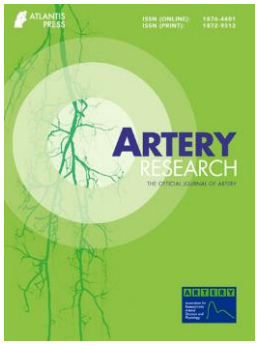

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# P4.30: ENDOTHELIAL DYSFUNCTION AND CARDIOVASCULAR RISK PROFILE IN PATIENTS WITH CHRONIC HEPATITIS C VIRUS INFECTION

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different stages of renal insufficiency (n=103, 64.8±13.3 years, 50 males, eGFR 40±21 mL/min/1.73m$^2$). Univariate and multiple linear regression models were used for the statistical analysis.
According to our results, logFGF23 showed significant relation with serum phosphate, PTH levels and renal function. There were no significant correlations between FGF23 and PWV or CPP. AI, however, correlated negatively with logFGF23 (r= -0.24, p<0.05). By multiple regressions, serum phosphate, logFGF23, systolic blood pressure and heart rate proved to be the individual predictors of AI. ($R^2$=0.31, ß=0.31, -0.33, 0.21, -0.27, p<0.05). In the subgroup of patients with <45 mL/min/1.73m$^2$ eGFR, serum phosphate and logFGF23 remained the significant predictors ($R^2$ 0.21, ß=0.31, -0.39, p<0.05)
FGF23 may be a determinant of peripheral arterial elasticity independently of serum phosphate level especially in advanced stages of chronic kidney disease.
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### P4.27
### DIABETES-EVOKED PATHOGENIC CHANGES ASSOCIATED WITH ALTERED COPPER UPTAKE/TRANSPORT PATHWAYS IN THE AORTA OF STZ-DIABETIC RATS: EFFECTS OF TREATMENT BY CU(II)-SELECTIVE CHELATION

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**Objectives**: Cardiovascular disease is the commonest complication of diabetes. Previous studies from our group have identified diabetes-evoked changes in copper homeostasis that cause accumulation of chelatable-Cu(II) in the heart (1). We also showed that treatment by Cu(II)-selective chelation with TETA (triethylenetetramine) ameliorates cardiac left-ventricular/aortic damage in diabetes (2). This study aimed to define the pathogenic role of copper imbalance in diabetic arteriopathy and its response to TETA.
**Methods**: Pathological changes in the aorta of STZ-diabetic rats with/without TETA treatment were examined by histological and confocal imaging. Expression of genes and proteins involved in regulation of copper uptake/transport in aortic tissues were analysed by RT-qPCR and Western blotting.
**Results**: Diabetes-induced oxidative aortic damage was associated with increased expression of ET-1, ET-A, ICAM1 and eNOS, and decreased expression of Ctr1 (cell-membrane copper-uptake transporter-1) and Sco1 (copper-chaperone 1 for cytochrome c oxidase). We also identified up-regulation of CCS (copper chaperone for SOD1) and copper-binding metallothioneins (MT1/2) as further compensatory responses apparently aimed at up-regulating copper-related defences in response to altered aortic copper regulation in diabetes. TETA treatment further elevated MT1/2 levels. Moreover, diabetes lowered levels/activity of SOD2, both of which were restored by TETA treatment.
**Conclusions**: Dysregulation of cellular copper uptake/transport might be an important molecular process contributing to the pathogenesis of diabetic arteriopathy, and TETA treatment could be beneficial by restoring of these acquired defects, at least in part via activation of MT1/2 which are potent antioxidants, and SOD2, the main antioxidant enzyme that scavenges intra-mitochondrial superoxide radical.
References
(1) Cooper et al (2004) Diabetes. 53, 2501-2508.
(2) Gong et al (2006) Mol Pharmacol. 70, 2045-2051.

