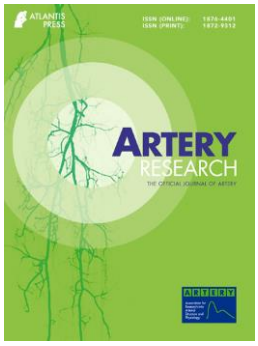

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5.5: AGE-DEPENDENT TELOMERE ATTRITION, SHORT TELOMERES AND ATHEROSCLEROSIS

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Methods: We studied 561 (50% male) normotensive and hypertensive subjects without kidney or other cardiovascular diseases or antihypertensive treatment. Supine and upright hemodynamics were recorded using continuous pulse wave analysis, whole body impedance cardiography and heart rate variability analysis. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI cystatin C equation.
Results: Mean eGFR was 99 (range 53-152) ml/min/1.73 m^2 and one third of the patients had values below 90. After adjustments for age, sex, body mass index and low density lipoprotein cholesterol level, regression analysis indicated significant associations between lower eGFR and higher systolic ($p<0.001$) and diastolic blood pressure ($p<0.001$) and systemic vascular resistance ($p=0.001$) regardless of body position. Lower eGFR was associated with higher low frequency to high frequency ratio of heart rate variability in supine but not in upright position. The level of eGFR was not associated with the level of cardiac output.
Conclusions: Even mild kidney impairment is associated with higher systemic vascular resistance and increased supine sympathovagal balance. However, changes in autonomic tone, as based on analysis of heart rate variability, do not seem to explain the relation between lower eGFR and higher systemic vascular resistance in the upright position. The close relationship between the regulation of GFR and systemic vascular resistance may play a role in the pathogenesis of primary hypertension.

5.2
AN ASSOCIATED WITH FAMILIAL HEMIPLEGIC MIGRAINE TYPE 2 MUTATION IN THE ALPHA-2 ISOFORM NA,K-ATPASE DISTURBS VASCULAR RESPONSES IN MOUSE BRAIN

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Objectives: Migraine attack is associated with severe changes in brain perfusion vasoconstriction-induced hypoxemia during aura and rebound vasodilation in subsequent headache. Familial Hemiplegic Migraine Type 2 is associated with point mutations (including G301R) in the $\alpha 2$ isoform Na,K-ATPase. Heterozygote mice bearing G301R mutation (FHM2) were recently characterized for several behavioral and neuronal abnormalities.
Methods: Vascular function of wild type (WT) and FHM2 mice was compared in vivo (telemetry and Laser Speckle measurements of brain perfusion), in vitro (myography) and in situ (changes in astrocytic $[Ca^{2+}]_i$and parenchymal arteriole diameter in brain slices to electric field stimulation (EFS)).
Results: Vascular abnormalities were shown for cerebral circulation while only minor or no significant changes were found in peripheral arteries. Accordingly, no difference in blood pressure was seen under resting conditions. Middle cerebral artery from FHM2 mice had large inner diameter and constricted stronger to U46619, endothelin and K^+-depolarization. This was associated with increased depolarization and Src-kinase-dependent sensitization to $[Ca^{2+}]_i$.
Isolated cerebral arteries from FHM2 mice have exaggerated relaxation to elevated $[K^+]_{out}$(4-12mM) due to increased role of the inward-rectifying K^+channels. Repeated EFS (>3 times) reduced the $[Ca^{2+}]_i$responses in astrocytic endfeet and increased relaxation of parenchymal arterioles in the FHM2 in comparison with WT. Flow responses to whiskers stimulation were also potentiated in FHM2 mice.
Conclusions: A knock-out mutation of the $\alpha 2$ Na,K-ATPase leads to both elevated contractility and increased relaxation of cerebral arteries. These dysfunctions could affect the blood supply to active neurons and thus disturb neurovascular coupling.

5.3
REVERSIBILITY OF ARTERIAL STIFFNESS AFTER KIDNEY TRANSPLANTATION: SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Chronic kidney disease is associated with increased arterial stiffness. Correction of the uremic milieu by kidney transplantation (KTx) may be improve arterial stiffness. However, results from clinical studies are not uniformly convincing. This could be related to small sample size of studies, heterogeneity in methods and timing of assessment of arterial stiffness after KTx. We aim to measure the reversibility of arterial stiffness after KTx.
Design and Method: Observational studies and randomized controlled trials with measurements of pulse wave velocity (PWV), pulse pressure (PP) and/or augmentation index (AIx) were extracted from MEDLINE, EMBASE, COCHRANE LIBRARY, and Web of Science from their inception to January 2016. Two reviewers independently identified eligible studies comparing PW, PP and/or AIx pre to post KTx and extracted data including population characteristics, interventions and outcomes.
Results: 13 studies of 981 met our inclusion criteria. 11 Studies (408 renal transplant) have been included in meta-analysis. There was a standard mean change of PWV by -0.45 (95% CI: - 0.68 -0.20, $I^2=58\%$) post-KTx. Both studies using aortic PWV (5 studies, 160 patients) and those using brachial-ankle PWV, showed a significant decrease of PWV by -1.58 m/s (95% CI: -2.97 - 0.19, $I^2= 87\%$) and by -1.21 m/s (95% CI: - 1.89 — 0.54, $I^2=0$ %) post-KTx, respectively. Analysis of central PP and AIx showed significant reduction post-KTx by -4.77 (95% CI: -9.19 -0.35, I2=55%) and by -11.59 (95% CI:-15.64 -7.53, I2=43%), respectively. Only two studies have reported adjusted parameters for mean arterial pressure.
Conclusions: There is a significant reduction in PWV, central PP and AIx after KTx. Heterogeneity among studies are globally moderate. Further analysis is required to examine the importance of changes in different vascular beds taking into account changes in blood pressure.

