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ABSTRACTS

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2.1. Does the aldosterone: renin ratio (ARR) predict the efficacy of spironolactone over bendroflumethiazide in hypertension? The RENALDO study

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Background: Targeting specific antihypertensive therapy to phenotypes who will best respond is an attractive concept. We hypothesised that subjects with a high aldosterone: renin ratio (HR) would respond better to spironolactone (spiro) than subjects with a low ratio (LR).

Methods: We conducted a double-blind, randomised, crossover, trial in hypertensives with either a HR (>750 and a plasma aldosterone >250 pmol/l), or LR (<300 and a plasma renin activity <10 ng/ml/h). Each stratum underwent 12 weeks treatment each with spiro 50 mg OD and bendroflumethiazide (BFZ) 2.5 mg OD in random order separated by a 2-week washout. The primary endpoint was the difference (Δ) in mean systolic ambulatory blood pressure (SABP) comparing the HR v LR (Δ Strata).

Secondary endpoints were mean diastolic, day & night time ambulatory BP and clinic BP.

Results: 111 subjects (60 HR and 51 LR) completed the study. SABP at 12 weeks in the HR group was 129.4 mm Hg on spiro v 134.4 mm Hg on BFZ (Δ -5.01 mm Hg P <0.0002). In the LR group SABP was 129.7 mm Hg on spiro v 133.1 mm Hg on BFZ (Δ -3.43 mm Hg P <0.01). The Δ Strata (HR v LR) was -1.58 mm Hg (P =0.394).

Results were similar for the secondary endpoints.

Conclusion: Spiro was more effective than BFZ in both HR and LR subjects. However, there was no greater response in the HR group compared to the LR group. The ARR does not predict the therapeutic response to the mineralocorticoid antagonist spironolactone.

2.2. Development and validation of a blinded electronic auscultatory blood pressure device

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Background: An auscultatory alternative to oscillometric blood pressure (BP) measurement is advisable, especially in those patient groups with a reported accuracy limitation (pregnancy, arrhythmia); observer errors remain a problem. The Nissei DM-3000 is an upper arm device that allows either manual or oscillometric measurement of BP. In addition, we have developed a mode that facilitates blinded auscultatory measurement of blood pressure, with specific relevance to clinical trials.

Methods: After reprogramming the device, we evaluated the manual and blinded modes of the device (both of which require observer auscultation) in 33 adults each, according to the International Protocol (IP). Two trained observers took nine

sequential same arm BP measurements from each subject. During the blinded mode the electronic mercury column disappeared and the observer indicated systolic and diastolic pressure by pressing a button on the device.

Results: Both the manual and blinded modes passed the IP criteria with 86/96/98 (SBP) & 89/99/99 (DBP) [manual] and 94/98/99 (SBP) & 96/99/99 (DBP) [blinded] readings out of 99 being within 5/10/15 mm Hg of the mercury standard. Both modes also fulfilled AAMI requirements, with mean difference (s.d.) of -0.5 (4.4) and -1.4 (2.7) mm Hg [manual] and -0.1 (2.6) and 0.04 (2.4) mm Hg [blinded] for systolic and diastolic pressures respectively.

Conclusion: The Nissei DM-3000 device can be recommended as an auscultatory alternative to mercury sphygmomanometry. Clinical trials will benefit from using the blinded mode of the

device, which achieves clinically recommendable results. This is the modern replacement of the Hawksley random zero sphygmomanometer.

2.3. Long term incidence of hypertension and cardiovascular events is significantly higher in women with pregnancy induced hypertension

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Introduction: Studies suggest that hypertension in pregnancy is associated with a higher incidence of hypertension in the later life. We investigated whether there is a relationship between hypertension in pregnancy and the subsequent incidence of hypertension and cardiovascular events (including ischemic deaths, MI, revascularisation, ischemic heart failure, stroke, TIA).

Methods: The current cardiovascular and hypertension status of 200 women with a history of pregnancy-induced hypertension was compared with that of 100 women delivered during the same period in the past. Data from this index pregnancy including age, family history, ischemic heart disease, diabetes mellitus, smoking, BMI and blood pressure was collected. Direct contact, questionnaire and general practitioner and hospital records established current cardiovascular status.

Results: These women were followed up over a mean period of 15 years (range 11–20 years). There was no significant difference between the mean age of the women (43 years, range 37–50 Years) in the two groups. Incidence of hypertension (51/197 vs 11/100, $P < 0.001$) and cardiovascular events (26/200 vs 4/100, $P < 0.003$) was significantly higher in women with pregnancy-induced hypertension compared with normotensive pregnancy. Using a multivariate binary logistic model (age, hypertension in pregnancy, smoking, diabetes, family history of IHD), pregnancy induced hypertension (OR4.74, 95% CI: 1.34–16.72, $P < 0.015$) and smoking (OR4.40, 95% CI: 1.4–13.62, $P < 0.010$) were the only significant independent predictors of future cardiovascular events.

Conclusion: Pregnancy induced hypertension is associated with increased future risk of hypertension and cardiovascular events.

2.4. The genetic basis of haemorrhagic stroke: a meta-analysis of 12 genes involving ~20 000 subjects

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Background: We have previously demonstrated a genetic basis to ischaemic stroke (Arch. Neurol. 2004). However, whether haemorrhagic stroke also has an underlying genetic aetiology remains controversial. Meta-analyses of published data provides much greater power than can be achieved by any single study. We performed a meta-analysis of all candidate gene association studies in haemorrhagic stroke (primary intracranial and cerebral amyloid angiopathy).

Methods: Electronic databases were searched until and including March 2007 for any candidate gene in haemorrhagic stroke. Cases were required to have neuroimaging or autopsy evidence of the diagnosis. Data from 54 case-control studies were included. Of 12 genes identified, 13 polymorphisms met our inclusion criteria.

Results: Our meta-analyses included 6324 cases and 13 393 controls. Statistically significant associations

with haemorrhagic stroke were identified for ACE/II (OR, 1.48; 95% CI, 1.20–1.83; $P = 0.0003$) and for SERPINE1/4G5G (OR, 1.42; 95% CI, 1.03–1.96; $P = 0.03$). A significant protective association against haemorrhagic stroke was found for factor V Leiden (OR, 0.30; 95% CI, 0.10–0.87; $P = 0.03$). APOE/ ϵ 2 and ϵ 4 alleles were significantly associated with cerebral amyloid angiopathy-related haemorrhage (OR, 3.36; 95% CI, 1.71–6.59; $P = 0.0004$ and OR, 2.69; 95% CI, 1.47–4.92; $P = 0.001$, respectively).

Conclusion: There is a genetic component to haemorrhagic stroke. Interestingly, some of these genes are similar to those we have previously identified in ischaemic stroke (with similar ORs), but there are notable exceptions. Our findings have important implications for understanding the genetic basis of all types of stroke.

2.5. Inducible nitric oxide synthase activity is increased in patients with rheumatoid arthritis and contributes to endothelial dysfunction

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Background: Recent *in vitro* studies have suggested that inducible nitric oxide synthase (iNOS) activity mediates endothelial dysfunction. Rheumatoid arthritis (RA) is a chronic inflammatory condition and as such can provide an interesting model to study the link between inflammation, endothelial dysfunction and cardiovascular risk. The aim was to establish the contribution of iNOS to endothelial function.

Methods and Results: Forearm blood flow (FBF) was measured during intra arterial infusions of acetylcholine (ACh), sodium nitroprusside (SNP), *N*-monomethyl-L-arginine (L-NMMA) and aminoguanidine (AG) in 12 RA patients and 13 control subjects. Levels of C-reactive protein (CRP) and myeloperoxidase (MPO) were assessed. Data are presented as mean percentage changes in the ratio of blood flow in infused/control arm \pm s.e.m. Forearm blood flow response to ACh was reduced in patients

with RA compared to control subjects (384 ± 72 vs $179 \pm 29\%$, respectively; $P = 0.01$), but SNP response was not ($P = 0.5$). FBF response to AG was different between patients and controls (-15 ± 2 vs $13 \pm 4\%$, respectively; $P < 0.001$), whereas the response to L-NMMA was not ($P = 0.4$). In multiple regression model logCRP, AG response were found to be independent predictors of endothelial function ($R^2 = 0.773$, $P < 0.001$).

Conclusion: We demonstrated that RA patients have endothelial dysfunction and increased iNOS activity in comparison to healthy controls. Furthermore, CRP and iNOS activity were independently associated with endothelial function. Our data demonstrates that inflammation is a key mediator in a process of endothelial dysfunction possibly via activation of iNOS and increased production of MPO, leading to uncoupling of endothelial NOS and subsequent reduction of NO bioavailability.

2.6. Pharmacogenetics of aspirin resistance: a comprehensive systemic review

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A genetic basis for aspirin resistance has been proposed. We performed a systematic review of all candidate gene association studies in aspirin resistance. Electronic databases were searched up until February 2007. Within 27 studies, 51 polymorphisms in 11 genes were identified. The PIA1/A2 polymorphism present in the GPIIb/IIIa platelet receptor was the most investigated, with 18 studies that included 1358 subjects. The functional methods used to measure aspirin resistance included light transmission aggregometry, platelet function analyser-100 (PFA-100), bleeding time and measuring prothrombin generation.

PIA1/A2 variant was significantly associated with aspirin resistance when measured by all methods in healthy subjects (OR, 2.36; 95% CI, 1.24–4.49; $P = 0.009$). However, combining genetic data from all studies (including studies with patients with cardiovascular disease) reduced the observed effect size (OR, 1.14; 95% CI, 0.84–1.54; $P = 0.40$). When PIA1/A2 was analysed according to platelet function methodology bleeding time/

prothrombin generation was highly significantly associated with aspirin resistance (OR 11.76, 95% CI, 3.05–45.37; $P = 0.0003$). Four other genes were also reviewed:

Gene (No of studies)	Variant	Genetic model	OR (95% CI)
GPIa (4)	C8087T	Recessive	1.37 (0.81, 2.31)
COX-1 (4)	A842G (C50T)	Recessive	1.07 (0.41, 2.77)
P2Y1 (2)	H1/H2	Recessive	0.80 (0.48, 1.33)
P2Y12 (3)	A1622G	Recessive	0.90 (0.48, 1.68)

Our data supports a genetic basis for aspirin resistance which seems to be most obvious in healthy subjects, with the effect diminishing in the presence of atherosclerosis. This work provides important information about the pharmacogenetics of antiplatelet intervention in cardiovascular disease.

3.1. Association of the WNK1 gene with essential hypertension, blood pressure variability and serum and urine electrolytes

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We have previously reported association between WNK1 and BP variation in families from the British Genetics of Hypertension (BRIGHT) Study and association has been reported with 24-h ambulatory BP in the GRAPHIC study. We set out to replicate and extend our findings with BP and essential hypertension (EH) and to test if phenotypes related to WNK1 function (serum Na, Cl, Ca and urinary Na and K) were also associated with WNK1.