### P4.28
### GLYCAEMIC HOMEOSTASIS, ARTERIAL STIFFNESS AND DIASTOLIC FUNCTION IN HEALTHY SUBJECTS

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**Objectives**: To examine the impact of glycaemic homeostasis on arterial stiffness and cardiac diastolic function in healthy subjects.
**Methods**: Subjects (100 male & 115 female) were normotensive and normolipidaemic and had normal oral glucose tolerance test responses. Carotid-femoral arterial stiffness (PWV) and atherosclerotic risk (carotid intima media thickness; CIMT) were measured. Early/late mitral valve filling velocity (MV E/A) and isovolumetric relaxation time (IVRT) was used to assess diastolic function. Glycosylated haemoglobin ($HbA_{1c}$) was used to determine long-term glycaemic homeostasis. Anthropometrical measurements such as height, body mass and waist circumference were also measured.
**Results**: Spearman's correlation identified significant association between $HbA_{1c}$ and age (r=0.40, P<0.0001), waist height ratio (r=0.18, P<0.01), PWV (r=0.26, P<0.001), CIMT (r=0.18, P<0.05), MV E/A (r=-0.37, P<0.0001) and IVRT (r=0.28, P<0.01). In multiple regression analysis's age remained the only independent predictor of PWV, CIMT, MV E/A and IVRT.
**Conclusion**: Despite being clinically healthy, $HbA_{1c}$ is associated with greater arterial stiffness and poor diastolic function.

### P4.29
### COMPARATIVE EFFECTS OF ANTIHYPERTENSIVE DRUGS ON OXIDATIVE STRESS AND INFLAMMATION

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**Objective**: Oxidative stress and vascular inflammation are increased in hypertension. These factors may contribute to target organ damage and increased cardiovascular risk in these patients. We studied the effect of four classes of antihypertensive drugs on oxidative stress and inflammatory markers in patients with essential hypertension.
**Design and method**: In this double-blind placebo-controlled crossover study we randomized 41 treatment-naïve hypertensive patients to receive doxazosin 4 mg, candesartan 16 mg , bisoprolol 5 mg, isosorbide mononitrate 50 mg, and placebo daily for 6 weeks. Brachial blood pressure (BP), plasma high sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), asymmetric dimethylarginine (ADMA), oxidized LDL (oxLDL), soluble intercellular adhesion molecule-1 (sICAM-1), oxLDL antibodies (OLAB), and urine 8-isoprostanes were measured after each treatment period.
**Results**: All drugs reduced systolic, diastolic, and mean arterial pressure (p<0.001) with candesartan having the greatest effect. None of the drugs reduced inflammatory or oxidative stress markers compared to placebo. There were significant differences in between-drug analysis. Doxazosin reduced OLAB and oxLDL levels the most (p<0.05). With bisoprolol there was a trend for hsCRP and ADMA level increase compared to other drugs (p<0.01). There were no differences regarding drug effects on sICAM-1, IL-6, or 8-isoprostane levels. Changes in oxLDL and to lesser degree hsCRP and sICAM-1 levels correlated with change in BP with study drugs.
**Conclusions**: In our study an alpha-blocker seemed to have the most favorable effect on oxidative stress and inflammatory markers while a beta-blocker had least effect. These effects are partially dependent on the BP-lowering effects of the drugs.

### P4.30
### ENDOTHELIAL DYSFUNCTION AND CARDIOVASCULAR RISK PROFILE IN PATIENTS WITH CHRONIC HEPATITIS C VIRUS INFECTION

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**Background/aims**: The impact of chronic hepatitis C (HCV) virus infection on atherosclerosis is controversial. In this pilot clinical study, we examined whether HCV patients significantly differed in markers of subclinical atherosclerosis compared to patients with alcohol-related chronic liver disease.
**Methods**: We enrolled 21 consecutive adult patients with HCV and 11 patients with alcohol-related chronic liver disease after detoxification from alcohol. Common carotid intima-media thickness (CIMT) and brachial artery flow mediated vasodilation (FMD) by ultrasonography and carotid-femoral

