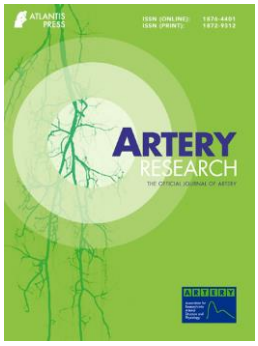

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P10.06: ABNORMAL VASCULAR PROGRAMMING OF ACID ARACHIDONIC METABOLISM COULD EXPLAIN HYPERTENSION IN RATS EXPOSED IN UTERO TO MATERNAL DIABETES

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Objective: to test whether $1,25(OH)_2D_3$ (active vitamin D) modifies contractility of proximal resistance vessels, dose-dependently.
Methods: Male Wistar rat mesenteric arteries were investigated by wire myography. 60 mM High Potassium Physiological Salt Solution (KPSS) was the reference for contraction and relaxation measurements. Noradrenaline (NA) responses were measured after 10 min, 30 min and 3 hours incubation with $1,25(OH)_2D_3$, as was endothelial function by Acetylcholine (Ach) response.
Results: KPSS-induced contraction was unaffected by $1,25(OH)_2D_3$, but slightly decreased after 3 h incubation in control and $1,25(OH)_2D_3$ groups (generally $n = 5$ arteries each). After 10 min NA-induced contraction at 10^{-5} M, a small dose response occurred (controls 192±22%; vitD 10 nM 183%, 100 nM 169%), but after 3 h incubation with 100 nM $1,25(OH)_2D_3$, contraction decreased at $3x10^{-6}$, and at 10^{-5} M NA to 118.6±10.3%, compared with controls (mean± SE: 145.4 ±13.9%). While differences were individually 'significant' ($p = 0.04$, Wilcoxon test), 2-way ANOVA demonstrated clear vitD ($F_{3,80}$ 6.3, $p = 0.001$) and NA effects ($F_{4,80}$ $p < 0.000$), without interaction. Ach-induced *relaxation* (at 10^{-9} to 10^{-5} M) after 30 min incubation was not enhanced by any 1,25(OH)2D3 dose. After 3 h, higher concentration Ach (10^{-6}, 10^{-5} M) induced constriction. Paradoxically, 100 nM $1,25(OH)_2D_3$ marginally *increased* contractions (105.2±4.8%; control 91.7+4.7%), not individually 'significant' but by 2-way Anova, both vitD & Ach dose effects were ($F_{3,78} = 6.6$, $p < 0.001$).
Conclusion: To our knowledge, these are the first vitD experiments on proximal resistance vessels. 100 nM vitamin D may decrease NA-induced contraction but paradoxical endothelial effects may underlie its variable in-vivo actions.

P10.05
REDUCED MOLECULAR FLEXIBILITY IN THE LARGE ARTERIES OF DIABETIC RATS

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In Type 1 and 2 diabetes tissue stiffening is evident from measurements of the gross mechanical properties of the vasculature. In general, pathological glycosylation of extracellular matrix proteins may play an important role in increasing stiffness in diabetic patients. However, the effects of diabetes on individual elastic fibre components remain poorly defined.
Fibrillin microfibrils, a key elastic fibre component, have a 'beads-on-a-string' structure with a periodicity of approximately 56 nm. We tested for possible disruption due to diabetes in fibrillin microfibrils isolated from rat aorta. Diabetes was induced in 250 g adult Wistar rats by streptozotocin (STZ) injection (55 mg/kg) and were sacrificed 8 weeks later along with age-matched controls. At sacrifice, the STZ-treated rats had severe hyperglycaemia (+/- 28 mmol/l). Fibrillin microfibrils were isolated and purified by well-established bacterial collagenase digestion and size-exclusion chromatography prior to imaging with atomic force microscopy.
Initial experiments show that fibrillin microfibril periodicity is reduced following STZ treatment; 52.0 +/- 0.4 nm (STZ) vs 56.9 +/- 0.4 nm (Control), $n = 600$ periodicity measurements, 2 animals per group), ($p < 0.01$). In young, healthy tissues the structure of fibrillin microfibrils is stabilised by both intra- and inter-chain disulphide bonds and by transglutaminase cross-links which permit reversible extension *in vivo*. These observations suggest that the formation of pathological cross-links may limit microfibril elasticity and hence play an important role in increasing the stiffness of the diabetic vasculature.