Twenty eight tag SNPs (tSNPs) that capture 100% of HapMap II were genotyped in 1700 cases and 1700 controls from the BRIGHT resource. Logistic regression was used to test for association with EH and linear models for quantitative analyses. Haplotype associations were explored using haplo.stats. Analyses were adjusted for age, sex, BMI and geography to adjust for population stratification.

Multiple tSNPs were significantly associated with both SBP (min $P=0.0011$) and DBP (min $P=0.0025$). Haplotype analysis revealed striking associations with SBP (global $P=1.15 \times 10^{-10}$), DBP ($P=1.28 \times 10^{-10}$) and EH, ($P=1.22 \times 10^{-14}$). Notably, tSNPs spanning the length of WNK1 were also significantly associated with ionised serum Ca^{2+} (min $P=0.0014$), Na (min $P=0.0053$) and Cl (min $P=0.0099$), and urine K (min $P=0.0011$) and Na (min $P=0.0099$).

Our analysis confirms association of WNK1 with BP, and now provides novel evidence for association with EH and electrolyte homeostasis. These new data provide compelling evidence to initiate further genetic and functional studies to identify causative variants and explore the role of WNK1 in BP regulation and EH.

3.2. Expression of the epithelial Na⁺ channel and other components of an aldosterone response pathway in human zona glomerulosa cells

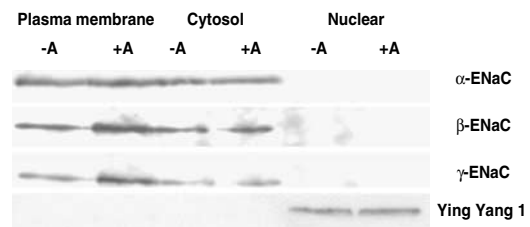
TJ Burton, G Cope and MJ Brown

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Introduction: Aldosterone stimulates Na⁺ reabsorption by up-regulation of the amiloride-sensitive epithelial Na⁺ channel (ENaC), the rate-limiting step in transepithelial Na⁺ transport. In many ENaC-expressing tissues Nedd4-2 (neuronal precursor cell-expressed and developmentally down-regulated protein 4-2) and Sgk-1 (serum and glucocorticoid-inducible kinase type 1) have a pivotal role in determining the number of ENaC channels at the membrane and responsiveness to aldosterone. 11 β -HSD type II (11 β -hydroxysteroid dehydrogenase type II) confers mineralocorticoid specificity. We have previously shown that the three subunits of ENaC are expressed in human adrenal zona glomerulosa (ZG) cells. Our aim was to determine whether ZG cells contain all the components of a functional aldosterone response pathway.

Results: We show using RT-PCR that in addition to α -, β - and γ -subunits of ENaC, ZG cells express the mineralocorticoid receptor, Nedd4-2, Sgk-1 and 11 β -HSD type II. Using Western blotting and cell fractionation techniques we show that α -, β -

and γ -ENaC are present in both the plasma membrane and cytosol and upon aldosterone stimulation of primary cultured human ZG cells, the levels of β - and γ -ENaC expression at the cell surface are increased.



Conclusion: We conclude that the components of a functional aldosterone response pathway are present in ZG cells. We postulate that this may allow aldosterone to exert a negative influence on its own release and form the route through which ZG cells sense circulating Na⁺ levels.

3.3. A prospective study of maternal endothelial function, angiogenic factors and placental function in women at risk of pre-eclampsia

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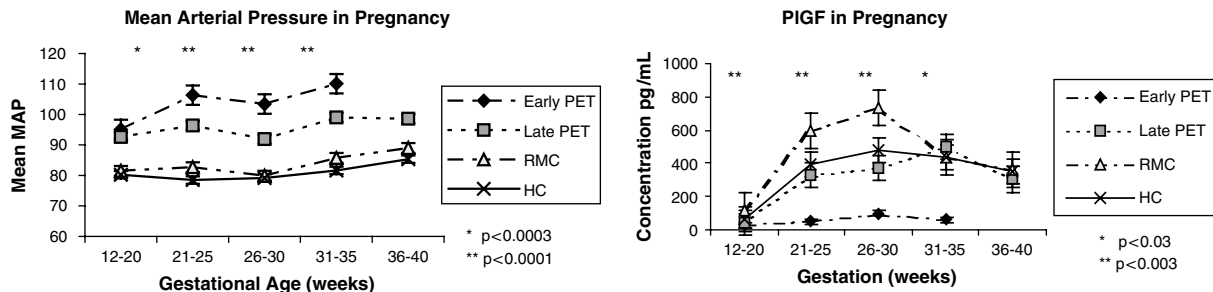
Inhibitors of angiogenesis have been associated with the development of pre-eclampsia (PET) in cross-sectional studies, possibly by inducing maternal endothelial dysfunction

Aim: To investigate the relationship between maternal endothelial function, placental perfusion and angiogenic factors and their inhibitors in a prospective study.

Methods: We followed 240 women through pregnancy; 120 with risk factors for PET and 120 healthy controls. Nineteen women who developed PET were matched with 19 risk-factor controls who did not develop PET (RMC), and 19 normotensive controls (HC). Endothelial function (Flow-mediated dilatation), mean arterial pressure (MAP), and levels of vascular endothelial growth factor (VEGF), soluble VEGF-receptor-1 (sflt-1), soluble endoglin and placental growth factor (PlGF) were measured serially and, at 24 weeks gestation, uterine artery resistance index was measured.

Results: Women who developed PET had higher MAP and lower FMD throughout pregnancy compared with women who did not develop PET. Women who developed early PET (<37 weeks) had lower levels of PlGF from 21 weeks compared with all other groups. Elevations in sflt-1 and sEndoglin were detected 6–10 weeks before delivery in women who developed PET, but only after identification of high pulsatility index of uterine arteries, and maternal endothelial dysfunction.

Conclusion: Women at risk who eventually develop PET, have higher MAP, poorer FMD and placental perfusion, and lower levels of PlGF from 21 weeks gestation compared with women at risk who remain free of PET, as well as risk factor free women who remain healthy. The rise in sflt-1 and s-endoglin appear to be a consequence rather than cause of these changes.



3.4. Cardiac overexpression of angiotensin converting enzyme 2 (ACE2) in stroke prone spontaneously hypertensive rats (SHRSP) leads to fibrosis

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Objective: Optimise adeno-associated virus serotype 6 (AAV6)-mediated gene delivery to myocardium *in vivo* in SHRSPs, and assess the effect of ACE2 overexpression *in vivo* on heart function and blood pressure.

Methods: We administered a single intravenous injection of AAV6CMVlacZ at three doses (2×10^{11} , 1.5×10^{12} and 3×10^{12} vp/rat) into 6 week old SHRSP. Animals were sacrificed 14 days post delivery and tissues stained for β -galactosidase

(β -gal) expression which was confirmed by immunohistochemistry (IHC). To assess the effect of ACE2 overexpression in SHRSP, 4 groups of animals ($n=6$ /group) were included in the study; PBS, Enalapril, AAV6-alkaline phosphatase (control reporter gene) and AAV6-ACE2. Blood pressure was monitored by tail cuff and echocardiography (ECHO) used to assess cardiac function. Haematoxylin and eosin (H&E) staining was used to assess cardiac structure and Masson's trichrome and

picrosirius red were employed to evaluate cardiac fibrosis.

Results: AAV-6-mediated gene transfer was high in heart and skeletal muscle and a dose-dependent response was observed. β -gal staining and IHC confirmed transgene expression was limited to these tissues. ACE2 was overexpressed selectively in the AAV6-ACE2-injected animals. ECHO showed substantial systolic dysfunction in these animals compared to controls. H&E revealed abnormal

cardiac structure. Masson's trichrome and picrosirius red indicated extreme cardiac fibrosis. Blood pressure was significantly lower ($P < 0.001$) in the ACE2 group in weeks 9, 10 and 11 post infusion compared to PBS and control virus infused animals.

Conclusions: AAV-6 demonstrates a favourable profile for cardiac gene delivery in rodent models. Overexpression of ACE2 in SHRSP myocardium led to severe cardiac fibrosis.

3.5. Improvement of cardiovascular function by mitochondrial-targeted antioxidant treatment

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Background: Protecting mitochondria from oxidative damage emerges as an effective therapeutic strategy for cardiovascular disease, however conventional antioxidants have limited efficacy due to their inability to cross the mitochondrial membrane. The aim of this study was to investigate the role of mitochondrial oxidative stress during development of hypertension in the stroke-prone spontaneously hypertensive rat (SHRSP), using the recently developed mitochondrial-targeted antioxidant, MitoQ.

Methods: 8-week-old male SHRSP were treated with MitoQ (500 μ M) ($n = 13$) or vehicle ($n = 12$) in drinking water for 8 weeks. Systolic blood pressure (SBP) was measured weekly by tail-cuff plethysmography. Cardiac hypertrophy was estimated by measurement of heart and body weight at sacrifice. Superoxide levels in thoracic aorta and kidney were measured by lucigenin-enhanced chemiluminescence. NO bioavailability and relaxation to rotenone were measured in thoracic aorta (organ bath studies)

and mesenteric resistance arteries (wire myography). Mitochondria were localised in aorta and kidney using Mitotracker red and two-photon confocal microscopy.

Results: SBP was significantly reduced over the 8-week MitoQ treatment period ($F = 19.0$, $P = 0.0001$) compared to controls. MitoQ treatment significantly improved thoracic aorta NO bioavailability (AUC, MitoQ; 1.15 ± 0.2 g/g vs control; 0.69 ± 0.07 g/g, $P = 0.029$), and significantly reduced cardiac hypertrophy (MitoQ; 4.00 ± 0.09 mg/g vs control; 4.37 ± 0.12 mg/g, $P = 0.040$) but did not affect body weight.

Conclusions: Administration of the mitochondrial-targeted antioxidant MitoQ protects against the development of hypertension, improves endothelial dysfunction and reduces cardiac hypertrophy in young SHRSP. MitoQ provides a novel approach to investigate the role of mitochondrial-specific oxidative damage and has potential as a new therapeutic target in human cardiovascular disease.