pulse wave velocity (cf-PWV) by applanation tonometry were measured in all participants by a single trained operator, who was blind to clinical features of participants.
**Results**: Compared with those with alcohol-related liver disease, patients with HCV had markedly lower FMD (4.57±1.50 vs. 9.84±3.60%, $p<0.0001$) (Table 1). They also had significantly lower total cholesterol level (4.60±1.34 vs. 5.87±1.40 mmol/L, $p<0.05$), lower serum liver enzymes (AST/ALT ratio: 0.87±0.3 vs. 1.26±0.6U/L, $p<0.05$; GGT: 54±42 vs. 137±117 U/L, $p<0.01$) and higher urea nitrogen (4.98±1.5 vs. 3.69±1.0 mmol/L, $p<0.05$). No significant differences were found in CIMT, cf-PWV, age, sex, body mass index, waist circumference, smoking status, blood pressure, serum triglycerides, creatinine, glucose and insulin resistance (as estimated by HOMA-IR score) between the two groups. Notably, as shown in Figure 1, the marked differences in FMD observed between the groups were only slightly weakened after adjustment for potential confounding variables.
**Conclusions**: Our results suggest that chronic HCV infection is strongly associated with endothelial dysfunction.

### P4.31
### ARTERIAL STIFFNESS AND HAEMOSTASIS CHANGES IN OBESE ZUCKER RATS

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**Objectives:** The metabolic syndrome (MetS), a cluster of risk factor including abdominal fat, hypertension, dyslipidemia and raised fasting plasma glucose, is associated with modifications in the arterial wall, endothelial dysfunction and atherothrombosis. To explore the course of events we characterized the coagulation, fibrinolysis and vascular phenotypes in 25 and 80-week-old Zucker rats, that mimics human MetS.
**Methods:** Arterial phenotype was assessed using ultrasonic echo-tracking. Thrombin generation was monitored using calibrated automated thrombography. Fibrinolysis was measured by a clot lysis assay.
**Results:** Endothelial dysfunction was evidenced by a high plasma concentration of von Willebrand factor at both ages. The arterial wall stress/modulus curves were superimposed at 25 weeks and shifted towards the left with age, the shift being more pronounced in obese rats. Media thickness was not modified with MetS but was increased with aging in obese and lean rats. *In vitro* thrombin generation was higher in 25-week-old obese rats than in age-matched control lean rats (428±29 versus 328±27 nM.min) and still higher at 80 weeks (422±30 versus 306±11 nM.min). Regarding fibrinolysis, half-time lysis clot was increased in obese rats compared to control lean rats (46.5±1.2 versus 41.5±0.7 min at 25 weeks) and increased with age (54.1±1.1 versus 49.3±1.8 min at 80 weeks).
**Conclusions:** We have shown that thrombin generation increased and fibrinolysis decreased *in vitro* with obesity as early as 25 weeks of age. Theses alterations of hemostasis may participate to the accelerated arterial aging as assessed by increased arterial stiffness triggered by obesity and metabolic disorders in SMet.

### P4.32
### INACTIVATION OF SERUM RESPONSE FACTOR CONTRIBUTES TO DECREASE VASCULAR MUSCULAR TONE AND ARTERIAL STIFFNESS IN MICE

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**Rationale**: Vascular smooth muscle cell (VSMC) phenotypic modulation plays an important role in arterial stiffening associated with ageing. Serum response factor (SRF) is a major transcription factor regulating smooth muscle (SM) genes involved in maintenance of the contractile state of VSMCs.
**Objective**: We investigated whether SRF and its target genes regulate intrinsic SM-tone and thereby arterial stiffness.
**Methods and results**: The SRF gene was inactivated ($SRF^{SMKO}$) specifically in VSMCs by injection of tamoxifen into adult transgenic mice. Fifteen days later, arterial pressure and carotid thickness were lower in $SRF^{SMKO}$ than in control mice. The carotid distensibility/pressure and elastic modulus/wall stress curves showed a greater arterial elasticity in $SRF^{SMKO}$ without modification in collagen/elastin ratio. In $SRF^{SMKO}$, vasodilation was decreased in aorta and carotid arteries whereas a decrease in contractile response was found in mesenteric arteries. By contrast, in mice with inducible SRF overexpression, the *in vitro* contractile response was significantly increased in all arteries. Without endothelium, the contraction was reduced in $SRF^{SMKO}$ compared with control aortic rings due to impairment of the NO pathway. Contractile components (SM-actin and myosin light chain), regulators of the contractile response (myosin light chain kinase, myosin phosphatase target subunit 1 and protein kinase C-potentiated myosin phosphatase inhibitor) and integrins were reduced in $SRF^{SMKO}$.
**Conclusion**: SRF controls vasoconstriction in mesenteric arteries via VSMC phenotypic modulation linked to changes in contractile protein gene expression. SRF-related decreases in vasomotor tone and cell-matrix attachment increase arterial elasticity in large arteries.

