/L; p< 0.001), but yet without any change in LV systolic function. The 2nd analysis was performed after the ten DAU cycles (cumulative dose ~500 mg/m^2) which induced significant LV systolic dysfunction (FS 41.2 ± 0.4 % vs 29.0 ± 2.9 %; p<0.001 and dP/dt$_{max}$ 8714 ± 275vs 5341 ± 499 mm Hg; p<0.001) and typical histopathological hallmarks of chronic ANT cardiotoxicity.

Results

Based on results obtained from TaqMan® Advanced miRNA Human A and B Cards we selected 32 miRNAs for confirmation by Real-time PCR with specific assays (TaqMan® Advanced miRNA Assay systems). After 5 weeks, 10 miRNAs were significantly up-regulated: miR-let-7f-2-3p (p<0.05), miR-20b-5p (p<0.05), miR-21-3p (p<0.05), miR-21-5p (p<0.05), miR-34a-3p (p<0.001), miR-34a-5p (p<0.001), miR-34c-5p (p<0.01), miR-142-3p (p<0.05), miR-155-5p (p<0.001) with dominant change in miR-1298-5p (29-fold change, p<0.01) . miR-34a-5p and miR-21 were related to p53-mediated DNA damage signalling. After 10 weeks only miR-504-3p (p<0.01) was significantly down-regulated and 11 of miRNAs were significantly up-regulated: miR-21-3p (p<0.01), miR-21-5p (p<0.001), miR-34a-3p (p<0.01), miR-34a-5p (p<0.001), miR-34c-5p (p<0.001), miR-142-3p (p<0.01), miR-155-5p (p<0.001), miR-223 (p<0.001), miR-433-3p (p<0.05), miR-1298-5p (p<0.001) with the dominant change in 34a-5p (76-fold change). Most of miRNAs measured after 10 weeks of the treatment very significantly positively correlated with cTnT and negatively with parameters of systolic dysfunction (LVFS and dP/dt$_{max}$). The best correlation has been achieved between miR-21-5p and LVFS and dP/dt$_{max}$, respectively and (-0.959; p<0.001, resp. -0.890; p<0.001) and miR-223-3p (-0.911; p<0.001; resp.- 0.803; p<0.001), which are probably involved in the alteration of cross-bridge cycling and fibrosis.

Conclusion

To our knowledge, this is the first study describing the changes of miRNAs profile in chronic ANT cardiotoxicity with precisely defined stages of cardiomyopathy development.

B 08-45

Effects of choline and CDP-choline on heart rate variability and total choline levels in rats.

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Introduction

Heart rate variability (HRV) is a measure of the variation of the time distance between two consecutive heartbeats which reflects autonomic nervous system function along with the relative contributions of sympathetic and parasympathetic nervous systems (PNS) (1). Choline and CDP-choline modulate autonomic functions by increasing acetylcholine synthesis and cholinergic neurotransmissions (2). This study aims to evaluate the possible effects of cholinergic system-acting drugs; choline and CDP-choline on HRV parameters.

Methods

The experimental study was approved by the local Ethics Committee for Animal Experimentations and experiments have been carried out in accordance with the Declaration of Helsinki. 12-16 weeks old Wistar male rats were anesthetized with Ketamine (75 mg/kg) and Xylazine (10 mg/kg) combination and randomized into three groups (each n=8): 1. Control (1 ml Saline), 2. Choline (100

mg/kg), 3. CDP-choline (400 mg/kg). 0.9% Saline, Choline, and CDP-choline were applied intraperitoneally. After the drug administration, electrocardiography (ECG) recordings were obtained for 45 minutes. After detecting R waves with the Pan-Tompkins algorithm, the tachogram of RR intervals was generated and frequency domain HRV analyses were performed. After the ECG recordings animals were sacrificed with cervical dislocation. Total choline/acetylcholine levels in blood and heart tissues of experimental groups were measured by a commercially available kit according to the manufacturer's instructions by spectrophotometer (3). One-way analysis of variance (ANOVA) with Tukey test for multiple comparison tests was used for statistical analysis. $p<0.05$ was accepted significant.

Results

Power of high frequency (HF) and total power (TP) was significantly increased in both choline and CDP-choline groups within 15 minutes. Heart rate, Power of low frequency (LF) significantly decreased in the choline treated group whereas the power of very low frequency (VLF) significantly decreased in the CDP-choline treated group. LF/HF ratio significantly decreased by the choline treatment within 15 minutes whereas significant changes were obtained for CDP-choline within 45 minutes (Fig 1). Total choline/acetylcholine levels significantly increased in serum and heart tissues of choline and CDP-choline treated animals compared to control (Fig 2). The level was significantly higher in the choline group compared to both CDP-choline and the control groups.

Conclusion

Our HRV analysis results suggested parasympathomimetic activation by choline and CDP-choline treatments by increasing HF and TP and decreasing LF/HF. Parallelly, increased total choline/acetylcholine levels in both serum and heart tissues also showed increased parasympathomimetic activation. Furthermore, our data suggest a more rapid response on HRV parameters by choline treatment compared to CDP-choline which is supported by the significant difference in total choline acetylcholine levels in tissues.