3.6. The highly conserved acidic motif of WNK4 is essential for its role in the regulation of renal potassium handling through suppression of ROMK expression

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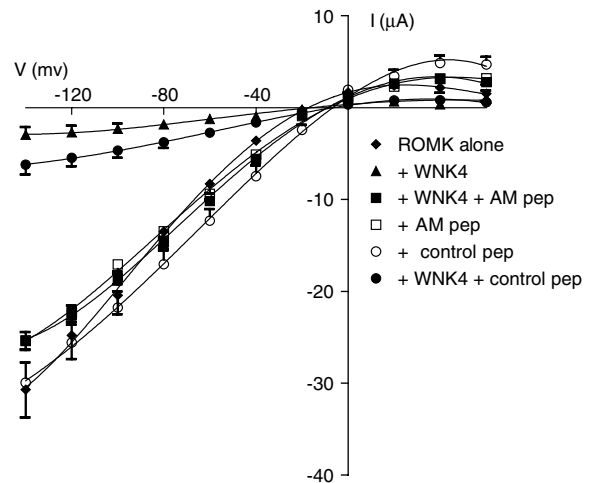
WNK4 regulates expression of the renal outer medullary potassium channel (ROMK) by controlling its endocytosis. The WNK family contains a unique run of acidic amino acids called the acid motif (AM, EPEEPEADQH). Its function is not known but the charge-changing mutations causing Gordon's syndrome (familial syndrome of hypertension and hyperkalemia) cluster within the AM.

To investigate further the function of the AM we generated WNK4 fragments containing the acidic motif and the kinase domain (KD) (1–620 aa), a C-

terminal fragment containing neither the KD nor AM (620-C terminus) and a WNK4 that had just the AM motif internally deleted (delAM). The effects of these constructs on ROMK-EGFP expression was explored by coexpressing in *Xenopus* oocytes and quantifying membrane fluorescence using confocal microscopy. In this system wildtype WNK4 reduces ROMK-EGFP expression by > 70%. The N-terminal fragment (1–620) mimicked the effect of WNK4, but the 620-C terminal fragment and delAM were not able to significantly suppress ROMK-EGFP expression.

We investigated AM function further by studying the effects of a 10mer peptide made up to the AM residues (EPEEPEADQH). This was coinjected with WNK4 and ROMK into oocytes and K currents measured directly by two voltage electrode clamping (see figure). The AM peptide had no effect on ROMK current on its own but completely inhibited the suppression seen when WNK4 and ROMK were coexpressed. A control peptide with the AM sequence scrambled was not able to reproduce this blocking effect of the AM peptide.

These data suggest that the AM is a crucial functional motif in its interaction with ROMK and explain why the Gordon's mutations disrupt WNK4 function so effectively.



4.1. Novel vasoconstrictor activity of the chemokine MIP1- β in human vasculature *in vitro* is antagonised by the CCR5 receptor antagonist maraviroc

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HIV-Infected individuals are at increased risk of cardiovascular events. The chemokine receptor, CCR5, a co-receptor for the HIV virus, is expressed with its ligand MIP1- β in vascular smooth muscle (Schechter *et al.*, 2000). A direct effect of chemokines on vascular tone has not been reported therefore we have determined whether MIP1- β has constrictor or dilator actions in human saphenous vein (SV) *in vitro*.

With ethical approval, rings (4 mm) of human SV were denuded of their endothelium (confirmed by lack of response to acetylcholine) and mounted in 5 ml baths containing oxygenated Krebs' (37°C) for isometric tension recordings. Maraviroc (300 nM) or vehicle (0.01% DMSO) were added to the bathing medium and 30 min later cumulative concentration-response curves (CRC) were constructed to MIP1- β (1×10^{-11} – 1.1×10^{-7} M). CRC were repeated in veins

precontracted with 10 nM endothelin-1. MIP1- β responses were expressed as %phenylephrine or %reversal of ET-1, respectively. Data were analysed to determine values of potency (pD₂), expressed as mean \pm s.e.mean. n-Values are the number of patients from whom tissue was obtained.

In ET-1 constricted SV, MIP1- β had no direct dilator actions over the concentration range tested. In contrast MIP1- β contracted SV with pD₂ of 7.73 ± 0.17 ($n = 12$). This was abolished by maraviroc ($n = 4$).

These data reveal an as yet unidentified role for MIP1- β as a potent constrictor of human SV, an effect mediated via the smooth muscle CCR5 receptor.

Schechter AD *et al.* (2000). *J Biol Chem* **275**, 5466–5471.

4.2. Acute blood pressure (BP) lowering and vasoprotective effects of beetroot juice: relationship to nitrite derived from dietary nitrate

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Diets rich in fruits and vegetables reduce BP (DASH: Appel *et al.*, NEJM 1997;336:1117–1124) and the risk of cardiovascular events (Joshi *et al.*, *Ann. Intern. Med.* 2001;19:134:1106–1114). However, the mechanisms of this effect are uncertain. The greatest protection is afforded by a diet containing green

leafy vegetables. These vegetables are rich in dietary nitrate (NO₃⁻), a characteristic shared by beetroot. We hypothesized that dietary nitrate might provide, by sequential reduction via nitrite, a source of NO that lowers BP and preserves endothelial function following ischaemia-reperfusion.

The effects of beetroot juice ingestion (500 ml) on BP and simultaneous changes in plasma [nitrate] and [nitrite] were investigated in 14 healthy volunteers in a cross-over study with water as control. In a further 10 subjects, the effect of beetroot juice on endothelial function was assessed using flow-mediated dilatation (FMD) in a model of forearm ischaemia-reperfusion.

Beetroot juice reduced BP by 10.4/8 mm Hg (compared to water) at 2.5–3 h following ingestion ($P < 0.01$), coinciding with the peak increase in plasma nitrite concentration. At 24 h the change in systolic BP from basal was 8.8 mm Hg lower

with beetroot juice than water ($P < 0.05$). Decreases in BP were correlated with changes in plasma nitrite ($P < 0.01$) but not nitrate concentration. Ischaemia-reperfusion caused endothelial dysfunction, reducing FMD from $7.5 \pm 0.8\%$ to $3.1 \pm 0.5\%$ in control ($P < 0.01$); however, prior ingestion of beetroot juice prevented this dysfunction ($P < 0.05$).

Dietary nitrate is likely to contribute to the hypotensive and cardioprotective effects of vegetables, suggesting the therapeutic potential of a high nitrate diet in the prevention and treatment of hypertension.

4.3. Patients with type 2 diabetes mellitus have an exaggerated brachial and central blood pressure response to exercise: relation to left ventricular hypertrophy

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Background: A hypertensive response to exercise independently predicts cardiovascular mortality. Patients with type 2 diabetes mellitus (T2DM) have vascular abnormalities which may predispose to exaggerated brachial and central blood pressure (BP) during exercise. This study aimed to test this hypothesis and determine the clinical significance of exercise BP by examining its relation to left ventricular mass.

Methods: Brachial and central (ascending aorta) BP were recorded at rest and post maximal exercise in 73 T2DM patients (aged 54 ± 10 years) and 73 matched controls (aged 53 ± 12 years). Brachial BP was determined by sphygmomanometry and central BP was measured by exercise-validated radial tonometry. Left ventricular mass was determined by 2D-echocardiography and indexed to height^{2.7} (LVMI).

Results: At rest there were no significant ($P > 0.05$) differences between groups in brachial or central BP.

The T2DM patients had significantly increased exercise brachial systolic BP (SBP: 199 ± 25 mm Hg vs 185 ± 21 mm Hg; $P = 0.001$) and central SBP (158 ± 17 mm Hg vs 149 ± 15 mm Hg; $P = 0.001$). There was also a significantly higher prevalence of an exaggerated BP response to exercise ($\geq 210/105$ mm Hg; men and $\geq 190/105$ mm Hg; women) in the T2DM patients (51 vs 22%; $P < 0.01$). Compared to those with normal exercise BP, LVMI was significantly higher (44 ± 12 g/m^{2.7} vs 40 ± 11 g/m^{2.7}; $P < 0.001$) and left ventricular hypertrophy more prevalent (35 vs 16%; $P < 0.05$) in those with exaggerated exercise BP. Exercise central SBP was independently associated with left ventricular relative wall thickness ($\beta = 0.35$; $P < 0.001$).

Conclusion: Patients with T2DM have increased brachial and central BP during maximal exercise, which may contribute to cardiovascular risk via adverse cardiac remodelling.

5.3. Acute aldosterone responses to ACTH predict both cortisol responses and blood pressure

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Background: Plasma aldosterone levels are reported to be associated with risk of hypertension. Aldosterone secretion from the zona glomerulosa is regulated acutely by the renin/angiotensin system and plasma potassium. The role of ACTH in chronic regulation of aldosterone secretion is unclear.

Aim: We aimed to examine the relationships between aldosterone and blood pressure, and the

association between regulation of cortisol and aldosterone.

Methods: Aldosterone was measured in stored serum samples from 205 men and 106 women aged 67–78 year, from Hertfordshire UK, in whom birth-weight was recorded. Participants underwent an overnight low dose (0.25 mg) dexamethasone (dex) suppression test and a low dose (1 μ g) ACTH stimulation test.

Results: Median aldosterone was 6.22 ng/dl (range 0.15–38.74), and was higher in men than women ($P < 0.0001$). There were significant correlations between aldosterone and blood pressure in men (systolic $r = 0.21$, $P = 0.004$; diastolic $r = 0.17$, $P = 0.02$) with a similar trend in women (systolic $r = 0.17$, $P = 0.08$). Post-dex aldosterone concentrations and cortisol were correlated ($r = 0.36$, $P < 0.0001$ for men and $r = 0.29$, $P = 0.003$ for women) with similar associations for ACTH-stimulated values. Aldosterone levels were significantly correlated with fasting plasma cortisol measured 6

years previously ($r = 0.31$, $P < 0.001$). Aldosterone levels following both dex and ACTH-stimulation were inversely associated with birthweight ($r = -0.37$, $P < 0.0001$).

Discussion: Our findings support existing evidence that aldosterone is an important regulator of blood pressure and identify a common component in regulation of aldosterone and cortisol. The findings of higher aldosterone levels in subjects of low birthweight supports the hypothesis of the early origins of adult disease in the development of subsequent hypertension.

5.4. Impact of heart rate on the differential effect of blood pressure lowering agents on peripheral and central pressures: data from the Conduit Artery Function Evaluation (CAFE) Study

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The Conduit Artery Function Evaluation (CAFE) study demonstrated less effective central aortic pressure lowering with atenolol-based vs amlodipine based therapy in people with hypertension. The present study examined the importance of heart rate (HR) as a determinant of the differential impact of blood pressure lowering treatments on central aortic pressures and haemodynamics.

Central pressures were derived from brachial pressure and radial pulse wave analysis in 2073 patients using the Sphygmocor[®] device. 7146 measurements were recorded and analyzed over follow-up for up to 4 years. HR was inversely related to central SBP ($P < 0.0001$), but showed only a marginal relationship with brachial SBP ($P = 0.09$). Strong, inverse relationships were seen between HR and the difference between brachial and central SBP ($P < 0.0001$), and augmentation index ($P < 0.0001$), indicative of depressed pressure amplification and

increased wave reflection at lower HR. Multiple regression analysis showed HR to be the major determinant of central pressures after brachial blood pressure. After adjustment for HR, central pressure and haemodynamic differences between treatment arms in the CAFE study were markedly attenuated (e.g. Δ central SBP [amlodipine – atenolol pre HR adjustment; 4.3 mm Hg, $P < 0.001$, after HR adjustment; 1.1 mm Hg, $P = 0.07$]).