## P5 Clinical Science 2

### P5.01
### ASSESSMENT OF THE EFFICACY OF TREATMENT OPTIONS IN CRITICAL LIMB ISCHAEMIA ACCORDING TO PATIENT-ORIENTED OUTCOMES

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**Objectives:** Traditional outcomes after vascular intervention include vessel patency, limb salvage rates and mortality but correlate poorly with functional goals. Patent-oriented outcomes are patient-reported functional outcomes. The aim of this study is divided into 2 complementary parts: Part A: To define patient-oriented outcomes by performing a patient survey. Part B: Systematic review of treatment options in lower limb CLI according to patient-oriented outcomes, defined by part A.
**Methods:** Part A: CLI patients ranked 10 outcomes according to importance. Part B: A systematic review of randomised control trials assessing angioplasty, stenting and bypass surgery according to patient-oriented outcomes.
**Results:** Part A: A patient survery indicates that QOL, symptom relief, living status, amputation-free survival and mobility should be considered patient-oriented outcomes. Patients place little importance is placed on vessel patency and reintervention. Part B: 6 RCTs involving 1166 patients assessed QOL, symptom relief, and amputation-free survival following vascular intervention. There is no significant difference in QOL between bypass surgery and angioplasty. There is no difference in symptom relief between sirolimus-eluding stents and angioplasty. Bare-metal stents and angioplasty were not significantly different in providing symptom relief. There was poor correlation between traditional outcomes and patient-oriented outcomes.
**Conclusion:** There is no evidence supporting a single superior treatment between angioplasty, stenting and bypass surgery when assessed by patient-oriented outcomes.

### P5.02
### RELATIVE CONTRIBUTION OF PRE AND AFTER-LOAD IN REDUCTION OF TIME-VARYING MYOCARDIAL STRESS BY NITROGLYCERIN

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**Background:** Nitroglycerin (NTG) reduces cardiac pre-load and after-load through venodilation and arterial dilation respectively but the relative contributions of these effects to reduction in myocardial wall stress is unknown.
**Methods:** We estimated myocardial wall stress from transthoracic echocardiographic imaging of the left ventricle (LV) and LV pressure estimated from carotid tonometry during systole. Nineteen subjects aged 43.3 ± 2.7 (mean ± SE) years were studied before and 7-12 min after NTG (400 ig sublingually). Carotid pressure calibrated by mean and diastolic blood pressure (BP) was used to calculate time-varying LV wall stress from endocardial and epicardial volumes obtained from Tomtec wall tracking analysis. The relative contributions of reductions in systolic pressure and in LV volumes and to overall reduction in LV wall stress were calculated assuming that volume or pressures after NTG were identical to baseline values.
**Results:** NTG decreased peak LV stress (pre: 387±22; post: 329±22kdynes/$cm^2$, $P<0.001$), mean stress (pre: 335±19; post: 277±20 kdynes/$cm^2$, $P<0.001$) and peak stress time over ejection time (pre: 0.37±0.03; post: 0.30±0.01, $P<0.05$) due to reduction of LV end-diastolic volume (pre: 107±7.3; post: 95.6±7.3ml, $P<0.01$), end-systolic volume (pre: 47.9±4.4; post: 40.1±3.7ml, $P<0.01$) and central systolic BP (pre: 138±5.9; post: 122±4.8 mmHg, $P<0.001$). Percentage change in mean stress attributable to reductions in pressure and volume were 11.2% and 9.5% respectively