5.4
HIGH PWV IS ASSOCIATED WITH NANO-SCALE CHANGES IN THE MEDIAL LAYER OF THE INTERNAL MAMMARY ARTERY

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Background: Arterial stiffening occurs as part of the natural ageing process. Degradation of the extracellular matrix (ECM) in the medial layer is typically implicated in arterial stiffening. However, little is known about how localised changes in arteries in terms of both structure and mechanical properties contribute to the overall stiffening of arteries.
Aim: To determine localised differences in the nano-structure and mechanical properties in the medial layer of internal mammary arteries (IMA) in patients with high and low pulse wave velocity (PWV).
Methods: IMAs were collected form coronary bypass operations from 7 patients with high (13.8 3.3 m/s) and 7 patients with low (8.6 0.7 m/s) PWV. The samples were cryo-sectioned to a nominal thickness of 5 μm for atomic force microscopy (AFM) measurement. All the samples were tested hydrated. Histological analysis was used to determine collagen and elastin content. Data are presented as means SEMs.
Results: The medial layers of IMAs in the high PWV group were significant stiffer than in the low PWV group (Low 228.4 15.6 kPa, High 735.8 108.8 kPa,) ($p < 0.0001$). Topographical features as visualised with AFM were similar in both groups but the higher nanomechanical stiffness was found to correlate with histological data.
Conclusions: Nanomechanical properties of the medial layer in the IMA associate with PWV data. Changes in composition in the ECM drive the profound localized changes in tissue stiffness.

5.5
AGE-DEPENDENT TELOMERE ATTRITION, SHORT TELOMERES AND ATHEROSCLEROSIS

Dr Simon Toupance [1], Dr Anna Kearney-Schwartz [2], Dr Mohamed Temmar [3], Mrs Cécile Lakomy [1], Mr Carlos Labat [1], Professor Patrick Rossignol [4], Professor Faiez Zannad [4], Dr Patrick Lacolley [1], Professor Abraham Aviv [5], Professor Athanase Benetos [2]
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Background: Short leukocyte telomere length (LTL) is associated with atherosclerosis. The prevailing view is this association exists since LTL is a biomarker of cumulative inflammation and oxidative stress during adult life. However recent studies show that LTL in adults is defined

mainly by LTL at birth and attrition during childhood. Therefore we can suggest that short LTL might precede clinical expression of atherosclerosis.
Objectives: To examine the directionality in the relation between carotid atheroma and LTL dynamics.
Methods: LTL was measured by TRF in samples donated 9 years apart on average by 257 men and women aged 41 to 80 at the inclusion.
Results: LTL attrition during follow-up (FU) period was 25±17 bp/year. No relation was observed between LTL attrition and presence of carotid atherosclerotic plaques (PCAP). Baseline (BL)-LTL was highly correlated ($r=0.96$, $p<0.0001$) with FU-LTL. In 87.9%of the subjects LTL ranking by deciles was the same 1 decile at BL and FU. BL- and FU-LTL were inversely associated with PCAP ($p<0.01$). After adjusting for age and gender, BL-LTL was 6.50±0.04 Kb in subjects without PCAP 6.46±0.06 in those with PCAP only at the FU visit and 6.27±0.06 in those with PCAP in both BL and FU visits ($p=0.027$). LTL attrition was the same in these groups.
Conclusions: LTL attrition in adulthood is not influenced by PCAP and does not play a significant role in LTL ranking. By contrast, patients with shorter telomeres present CAP earlier in life. Telomere length could be considered as a bio-determinant for atherosclerosis.

5.6
CARDIOVASCULAR CONSEQUENCES OF EXTREME PREMATURITY: A FOLLOW-UP FROM THE EPICURE STUDY

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Background: Long-term outcomes following extremely preterm (EP) birth are becoming increasingly relevant, given improved survival rates. We previously reported altered arterial haemodynamics in 11 year olds who were <25 weeks gestation. The same individuals have now been re-evaluated in young adulthood.
Methods: EP subjects ($n=130$) and term-born matched controls ($n=64$) were seen at age 19 years for detailed hemodynamic assessments including blood pressure (BP), augmentation index (AIx), aortic pulse wave velocity (aPWV), cardiac output (CO) and peripheral vascular resistance (PVR). All subjects were drawn from the UK 1995 EPICure Study cohort.
Results: Brachial diastolic and mean BP was higher in EP versus controls ($P<0.01$ for both). Similar to findings at 11 years, AIx was significantly higher in EP subjects (mean difference 6.1% 95% CI 3.4-8.7%, $P<0.001$) whereas aPWV was not different. Cardiac index was similar between groups, but stroke volume index was lower and heart rate higher in EP ($P<0.05$ for both). PVR was also significantly higher in EP (mean difference 96 dynes.sec.cm5, 95% CI 27-165 dynes.sec.cm5, $P<0.001$).
Conclusions: There remains no difference between groups in aPWV from age 11 years into young adulthood, but significant differences in AIx have persisted from childhood and are associated with significantly elevated PVR. These findings suggest abnormalities in the resistance vasculature, which may be structural or functional in origin. Long-term monitoring of cardiovascular risk is recommended in this population.