These data suggest that when comparing β -blocker based treatments with other blood pressure lowering strategies, the reduction in heart rate with β -blockers is the main mechanism accounting for less effective central aortic pressure reduction per unit change in brachial pressure. These findings suggest that therapies influencing HR could have significant impacts on central aortic pressures and haemodynamics in people with hypertension.

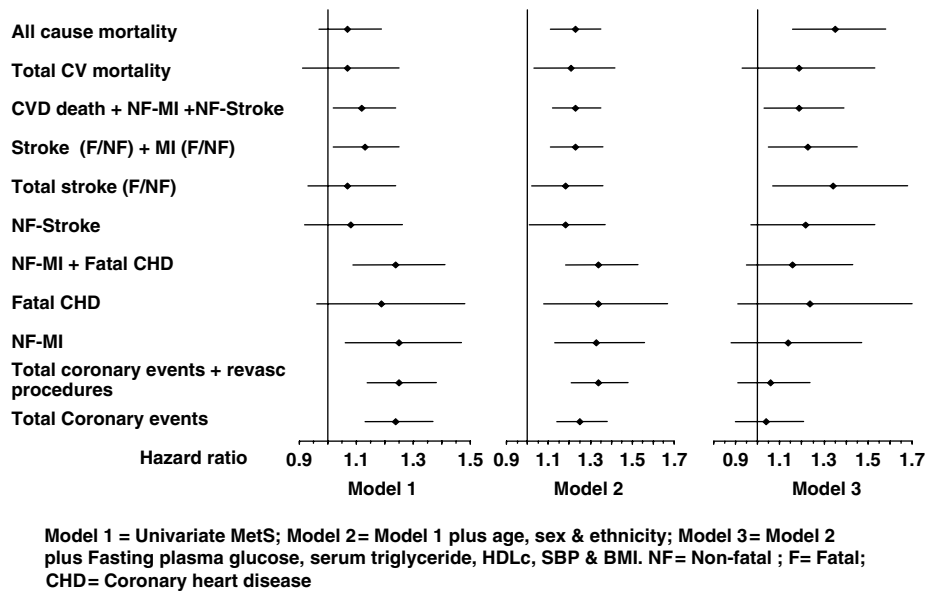
5.5. Role of metabolic syndrome, independent of its components, in prediction of cardiovascular outcomes in hypertensive patients in the ASCOT-BPLA

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Background: Controversy exists whether metabolic syndrome (MetS) adds to cardiovascular disease (CVD) prediction, beyond the predictive value of its individual components. We addressed this question among hypertensive participants in ASCOT-BPLA. **Material and Methods:** Among 19257 hypertensive patients in ASCOT-BPLA, 8091 (42%) had MetS at baseline (defined using modified ATP III criteria; replacing waist circumference with BMI > 30 kg/m²). Three separate Cox proportional models were

developed to assess predictability of MetS, for pre-specified cardiovascular (CV) outcomes (see Figure). **Results:** Unadjusted MetS (Model 1) was associated with significantly increased risk of coronary disease outcomes but not for other CV outcomes and all cause mortality. (see Figure). In Model-2, after adjusting for age, sex and ethnicity, MetS also predicted other CV outcomes significantly. When individual components of MetS were included in Model-3, MetS was associated with significantly



increased risk for various outcomes which included total stroke and all cause mortality but not coronary outcomes.

Conclusion: MetS remains an independent predictor for stroke and all cause mortality but not for

coronary events after adjusting for the risk associated with its individual components.

Figure: Risk of CVD associated with MetS, when adjusted for age, sex, ethnicity and components of syndrome itself.

5.6. Association of the CYP11B1 and CYP11B2 gene polymorphisms with hypertension in the British Genetics of Hypertension case-control study

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Background: Variation at the CYP11B2 gene, that encodes aldosterone synthase, is associated with hypertension, with the -344T allele implicated in some but not all studies. This polymorphism is also associated with reduced 11-hydroxylase efficiency, accounted for by variation in the 5' UTR of the adjacent gene CYP11B1, that encodes 11- β hydroxylase. Here we study polymorphisms of the CYP11B1/B2 genes in a large hypertensive case/control population.

Methods: We genotyped three polymorphisms (-1859G/A in the 5' region of CYP11B1; -344C/T in the 5' region and the intron 2 conversion (IC) of CYP11B2) in 1642 cases and 1699 controls from the MRC BRIGHT study. All were in Hardy Weinberg Equilibrium.

Results: Single marker association was strongest with the IC genotype (conv), with a 16% increased risk of hypertension compared to the wild type genotype (Wt) (OR 1.165 95%CI [1.02-1.24];

$P=0.002$); the evidence for association increased using a dominant model ($P=10^{-5}$). The -344T allele was also nominally significant (OR 1.125[1.06-1.28]; $P=0.016$). Haplotype analysis showed 8 haplotypes with frequencies >1% that explained all variation in this region. The ACWt haplotype (OR 0.84[0.76-0.93]; $P=0.0005$) and the ACConv (OR 3.74[2.14-6.53]; $P=10^{-7}$) showed the most significant associations. After controlling for the effect of haplotypic background and of individual SNPs, both -1859 and the IC showed independent effects, but neither of them could independently explain all haplotype association.

Conclusions: Our results demonstrate either epistatic effects of the CYP11B1/2 gene complex or the presence of a causal variant in LD elsewhere in the region. Further studies to clarify the nature of this interaction and the causal nature of the link between genotype and phenotype are indicated.

PA.1. Improved left ventricular mass index and left ventricular function in a hypertensive congenic strain

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Objective: Previously we identified a left ventricular mass index (LVMI) quantitative trait locus (QTL) on rat chromosome 14. This study aimed to confirm the QTL by speed congenic strain production and evaluate left ventricular (LV) function using post analysis strain rate imaging.

Methods: A chromosome 14 congenic strain (SP.WKYGla14a) was generated by introgression of a 63cM WKY region into the SHRSP genetic background. LVMI (g/g), relative wall thickness (RWT) expressed as a ratio of wall thickness to LV radius, ejection fraction % and strain rate determined at end systole (SR_s) and end diastole (SR_d) were calculated using 2-D echocardiographic images. SBP was measured by tail cuff plethysmography in SHRSP, WKY and SP.WKYGla14a animals, aged 12 weeks.

Results: SBP was significantly increased in SHRSP (170 ± 6 mm Hg, $P = 2.8 \times 10^{-7}$, $n = 6$) and SP.WKY-

Gla14a (167 ± 2 mm Hg, $P = 7.6 \times 10^{-7}$, $n = 5$) vs WKY (136 ± 1 mm Hg, $n = 9$) with no significant difference observed between SHRSP and SP.WKYGla14a. LVMI and RWT was significantly higher in SHRSP ($3.31 \times 10^{-3} \pm 3.4$; 0.64 ± 0.02 , $n = 5$) vs SP.WKY-Gla14a ($2.74 \times 10^{-3} \pm 0.06$, $P = 0.002$; 0.52 ± 0.01 , $P = 2.86 \times 10^{-7}$, $n = 5$) and WKY ($2.31 \times 10^{-3} \pm 0.05$, $P = 0.0001$; 0.54 ± 0.02 , $P = 1.16 \times 10^{-5}$, $n = 5$). LV diastolic function was significantly decreased in SHRSP ($SR_s = -1.0 \pm 0.3s^{-1}$, $SR_d = 0.8 \pm 0.2s^{-1}$; $P < 0.001$) vs SP.WKYGla14a ($SR_s = -1.8 \pm 0.2s^{-1}$, $SR_d = 4.20 \pm 0.5s^{-1}$) and WKY ($SR_s = -3.8 \pm 0.3s^{-1}$, $SR_d = 4.8 \pm 0.6s^{-1}$) with no significant difference in ejection fraction % between groups.

Conclusions: We confirmed a QTL for LVMI that was blood pressure independent. This is associated with diastolic dysfunction as measured by strain rate imaging.

PA.2. RNA-interference and adenovirus mediated selective modulation of cardiovascular candidate genes

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Objective: Our previous studies identified glutathione s-transferase mu-type I (*Gstm1*) as a positional and functional hypertension candidate gene in the stroke-prone spontaneously hypertensive rat. Reduced *Gstm1* expression may contribute to both increased oxidative stress and hypertension in this model. A lack of selective pharmacological agents has made elucidation of the precise role of *Gstm1* difficult. Thus the aim of this study was to develop RNAi and adenoviral tools to facilitate the dissection of *Gstm1*'s role.

Design and Method: Rat kidney tubular epithelial cells (NRK52E) were transfected with *Gstm1* siRNA (30 to 100nM). Protein and mRNA levels were determined 48 h later by qRT-PCR and Western blot. Adenoviruses were constructed to express shRNAi sequences targeted against the *Gstm* gene family (Ad-shGstmf), and to overexpress *Gstm1* (AdGstm1).

Results: *Gstm1* mRNA expression was reduced 85% vs control siRNA, accompanied by a consistent and reproducible reduction in *Gstm1* protein. Ad-shGstmf knocked-down *Gstm* isoforms in NRK52E by up to 63% at 48 h (100 pfu/cell). Transduction of HeLa cells with AdGstm1 (100 pfu/cell) increased total GST enzymatic activity 3-fold.

Conclusions: The molecular tools developed in this study allow selective modulation of *Gstm1* expression as a means to defining its role in hypertension. Our previous studies have demonstrated the ability of adenoviral based vectors to improve vascular function locally and to lower blood pressure when targeted to specific tissues and administered systemically. The successful development of the tools described here extends the applicability of this approach to other genes identified via high-throughput technologies.

PA.3. Microarray analysis identifies salt sensitive candidate genes in the SHRSP

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Objective: The SHRSP is an excellent model of human essential hypertension and exhibits salt

sensitivity. The aims of this study were to utilise a combination of microarray expression profiling

and a salt resistant congenic strain to identify genes and pathophysiological pathways involved in salt-sensitive hypertension.

Methods: Renal microarray gene expression profiling was undertaken to identify differentially expressed genes in non-salt ($n=3$ males/strain) and salt loaded ($n=3$ males/strain) 21 week old rats between SHRSP, WKY and SP.WKYGla2a (2a) congenic strain using the Affymetrix Rat230-2 GeneChips. Data were normalised with Rosetta Resolver error models and significant differential expression was determined by one-way ANOVA ($P<0.01$) with Tukey-Kramer post-hoc test ($P<0.1$). Strain-salt interactions were investigated with two-way ANOVA ($P<0.01$) and salt regulated pathways explored using Ingenuity Pathway Analysis ($P<0.05$).