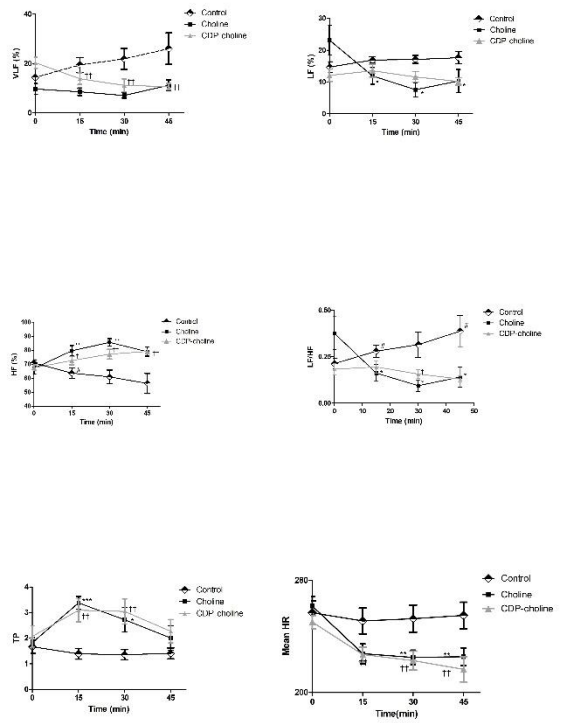

Figure 1
HRV parameters in control, choline and CPD-choline groups.

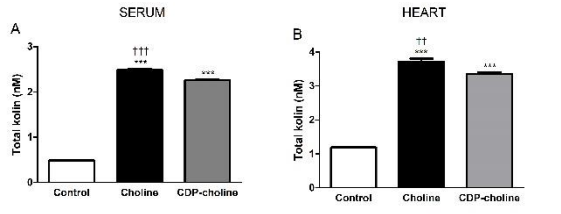

Figure 2
Total choline levels in control, choline and CPD-choline groups in serum and heart tissues.

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B 08-46

Characterisation of carotid body mitochondrial function in healthy and heart failure sheep.

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Carotid bodies (CBs) are the main peripheral oxygen sensors implicated in the progression of many diseases, including heart failure (HF) [1]. In HF, CB function is enhanced and contributes to the sympathetic overdrive [2]. While CBs are an attractive target for future therapies, therapeutic development has been limited due to a lack of full understanding of the CB oxygen sensing mechanism in health and HF. Previous reports showed that elevated reactive oxygen species (ROS) contribute to altering the oxygen chemotransduction cascade in HF [3]. However, the effects on CB mitochondrial function have not been investigated. Investigating mitochondrial function is important as it has been hypothesised that the unusually low oxygen affinity of cytochrome c oxidase (complex IV) and mitochondrial ROS (mitoROS) may play an important role in the CB oxygen sensing mechanism [4]. However, these assumptions have not been validated by measurements of electron transport chain (ETC) function and mitoROS production in the CB. This study therefore sought to describe the ETC function, mitoROS production and oxygen affinity of complex IV in control and HF CB.

Tissue homogenates were prepared using CB and left ventricle from control and tachypaced HF sheep [5]. High-resolution respirometry was used to measure mitochondrial oxygen consumption and H_20_2 production by using substrate-uncoupler-inhibitor titration protocols (normalised to citrate synthase activity), as well as the kinetics of mitochondrial oxygen affinity. A citrate synthase assay was used to estimate mitochondrial content in each homogenate sample. Additionally, the protein abundance of mitochondrial complexes per total protein was measured by Western blot.

CB mitochondria have a low aerobic capacity and a high complex IV oxygen affinity compared to the heart. H_2O_2 production rate was comparable between tissues. Mitochondrial oxygen consumption was statistically increased during leak respiration with complex I substates in HF CBs. Surprisingly, the rate of H_20_2 production was comparable between control and HF CB. Furthermore, oxygen affinity of CB complex IV was not affected by HF. Protein abundance of mitochondrial complexes and citrate synthase activity in control and HF CBs remained unchanged.

These results suggest that the CB mitochondrial function is altered in HF. An increase in leak respiration indicate that mitochondria are less efficient at producing ATP. The lack of an increase in H_20_2 production rate by CB mitochondria suggests that the increase in ROS levels observed in HF CBs may originate from non-mitochondrial sources. Provided that there was no change in complex IV oxygen affinity, there is a potential that the oxygen sensing mechanism was affected by extra-mitochondrial factors. However, these studies will have to be repeated in intact isolated glomus (sensory) cells to ensure that results were not influenced by the presence of other cell populations in the homogenate preparation.

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B 08-47

Cardiovascular effects of vitamin C on chloroquine induced cardiovascular dysfunction

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Introduction

Due to COVID19, two most commonly used drugs that are affordable and available off the counter in West Africa include Chloroquine (CQ) and Vitamin C. The World Health Organization has warned against the unorthodox use of CQ because of its possible cardiotoxic side effects. Thus modeling chloroquine cardiovascular dysfunction was of interest and how vitamin C affects cardiovascular function in this model was determined.

Methods

Male adults albino Wister rats (32) weighing between 180-200 g were randomly divided into four groups (n=7). Animal experimentation lasted for 7 days. Group 1 animals served as control group and were untreated. Group 2-4 animals were orally administered with CQ (970mg/Kg) on day 1. Groups 3 and 4 were daily administered with vitamin C 200 and 1000 mg/kg respectively. Cardiovascular, biochemical, histological and molecular parameters were determined at the end of the study.

Results

Chloroquine altered cardiovascular function evident by elevated blood pressure, cardiac arrhythmia, increased cardiac oxidative stress, alter cardiac histo-architecture and increased CnTI expression. Vitamins C especially at the higher dose of 1000 mg/Kg significantly mitigated these alterations which was associated with altered HDAC3 expressions when compared with control.