P10.06
ABNORMAL VASCULAR PROGRAMMING OF ACID ARACHIDONIC METABOLISM COULD EXPLAIN HYPERTENSION IN RATS EXPOSED IN UTERO TO MATERNAL DIABETES

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Epidemiologic studies have clearly demonstrated that cardiovascular risk is not only determined by conventional risk factors of importance in adult life, but also by early life events resulting of re-settings of key physiological functions. In our model of rats exposed *in utero* to maternal diabetes, we previously identified a specific gene expression profile of the thoracic aorta at a pre-hypertensive stage (3 months) in favour of vasoconstriction, which could explain the development of hypertension in the adult offsprings. We found an increase of CYP4f2 (however we failed to confirm its up-regulation at the protein level), and a decrease by 50 percent of the prostacyclin (IP) receptor at messenger and protein levels in aorta of rats exposed to maternal diabetes (DMO) compared to rats from control mothers (CMO). We demonstrated the functional implication of this down-expression of the IP receptor in a pharmacological study using a prostacyclin analogue: Iloprost (iv, 4 ng/kg/ml). Indeed, we showed that, even before the onset of hypertension, SBP reduction in response to Iloprost was attenuated in DMO rats (-10.7% vs -21.3% in CMO, $p < 0.05$). In parallel, we studied vascular reactivity and myogenic response of carotid and mesenteric arteries of 18-months-old CMO and DMO. At this later stage, we found similar results, i.e. vasodilation in response to Beraprost was reduced in DMO, and myogenic response was increased.
In this study, we clearly demonstrated a fetal programming of the vessels, which could explain the development of hypertension and a re-setting of physiological functions in adult rats exposed to maternal diabetes.

P10.07
A PPG MEASUREMENT SETUP AND PULSE WAVE ANALYSIS FOR ARTERIAL STIFFNESS

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The light energy absorption of whole blood in the visible and infrared range is partly caused by the oxidized and reduced haemoglobin. The measurement principle can be applied for photoplethysmography (PPG). Our PPG measures the blood flux in human vessels with means of red and infrared light absorption. The absorption of light varies with the oxygen concentration and amount of blood in vessels. The PPG device has phase sensitive detection electronics which proved to be a good solution for the measurement of small absorption signals simultaneously at two different wavelengths, 660 and 940 nm. In practice, the PPG waveforms, called pulse waves, can be rapidly and simply acquired by a PIN photodiode which measures the transmission of red and infra-red LED light through the forefinger and the second toe simultaneously. The waveforms are characteristics for the young person but different for the elderly person. The four template waveforms are in the consideration for waveform analysis and we get the accurate results enough. The PPG amplitude can increase and decrease caused by the autonomic fluctuation. In the wave analysis, the first wave is called a percussion wave, the second is called tidal wave, and the third is a dicrotic. The PPG measurements may provide cheap, simple and accurate methods of diagnosing arterial and, especially vascular diseases. Moreover, further development of the theoretical model that correlates the waveform of the detected finger tip wave caused by heartbeat oscillations and the hemodynamic parameters could improve the accuracy of the method and potentially lead to a better quantification of the measured parameters used for arterial stiffness.

P10.08
PULMONARY ARTERY CALCIFICATION IN RACEHORSES

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Vascular calcification (VC) has been sporadically reported in horses, but little is known regarding cause, pathogenesis and clinical significance.
We hypothesized that in horses, structural and molecular changes may occur during VC that are comparable to human and mouse models. We surveyed Thoroughbred and Standardbred racehorses ($n = 101$) for the prevalence, distribution and severity of VC. Histopathological, ultrastructural imaging and energy dispersive X-ray elemental analyses were used to examine the lesions. Immunohistochemistry for cell markers (smooth muscle α-actin, SM22α and Sox9) was performed in selected samples from control ($n = 10$), mildly ($n = 10$), and severely ($n = 10$) calcified arteries.
Results showed that calcification of the tunica media of mainly the pulmonary artery branches, was present in 82% of horses, and both breeds and genders were similarly affected. Lesions appeared as white-to-yellowish, hard, gritty plaques of variable size. Microscopically, elastic fibers were thin, fragmented and calcified, and surrounded by dense collagen matrix, as described for Mönckeberg sclerosis. Elemental analysis of the calcified areas was consistent with hydroxyapatite mineral.
No immunoreactivity for the smooth muscle cell markers, smooth muscle α-actin and SM22α was observed in cells found at the calcification site. Many of these cells had a chondrocytic phenotype appearance and showed immunoreactivity for Sox9, a chondrocyte marker.
Arterial calcification in horses share histopathological features with arterial medial calcification in humans and may result in similar physiological abnormalities such as vascular stiffness. The occurrence of VC in young racing horses indicates the need to investigate its pathogenesis and potential clinical implications.