Results: Renal expression profiles identified significant differences between the SHRSP and both 2a

and WKY rats for no-salt (113 genes), and salt-loading (101 genes) that mapped to the congenic interval. Of these, 89 positional candidate genes were shown to be specifically regulated by salt and involved in the most significantly disrupted inflammatory pathways and signalling networks. Furthermore, *Mme*, *Calm1*, and *Adh1c* are functional candidate genes as they have previously implicated in salt sensitive hypertension. A further 7 genes (*F3*, *Hmgcs2*, *Slc16a1*, *Fga*, *Tmem79*, *Adh1c*, *Scnm1*) exhibited strain-salt interactions.

Conclusions: A combination of microarray analysis and congenic strains represents a powerful strategy to dissect pathogenesis. This identifies positional candidate genes on chromosome 2 and illustrates the complexity of gene-gene and gene-environment interactions in salt sensitive hypertension.

PB.1. Effects of early growth on blood pressure of British European and South Asian origin children at 12 months of age

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Introduction: Blood pressure (BP), the leading intrinsic risk factor for adult disease globally, tracks throughout the life course yet little is known about its early determinants. We investigated early influences on postnatal growth and BP in healthy British born South Asian (SA) and European (E) origin infants.

Methods: We followed 560 infants prospectively from birth to 3 and/or 12 months with measures of anthropometry and resting BP, compared against a UK 1990 growth reference and analysed using regression methods.

Results: Measures of birth size were smaller in SA compared to E infants ($P<0.001$), however, SA females had higher subscapular skinfold thickness relative to birth weight (1.3 vs 1.2, mean difference 0.07, 95% CI 0.0009 to 0.14, $P=0.047$). SA boys showed a striking early increase in weight and

length compared with E boys, associated with significant accrual of subscapular fat (6.1 vs 5.3 mm, mean difference 0.8, 95% CI 0.3 to 1.3, $P=0.003$). In gender and ethnicity adjusted regression models, infants with the largest weight SDS increases in the first 3 months had the highest 12 month systolic BP ($\beta=2.4$, 95% CI 0.5 to 4.2, $P=0.01$), while those with the greatest birth length ($\beta=0.7$, 95% CI 0.05 to 1.4, $P=0.04$) but the smallest changes in length over 3 to 12 months ($\beta=-0.57$, 95% CI -0.95 to -0.19 , $P=0.004$) had the highest diastolic BP.

Conclusion: Ethnic and gender differences in growth and adiposity are present in early infancy. Weight gain during the first 3 months appears to drive the rise in systolic BP, among the top global risk factors for premature adult mortality.

PB.2. Small artery changes precede overt hyperglycaemia or 'diabetes': The Manchester Mothers' Vascular Health Study

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Small artery dysfunction is known in women with a history of gestational diabetes (GDM). In Manchester Mothers' Vascular Health Study, we hypothesised that women in the upper quartile (UQ) of plasma glucose during pregnancy, have impaired vascular function when compared with those in the lower half (controls). The UQ group was sub-divided into GDM and sub-GDM (glucose values below GDM

values). 29 participants were studied post-natally for structure and endothelial dependent (ED- carbachol induced)/non-endothelial dependent (nED-sodium nitroprusside induced) function of subcutaneous small arteries using wire myograph.

We conclude that in post-natal women, prior glycaemic change is associated with small arterial structural and functional differences.

Mean (95(percent) CI)	Control group (n = 8)	Sub-GDM (n = 13)	GDM (n = 8)
Media:lumen ratio	55 (39–71)	55 (47–64)	44 (27–61)
Max. ED-relaxation (percent)	70 (58–85)	49 (39–62)*	43 (30–62)*
Max. nED-relaxation (percent)	59 (40–78)	53 (39–57)	41 (17–65)

* $P < 0.05$ vs controls. Adjusting for glycaemic group, day in menstrual cycle and triglycerides, small artery parameters were independently influenced by:

Beta (P value)	Age	BMI	Smoking	SBP	Total cholesterol
Media:lumen ratio	—	2.6 (0.003)	—	-1.1 (0.01)	—
Max. ED relaxation (percent)	—	-1.9 (0.003)	12.6 (0.02)	—	-10.9 (0.01)
Max. nED relaxation (percent)	2.9 (0.04)	-3.5 (0.01)	—	—	—

PB.3. Investigating the relationship between microvascular rarefaction and systemic hypertension: a mathematical and computational model of the circulation

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Structural rarefaction has been demonstrated in hypertensive patients, normotensive offspring of hypertensive parents and animal models of hypertension during early life, leading to speculation on its aetiological importance in hypertension. We have simulated microvascular rarefaction in a circulatory mathematical model and investigated the functional relationship between microcirculatory rarefaction and macrovascular haemodynamics.

Systemic arteries are treated as a bifurcating tree of compliant and tapering vessels. Flow and pressure in the large arteries are predicted from a nonlinear one-dimensional cross-sectional area-averaged model. Smaller vessels within vascular beds are modelled as an asymmetric structured tree. Structural rarefaction is modelled by altering the area ratio between parent and daughter vessels at bifurcations, resulting in (i) fewer generations within the vascular tree and (ii) vessel radii decreasing in

size with generation number more rapidly than normal. Ascending aortic flow data measured by MRI from healthy individuals of varying ages (22–60 years) were used as input data for the model. Pressure and flow are generated at points spaced at 0.25 cm throughout the vascular tree at 0.0012 s intervals.

Pressure and flow waveforms at key points within the circulation were analysed. Increasing degrees of microcirculatory rarefaction resulted in increased systolic and (to a greater extent) diastolic blood pressure. Effects on pulse pressure, augmentation index and the pressure wave morphology were variable.

This pilot study supports the hypothesis that microcirculatory rarefaction increases systolic and diastolic blood pressure. The model also provides a general tool to investigate the influence of the microvasculature on systemic haemodynamics.

PB.4. The role of the central sympathetic drive in the growth of left ventricular mass as determined by MRI in human essential hypertension

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Central sympathetic activation occurs in essential hypertension (EHT) and is further augmented when left ventricular hypertrophy (LVH) is clinically detected by echocardiography or electrocardiography. However, the relationship between

sympathetic activation and left ventricular mass (LVM) has not been clearly defined in the absence of LVH.

This study was planned to determine that relationship, using cardiac MRI to accurately quantify

LVM, in EHT patients with and without LVH and normal subjects.

24 patients with uncomplicated and untreated EHT were compared to 25 patients with EHT and LVH (EHT+LVH) and 24 normal control subjects (NC). Resting muscle sympathetic nerve activity was quantified as multiunit bursts (MSNA) and single units (s-MSNA). LVM was quantified by cardiac MRI.

The LVM indexed to body surface area (LVMI) in EHT group ($67 \pm 2.1 \text{ g/m}^2$) was between those of EHT+LVH ($91 \pm 3.4 \text{ g/m}^2$) and NC ($57 \pm 2.2 \text{ g/m}^2$) groups. The sympathetic activity in EHT group (53 ± 1.3 bursts/100 cardiac beats and 63 ± 1.6 impulses/100 cardiac beats) was between (at least

$P < 0.001$) those of EHT+LVH (66 ± 1.7 bursts/100 cardiac beats and 77 ± 2.2 impulses/100 cardiac beats) and NC (39 ± 3.0 bursts/100 cardiac beats and 45 ± 3.4 impulses/100 cardiac beats) groups.

There was a significant positive correlation between sympathetic activity and LVMI in EHT and EHT+LVH groups (at least $r = 0.76$, $P < 0.0001$), but not in NC group. However, there was no consistent relationship between arterial blood pressure and sympathetic activity or LVMI.

These findings support the hypothesis that central sympathetic activation is implicated in causing sub-clinical as well as overt pathological increases in LVM in human hypertension.

PB.5. The contribution of central sympathetic drive to the reversal of left ventricular hypertrophy in human hypertension as quantified by microneurography and MRI

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Left ventricular hypertrophy (LVH) of hypertension is an independent cardiovascular risk, which is reduced by therapeutic regression of LVH. Anti-hypertensive regimens lead to varying degrees of left ventricular mass (LVM) regression, by reducing arterial pressure load and effects on sympatho-humoral factors.

We quantified the contribution of therapeutically inhibiting central sympathetic drive to regression of LVM.

In a prospective and randomised trial, we independently measured muscle sympathetic nerve activity (MSNA) by peroneal microneurography and LVM by MRI in two matched groups of newly diagnosed hypertensive patients. One group received Valsartan and Moxonidine (Val/Mox), and the other Bendroflumethiazide and Amlodipine (BFZ/Amlod). Doxazosin ensured similar reductions of arterial pressure.

At baseline, Val/Mox (15) and BFZ/Amlod (15) groups had similar (unpaired *t* test) age (54 ± 2.5 and

49 ± 2.5 years; mean \pm s.e.m.), BMI (28 ± 1.0 and $30 \pm 1.0 \text{ g/m}^2$), BSA (1.98 ± 0.04 and $1.97 \pm 0.05 \text{ m}^2$), heart rate (68 ± 1.8 and 69 ± 2.3 beats/min), arterial pressure (123 ± 3.3 and $122 \pm 3.2 \text{ mm Hg}$), MSNA (64 ± 2.6 and 61 ± 2.1 bursts/100beats), LVM index (87 ± 4.2 and $85 \pm 3.4 \text{ g/m}^2$) and gender ratio. After 6 months, Val/Mox decreased (paired *t* test, $P < 0.0001$) mean arterial pressure by $-24 \pm 3.0 \text{ mm Hg}$ ($19 \pm 2.3\%$) to a similar extent ($P > 0.3$) as BFZ/Amlod of $-25 \pm 3.5 \text{ mm Hg}$ ($-20 \pm 2.8\%$). The respective LVM index decreases were -13 ± 1.4 ($-15 \pm 1.4\%$) and $-9.5 \pm 1.2 \text{ g/m}^2$ ($-11 \pm 1.2\%$) ($P < 0.0001$). MSNA decreased only in Val/Mox (-11 ± 1.6 bursts/100 beats or $-17 \pm 2.6\%$, $P < 0.0001$). This was accompanied by a greater reduction of LVM ($P < 0.03$) and its percentage ($P < 0.02$) in Val/Mox than in BFZ/Amlod.

Therapeutic reduction of central sympathetic drive significantly enhanced LVH regression beyond that caused by reducing arterial pressure.

PC.1. EUROACTION: A European Society of Cardiology demonstration project in preventive cardiology – one year results for coronary patients and their partners

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Objective: EUROACTION is a cluster randomised controlled trial of a multi-disciplinary preventive cardiology programme which aims to manage coronary patients and their families to the European lifestyle, risk factor and therapeutic targets for cardiovascular disease prevention.

Methods: In each of 6 European countries, a pair of general hospitals was randomised to attend the 16 week EUROACTION programme or to be monitored for usual care. All patients and partners were assessed at one year.

Achieving European targets at one year (%)	Patients		Partners	
	INT	UC	INT	UC
Proportion of target group [†] not smoking	58	47	23	18
Saturated fat <10% of total energy	55*	40	60	42
Fruits and vegetables >400 g/day	72*	35	72*	37
Oily fish >3 times/week	16*	8	11	8
Achieving ideal waist circumference	35*	22	32	26
Physical activity target	54*	20	41	27
BP <140/90 mm Hg (<130/85 mm Hg in diabetics)	65*	55	67	63
TC <5 mmol/l	78	71	35	33
LDL-C <3 mmol/l	81	74	43	40
Hba1c <7% (in those with diabetes)	61	50	**	**
Antiplatelet therapy	93	92	14	14
Beta-blocker	76	80	17	17
ACE inhibitor	52	56	16	10
Statin	86*	80	19	15

* $P < 0.05$; [†]smoking in the month prior to event; **numbers too small for statistical testing.

Results: In intervention (INT) hospitals 1589 eligible patients (828 partners) were identified and 946 (401) participated at one year. In usual care (UC) 1499 eligible patients (802 partners) were identified and 994 (335) attended 1 year assessment.

Conclusions: The EUROACTION programme helped coronary patients and their families to achieve the European targets on cardiovascular prevention and to raise the standards of preventive cardiology in everyday clinical practice.

PC.2. Treating blood pressure not cardiovascular risk: could we be doing harm?

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Current guidelines suggest drug treatment independent of risk when pressures exceed 160 mm Hg systolic or 100 mm Hg diastolic. However benefit is proportional to placebo group events and trials including low risk patients or low risk subgroups suggest only little benefit or even harm.

Access to individual patient data from the original MRC study¹ allowed a test of net benefit in patients at low CVD risk. Sufficient baseline demographic data were abstracted to produce individual Framingham risk estimates. Age and gender specific HDL and missing total cholesterol values were imputed from the 1984 Scottish Heart Health study². Analysis was limited to those with estimated CVD risk <20% over 10 years but with baseline systolic blood pressure >160 mm Hg or diastolic >100 mm Hg.

Cox proportional hazard analysis shows that, although non-significant, the proportionate reduc-

tion in non-fatal stroke or MI in this group is similar to that in the trial as a whole with Hazard Ratio 0.78 (95% CI 0.50–1.19) and NNT 278. However overall mortality is significantly and substantially increased independent of sex with Hazard Ratio 1.67 (95% CI 1.05–2.64) and NNH 139.

The MRC study used propranolol or high dose bendroflumethiazide, drug classes shown to be slightly inferior to newer drugs if used in combination³. Nevertheless the ensuing equipoise makes a placebo controlled trial against modern treatment in low risk patients an ethical proposition.

1. MRC Working Party. *BMJ* 1985; **291**: 97–104.
2. Smith WCS *et al. Scot Med J* 1989; **34**: 550–555.
3. Dahlöf B *et al. Lancet* 2005; **366**: 895–906.

PC.3. New-onset diabetes in hypertensive patients: an evaluation of the association with drug therapy and cardiovascular mortality

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Background: Large prospective outcome trials have shown that thiazide diuretics and beta blockers (β B) convey increased risk of developing type II diabetes in patients with hypertension, while ACE inhibitors (ACE I) and angiotensin receptor blockers (ARB) reduce this risk. The prognostic significance of this is yet to be determined. We evaluated this in a group of hypertensive patients.

Methods: The Glasgow Blood Pressure Clinic database holds data on 6533 patients with diabetic status and blood glucose confirmed at first clinic visit. Follow-up for survival is available via the Scottish deaths register. Cox proportional hazards models were used. Drug regimens were defined as (1) no drug of interest, (2) β B and thiazide therapy and (3) ACEI or ARB therapy. Mortality was defined as ischaemic heart disease (IHD), stroke and all cause.

Results: During a median follow-up duration of 9.24 years, 5938 remained diabetes free, 332 had pre-existing diabetes and 263 developed new diabetes. No significant differences in new diabetes were seen across drug regimens.

There were 1621 deaths. IHD mortality was increased in those with pre-existing diabetes (HR 2.24, 95%CI 1.65–3.05) and those with new onset diabetes (HR 1.63, 95%CI 1.13–2.34) compared to those who remained diabetes free. Similar findings were seen for all cause mortality. Stroke mortality was only increased in those with pre-existing diabetes.

Conclusions: Our data differ from findings of recent prospective outcome trials but support the assertion that new onset diabetes in patients with hypertension is associated with significantly increased mortality, particularly that due to IHD.

PC.4. Urinary albumin excretion in hypertensive siblings in the British Genetics of Hypertension study

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Background: Urinary albumin excretion(UAE) is a marker of increased cardiovascular risk, even at levels below the threshold for microalbuminuria. UAE has also been associated with blood pressure progression, but its role in pathogenesis is still unclear. We studied the heritability and phenotypic association of UAE in a large cohort of severely hypertensive siblings.

Material and Methods: 1275 individuals from the MRC BRIGHT study had urinary albumin-creatinine ratio (UACR) measured. A UACR of 0–30 mg/mmol indicated presence of UAE. Heritability was determined by variance component methods. A random intercept logistic model was used to test associated traits with presence of UAE as it takes into account familial correlations.

Results: UAE was present in 826 individuals and 23 individuals with UACR > 30 were excluded from the study. The concordance rate for UAE among hypertensive siblings was 30% and the heritability of UACR as a normalised trait was 33%. After accounting for familial correlations, the significant traits associated with UAE are on-treatment SBP (OR 1.01 CI 1.01–1.02 $P = <0.0001$), Waist-Hip-Ratio (3.18 CI 1.03–9.77 $P = 0.044$), serum Na (1.05 CI 1.02–1.09 $P = 0.0025$), eGFR (0.99 CI 0.99–1.00 $P = 0.04$).

Conclusions: We have demonstrated in a large cohort of hypertensive siblings that UAE is heritable. We have also shown a strong association between UAE and waist-hip ratio. Further studies are needed to clarify whether UAE in these individuals are a consequence of vascular damage or a marker of high risk hypertensive subgroups.

PC.5. Serum uric acid and stroke mortality in patients with hypertension

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Background: Most epidemiological studies support an association between elevated serum uric acid (UA) and cardiovascular mortality. The relationship with stroke is less clear; studies have often been limited by low stroke rates. We examined this

association in hypertensive patients from the West of Scotland.

Methods: The Glasgow Blood Pressure Clinic database holds data on 11399 patients. Follow up for survival is available via the Scottish deaths register. A

Cox proportional hazards model was used to assess the relationship between UA and stroke mortality.

Results: UA results were available for 6207 patients (mean UA 0.34 mmol/l). There were 354 stroke deaths. Following full adjustment, a strong trend toward increased stroke mortality with increasing UA was apparent. However, sex specific analyses

revealed a significant positive association only in females (Table 1). The relationship appeared J-shaped.

Conclusions: Our results suggest that in hypertensive patients, UA is associated with increased stroke mortality but predominantly in females. This may be because of lower baseline risk.

Table 1. Results are expressed as Hazard Ratio (HR) \pm 95% CI

Stroke mortality across quintiles of serum uric acid			
Uric acid quintile	Whole population (HR+95% CI)	Males (HR+95% CI)	Females (HR+95% CI)
1	1.67 (1.16–2.4)	1.3 (0.75–2.26)	2.16 (1.33–3.5)
2	1	1	1
3	1.04 (0.69–1.45)	0.75 (0.44–1.26)	1.44 (0.85–2.43)
4	1.35 (0.95–1.92)	0.93 (0.58–1.47)	1.98 (1.18–3.32)
5	1.4 (0.98–2)	0.96 (0.6–1.52)	2.09 (1.23–3.55)

PD.1. The metabolism of asymmetric dimethyl L-arginine (ADMA) is increased in chronic kidney disease

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Background: Asymmetric dimethyl L-arginine (ADMA), an endogenous inhibitor of nitric oxide synthase, accumulates in chronic kidney disease (CKD). This has been attributed to diminished excretion and reduced metabolism to dimethylamine (DMA) by the enzyme dimethylarginine dimethylaminohydrolase (DDAH) which is widely expressed, especially within the kidney. The metabolism of ADMA *in vivo* has not been studied. We propose that the urinary DMA:ADMA ratio reflects DDAH activity, and that this method can be used to study ADMA metabolism in human CKD.

Methods: We collected serum and timed 24 h urine collections from CKD patients [$n=28$, creatinine clearance (CrCl) 54 ml/min] and from a matched population without CKD [$n=33$, CrCl 98 ml/min]. ADMA and symmetric dimethyl L-arginine (SDMA) were determined by electrospray mass spectrometry-mass spectrometry, and DMA by high-performance liquid chromatography with pre-

column derivitization with 9-fluorenyl-methylchloroformate.

Results: Serum ADMA, SDMA and DMA were, in the CKD and non-CKD groups respectively: 0.50 vs 0.43 μ mol/L ($P<0.001$); 0.75 vs 0.46 μ mol/L ($P<0.001$); 2.37 vs 1.3 μ mol/L ($P<0.001$). Urinary ADMA excretion was markedly reduced, whereas DMA excretion was unchanged. The urinary DMA:ADMA ratio was higher in the CKD group (14.3 vs 8.5 respectively, $P<0.001$), and correlated strongly with serum creatinine ($r=0.81$, $P<0.001$ [$n=61$]).

Conclusions: The metabolism of ADMA by DDAH increases in CKD, and this is inversely related to renal excretory function. Our findings suggest that DDAH activity prevents greater accumulation of ADMA in CKD than would otherwise be the case. Urinary DMA:ADMA ratios are a useful method for studying the metabolism of ADMA *in vivo*.

PD.2. The effect of fludrocortisone on plasma aldosterone levels in healthy volunteers and patients with Conn's syndrome

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Introduction: Fludrocortisone suppression tests with salt-loading have been used to diagnose hyperaldosteronism. In this study, we aimed to

dosing at ~9am on Day 1, and 6 h post the final dose on Day 3 (~3pm).

Results:

	Pre fludrocortisone			Conn's +	Post fludrocortisone		
	K ⁺ (mmol/l)	Renin (mu/l)	Aldosterone (pmol/l)		K ⁺ (mmol/l)	Renin (mu/l)	Aldosterone (pmol/l)
Mean	3.62	4.2	928.6		3.40	3.6	644.6
Range	3.4–3.9	3–5	362–1553		3.2–3.7	2–5	294–1325

	Pre fludrocortisone			Non-Conn's	Post fludrocortisone		
	K ⁺ (mmol/l)	Renin (mu/l)	Aldosterone (pmol/l)		K ⁺ (mmol/l)	Renin (mu/l)	Aldosterone (pmol/l)
Mean	4.33	17.6	379.7		3.97	11.8	<143.0
Range	3.8–5.2	6–31	200–593		3.6–4.5	2–19	<100–204

determine whether fludrocortisone suppresses plasma aldosterone without salt-loading in subjects on low-salt diets (urinary Na⁺ <160 mmol/24 h). Additionally, we hoped to gather further data to support the existence of an adrenal aldosterone receptor, since laboratory results indicate that the components of a functional aldosterone response pathway exist in human adrenal zona glomerulosa cells. **Study design:** 9 healthy subjects and 5 patients with Conn's tumours were enrolled in a double-blind, cross-over study. All were dosed for 3 days with fludrocortisone (400 µg/day) or placebo. Blood samples were taken for K⁺, renin and aldosterone before

Conclusions:

- Aldosterone secretion varies diurnally, especially in patients with Conn's tumours
- Fludrocortisone alone may suppress aldosterone levels (without Na⁺ loading) in healthy subjects
- Suppression of aldosterone secretion could be enhanced by the fall in plasma K⁺ with fludrocortisone treatment
- The fact that aldosterone levels fall despite no significant suppression of plasma renin in some volunteers suggests that there is a direct action on the adrenal gland

PD.3. Improved blood pressure control in hypertensive patients with osteoarthritis treated with lumiracoxib compared with ibuprofen: a randomized controlled trial

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In the TARGET study, patients treated with lumiracoxib 400 mg od (4 × recommended dose for osteoarthritis [OA]) had lower office blood pressure (BP) than those taking NSAIDs (naproxen 500 mg bid or ibuprofen 800 mg tid), at Week 4 and maintained to Week 52.^{1,2} We investigated whether lumiracoxib 100 mg od would have lower 24-h mean systolic ambulatory BP (MSABP) com-

pared with ibuprofen 600 mg tid in treated hypertensive patients with OA in a 4-week randomized, double-blind, double-dummy, parallel-group study. Eligible patients (≥50 years, office BP <140/90 mm Hg taking stable antihypertensive treatment) were randomized to lumiracoxib 100 mg od or ibuprofen 600 mg tid. The primary outcome was the change in 24-h MSABP from baseline at Week 4.

Secondary endpoints included 24-h mean diastolic ambulatory BP (MDABP) and efficacy (pain) measurements. 787 patients were randomized ($n=394$ lumiracoxib, $n=393$ ibuprofen). Compared with baseline, 24-h MSABP was 2.7 mm Hg lower for lumiracoxib and 2.2 mm Hg higher for ibuprofen at 4 weeks, estimated difference -5.0 mm Hg (least squares [LS] mean; $P<0.001$) in favour of lumiracoxib. The change in 24-h MDABP at Week 4 was -1.5 mm Hg (lumiracoxib), $+0.5$ mm Hg (ibuprofen), a difference of -2.0 mm Hg (LS mean;

$P<0.001$). Efficacy results were comparable. Adverse events (AEs) were similar in both groups. Six serious AEs were reported (lumiracoxib [$n=1$]; ibuprofen $n=5$). Conclusion: in OA patients with controlled hypertension, lumiracoxib treatment resulted in better BP control than a commonly used NSAID.

1. Farkouh *et al.* Lancet 2004; **364**: 675–684.
2. Farkouh *et al.* Arthritis Rheum 2006; **54** (Suppl. 1): S678.

PD.4. Acute elevation of free fatty acids has opposing effects on forearm and systemic vascular resistance

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Background: An acute elevation of plasma non-esterified fatty acids (NEFA) and triacylglycerol (TAG) by infusion of 'intralipid' markedly decreases forearm vascular resistance but tends to increase blood pressure. This suggests an increase in cardiac output or opposite changes in forearm and other vascular beds. The aim of this study was to investigate the effects of an infusion of intralipid on cardiac output (CO) and systemic vascular resistance (SVR).

oscillometry using an Omron 705CP. Cardiac output (CO) was determined by pulmonary uptake of soluble and inert gas tracers (Innocor, Innovision) and systemic vascular resistance (SVR) calculated from mean arterial blood pressure (MAP) and CO. Blood flow (velocity time integral, VTI) was measured in the radial artery by doppler ultrasound (Acuson CV 70, Siemens, USA).

Results:

Change (Δ) from baseline at 2 and 4 h (means \pm s.d.).

	Saline		Intralipid	
	2 h	4 h	2 h	4 h
Δ CO (L. min ⁻¹)	0.74 \pm 1.61	0.57 \pm 0.84	-0.40 \pm 1.22	-0.18 \pm 1.78
Δ SVR(mm Hg.L.min ⁻¹)	-2.78 \pm 4.26	-2.68 \pm 2.53	0.93 \pm 2.55*	0.63 \pm 3.06*
Δ MAP(mm Hg)	-2.8 \pm 8.04	-4.4 \pm 8.06	1.4 \pm 4.17	0 \pm 6.96
Δ VTI (ms ⁻¹)	-1.4 \pm 1.33	-0.58 \pm 3.15	3.43 \pm 1.71**	1.28 \pm 1.68
Δ HR (min ⁻¹)	4.15 \pm 6.30	4.3 \pm 6.20	-0.35 \pm 4.37	0.6 \pm 6.22

* $P<0.05$, ** $P<0.01$ vs saline.

Methods: Healthy men ($n=10$) received an infusion of intralipid (150 mg min⁻¹ of soybean oil: total fat 36 g) with heparin (0.2 unit kg⁻¹ min⁻¹) or saline placebo over 4 h in a single blind, 2-phase cross-over study. Blood pressure was measured by

Conclusion: Infusion of intralipid decreases forearm vascular resistance but increases SVR suggesting opposite changes in forearm and vascular beds other than those supplying skeletal muscle.

PD.5. Baroreceptor function changes with differing blood pressure treatment during the Anglo-Scandinavian Cardiac Outcomes Trial: principal results from the Cardiac Autonomic Reflex Assessment Trial (CARAT)

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Baroreflex function predicts outcome, but studies looking at BP lowering drugs have usually been of 3 months duration. The Cardiac Autonomic Reflex Assessment Trial (CARAT) measured baroreflex function during long-term follow up during ASCOT.

ASCOT assessed the impact of two BP lowering regimens; atenolol +/-thiazide (ATN) vs amlodipine +/-perindopril (AML) in 19 257 hypertensive patients. Carotid sinus baroreceptor reflex sensitivity (BRS) was assessed in 285 patients using graded square wave neck suction. In 191 of these patients baroreflex function was also assessed during 5 min of controlled breathing at 0.1 Hz (Davies).

Patients tested after 3 years, in 2001 (n=85) showed no difference in response to square wave neck suction whether treated with ATN or AML (BRS mean 1.4 ms/mm Hg vs 1.2 ms/mm Hg n.s.).

Later, at 5–6 years, BRS was similar in the ATN group, but significantly enhanced in those on the AML (n=61, BRS mean 1.5 ms/mm Hg vs n=57 BRS 2.1 ms/mm Hg, P<0.05 ANOVA).

At the close of ASCOT, Baroreflex sensitivity measured in 191 patients using the controlled breathing method, averaged 10.4 +/-0.6 ms/mm Hg on ATN, and was greater on AML, 12.9 +/-0.9 ms/mm Hg (P<0.01). Brachial blood pressures did not differ between the groups, and at closeout averaged 129.5 +/-1.1 mm Hg systolic in the ATN group and 129.8 +/-1.1 in the AML group, (diastolic pressures 76.3 +/-0.9 vs 75.4 +/-1.0 mm Hg).

CARAT provides the first data on BRS after prolonged administration of differing BP lowering regimens. Improved baroreflex sensitivity was shown after more than 4 years of therapy with AML. The improved BRS may reflect lower central blood pressures on amlodipine as measured in the CAFÉ study.

PD.6. Prediction of new-onset diabetes in patients randomly assigned to nifedipine or hydrochlorothiazide and amiloride: suggestive evidence for the importance of muscle blood flow in regulating glucose tolerance in hypertension

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New-onset diabetes (DM) during treatment with thiazide diuretics poses a major health hazard. In the International Nifedipine Study (INSIGHT), there was a 30% dose-related excess in the co-amilozide group. During recent design of a project to investigate pharmacogenetic prediction of DM, further analyses of INSIGHT were undertaken. Their aims were to assess the predictive value of baseline measurements, the additional contribution of treatments, and differences between these.

DM on entry to INSIGHT. Thiazide-induced DM was commoner in women. Unexpectedly we found a strong, inverse correlation with serum creatinine, stronger in the thiazide than nifedipine patients (Exp(B)=1.8 vs 1.0); a similar inverse correlation was found with DM on entry (Exp(B)=0.26, P=10⁻⁸). Baseline glucose was substantially lower in the 136 nifedipine than 176 co-amilozide cases (6.97 vs 7.41 mmol/L, P=0.003).

Table 1. Incidence of New-onset Diabetes by drug-group in INSIGHT

	Monotherapy		Combination			Total
	Low dose	High dose	+atenolol	+enalapril	+both	
Nifedipine	32	29	40	21	13	136
%	4.2	3.7	8.1	8.4	6.9	5.4
HCTZ/amil	31	58	43	17	27	176
%	3.9	8.2	8.9	7.1	10.1	7.0

(Brown MJ, Palmer CR, Castaigne A *et al. Lancet* 2000;356:366–342)

Logistic regression was performed of new-onset DM upon the five variables in Table 2, and eleven others, including urea, HDL, K⁺, BP. Whereas the model had 99.5% accuracy in excluding DM, only 38 cases (12%) were predicted overall, and 9.7% in the diuretic group. This low value for new DM contrasted with a 65% prediction for 1250 cases of

Table 2. Logistic Regression for New-onset DM

	B	Wald	Sig.	Exp(B)
Glucose	0.042	242.50	0.00000	1.04
Creatinine	-2.06	29.06	0.00000	0.14
Gender	0.64	16.82	0.000	1.91
BMI	0.060	16.49	0.00000	1.06
Treatment	-0.43	9.81	0.001	1.52

Thiazide treatment powerfully influences risk of DM. The fascinating creatinine result, not described in normotensive populations, is compatible with a major role for skeletal muscle in disposing of glucose in hypertensive patients. Reduced muscle blood flow may contribute to new-onset DM on co-amilozide.

PE.1. Changes in arterial reservoir function, not wave reflection, account for the effect of ageing on pressure augmentation in the proximal aorta

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Background: Augmentation of the aortic pressure waveform is increasingly being recognised as mechanistically important in cardiovascular disease. It is usually explained by earlier arrival of a distally reflected wave. Yet, it might be explained alternatively by capacitive properties of the aorta and other elastic arteries (arterial reservoir function or Windkessel). In this study we determined the respective contributions of the arterial reservoir and the forward and backward travelling waves to pressure augmentation, and assessed how these contributions change with age.

Method and Results: In 18 subjects (aged 53 ± 10 years) we measured pressure and Doppler velocity simultaneously in the proximal aorta using intra-arterial wires. We applied an established pressure separation technique which ignores the arterial reservoir and a new wave-reservoir approach, which accounts for the arterial reservoir, to calculate the components of augmentation pressure. Augmentation pressure was 22.7 ± 13.9 mm Hg.

When reservoir pressure was ignored this was separated into a small forward wave pressure (6.5 ± 9.4 mm Hg) and a larger backward (reflected) wave pressure (16.2 ± 7.6 mm Hg). After accounting for the reservoir pressure, the backward wave pressure was reduced by 68% to 5.1 ± 5.5 mm Hg ($P < 0.001$) and reservoir pressure was found to be the largest component of augmented pressure (17.6 ± 13.2 mm Hg, $P < 0.001$). Forward pressure was found to no longer contribute to augmentation pressure. Reservoir pressure was found to increase with age (5.8 mm Hg/decade, $r = 0.67$, $P < 0.002$) and correlated closely with aortic pulse wave velocity ($r = 0.69$, $P < 0.001$).

Conclusions: Augmentation pressure is principally determined by the reservoir function of the aorta and other elastic arteries and only to a minor extent by reflected waves. Changes in reservoir function rather than wave reflection account for the changes in the aortic pressure waveform which occur with ageing.

PE.2. Exercise pulse wave velocity can be measured by photoplethysmography and increases with cardiovascular risk

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Resting pulse wave velocity (PWV) and exercise BP are better predictors of cardiovascular outcome than resting BP. The utility of exercise PWV is unclear, as motion artefact makes measurement technically challenging. This study evaluated exercise PWV measured by a simpler technique, photoplethysmography (PPG).

Study 1: PPG-PWV was measured from finger/ear waveforms (PWV-EF), and compared against radial-carotid applanation tonometry (PWV-CR) in 18 healthy subjects at rest, during and after exercise. Study 2: PWV-EF was evaluated following maximal exercise in young, healthy individuals with ($N = 14$, male = 6) and without ($N = 24$, male = 13) a cardiovascular disease family history (FH).

Study 1: PWV-CR increased from 6.9 ± 0.7 m/s (rest) to 8.3 ± 0.6 m/s (peak exercise) ($P = 0.002$). PWV-EF increased from 7.8 ± 0.9 m/s to 8.9 ± 1.4 m/s ($P = 0.024$). PWV-CR returned to baseline at 5-min, but PWV-EF remained elevated at 10-min

(8.3 ± 0.9 m/s, $P = 0.027$). Overall, PWV-EF was higher than PWV-CR (0.8 ± 1.1 m/s, $P < 0.001$), but the degree of difference between the two methods did not vary over time ($P = 0.42$, repeated-measures ANOVA). Change from baseline was also not significantly different between methods ($P = 0.20$, rmANOVA). Study 2: no significant differences in resting BP, mean pressure or PWV were found between FH- and FH+ groups ($123/73 \pm 17/8$ vs $120/74 \pm 11/6$ mm Hg, $P > 0.51$; 92 ± 7 vs 94 ± 8 mm Hg, $P = 0.30$; 11.3 ± 1.7 vs 10.6 ± 1.6 m/s, $P = 0.25$ respectively). Following exercise, no differences were found in the increase in BP ($+62/-2 \pm 24/14$ vs $+59/3 \pm 15/19$ mm Hg, $P > 0.41$) or mean pressure ($+22 \pm 18$ vs $+27 \pm 15$ mm Hg, $P = 0.66$), but PWV increased significantly more in the FH+ group ($+1.8 \pm 1.4$ vs $+3.0 \pm 1.9$ m/s, $P = 0.035$).

PWV is relatively easily measured during exercise by PPG, and may have a role in cardiovascular risk assessment.

PE.3. Ambulatory recording of orthostatic hypotension is associated with increased arterial stiffness in chronic kidney disease

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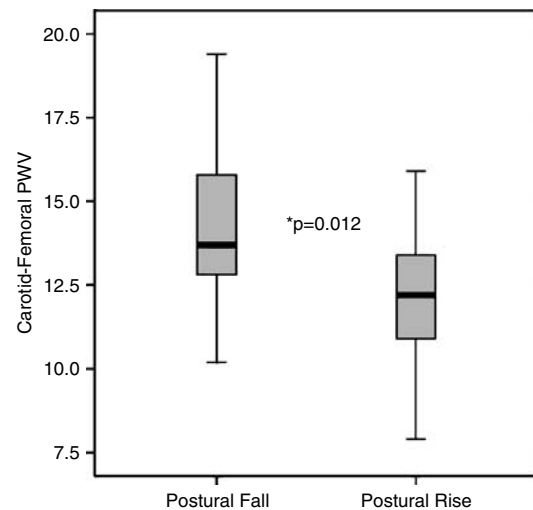
Objective: Chronic Kidney Disease (CKD) is associated with increased cardiovascular risk and autonomic dysfunction. Aortic stiffening has been associated with orthostatic hypotension but association between postural blood pressure variation over 24 h and arterial stiffness has not previously been reported.

Design and Method: 58 subjects with MDRD GFR 15–60 mls/min underwent measurements. Pulse wave velocity was measured in the carotid-femoral region using Complior[®]. Augmentation Index (AI) was measured at the right radial artery using Sphygmacor[®]. 24-h ambulatory blood pressure monitoring (24-hr ABPM) with validated integral position sensor was performed. Results were divided into groups whose mean 24-hr systolic blood pressure (SBP) rose ('postural rise') or fell ('postural fall') compared to mean 24-hr lying SBP.

Results: 12 subjects experienced a fall in mean SBP on standing. There was no significant difference in age (67.2 ± 1.7 vs 70.1 ± 3.3 years, $P=0.45$), MAP (111.1 ± 3.4 vs 105.9 ± 1.5 mm Hg, $P=0.14$) or smoking history (22.9 ± 5.3 vs 22.6 ± 5.7 pack years, $P=0.56$) between the groups. The postural fall group had higher eGFR than the postural rise group (31.9 ± 3.5 vs 28.7 ± 1.5 mls/min/1.73m², $P=0.03$). Protein: creatinine ratio was greater in the postural fall group (170.0 ± 75.5 vs $74.1 \pm$

15.7 mg/mmol, $P=0.05$). C-F PWV (14.2 ± 0.82 vs 12.2 ± 0.33 m/s, $P=0.01$) and radial AI (31.9 ± 3.3 vs 27.2 ± 1.6 %, $P=0.02$) were greater in the postural fall group.

Conclusions: Arterial stiffness is increased in patients whose SBP falls whilst standing, when measured over 24 h. This may contribute to the high cardiovascular morbidity and mortality in this group.



PE.4. Pulsatile arterial pressure is predominantly determined by the aortic reservoir, which can be determined non-invasively from peripheral measurement sites

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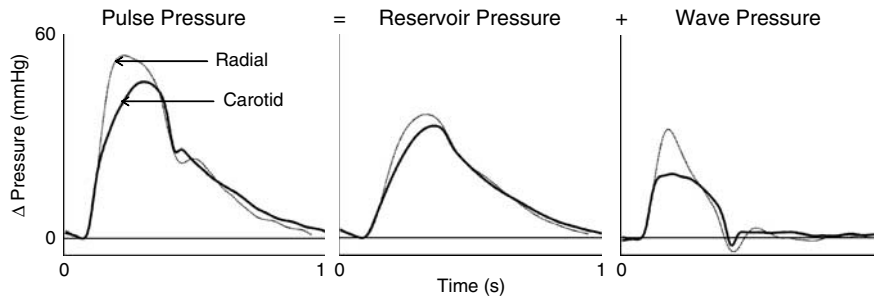
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Introduction: There is a large variation in the pulse pressure waveform in systole throughout the arterial system. However, at these corresponding sites, the diastolic phase appears almost identical. We hypothesise that this is because diastolic pressure is predominately determined by the reservoir properties of the central elastic arteries, despite large differences in wave reflection and local compliance of the peripheral arteries themselves. Using a new technique to calculate the arterial reservoir, we compare these properties at two arterial sites to assess the contribution of the central reservoir in the determination of the peripheral pressure waveform.

Method and Results: Pressure and velocity were measured non-invasively at right common carotid and radial arteries in 14 healthy volunteers (9 male,

49 ± 11 years). using tonometry, calibrated to brachial blood pressure, and Doppler ultrasound. We calculated the reservoir pressure and compliance (local pulse wave velocity). The time constant of the diastolic decay was calculated from the exponential rate of decline in pressure after the dicrotic notch. Reservoir pressure was the largest overall contributor of pressure in the carotid (28.0 ± 4.8 mm Hg), and radial (32.0 ± 6.2 mm Hg). The diastolic decay was similar in each artery (carotid: 427 ± 281 ms vs radial: 427 ± 320 ms ($P>0.99$)) despite large differences in local pulse wave velocity (carotid: 7.2 ± 2.6 ms⁻¹ vs radial: 10.9 ± 5.0 ms⁻¹, $P<0.05$).

Conclusion: The reservoir is the largest determinant of pulsatile pressure and is similar in central and peripheral arterial sites, despite local compliance



varying significantly. Estimation of reservoir pressure in the radial artery may be a simple and useful

indicator of the properties of the aorta and large elastic arteries.

PE.5. A comparison of atenolol and nebivolol in isolated systolic hypertension

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Atenolol is less effective in reducing central blood pressure than other antihypertensive drugs, which may explain the higher rate of events in subjects randomized to atenolol in recent trials. We hypothesized that nebivolol would be more effective than atenolol in reducing central blood pressure and augmentation index (AIx). The aim of the present study was to test this in a double-blind, randomized, cross-over study, in a cohort of subjects with isolated systolic hypertension.

Following a 2 week placebo run-in, 16 never-treated hypertensive subjects received atenolol (50 mg), nebivolol (5 mg), and placebo, each for 5 weeks, in a random order. Seated brachial blood pressure and heart rate were measured. Aortic blood pressure, AIx and pulse wave velocity (PWV) were assessed non-invasively.

The placebo-corrected fall in brachial pressure was similar between nebivolol and atenolol, as was the reduction in PWV (mean change \pm s.e.m: -1.0 ± 0.3 and -1.2 ± 0.2 m/s; $P=0.2$). However, there was less reduction in heart rate (-19 ± 2 vs -23 ± 2 beat/min; $P<0.01$), and increase in AIx ($+6 \pm 1$ vs $+10 \pm 1$ %; $P=0.04$), following nebivolol. Aortic pulse pressure was significantly lower (50 ± 2 vs 54 ± 2 mm Hg; $P=0.04$) after nebivolol. N-terminal proBNP increased similarly after both drugs (101 ± 31 vs 77 ± 24 pg/mL; $P=0.6$).

Nebivolol and atenolol have similar effects on brachial blood pressure and aortic stiffness. However, nebivolol reduces aortic pulse pressure significantly more than atenolol, which may be related to a less pronounced rise in AIx and bradycardia. Whether this will translate into differences in clinical outcome requires further investigation.

