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The number of each abstract on the following pages corresponds to that which appeared in the program. Only abstracts that authors approved for publication appear. AAS and AVBS abstracts are not included.

Editor: **Brian J Morris, AM DSc PhD FAHA**

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RD Wright Lecture

Early vascular aging in hypertension: from EVA to SUPERNOVA

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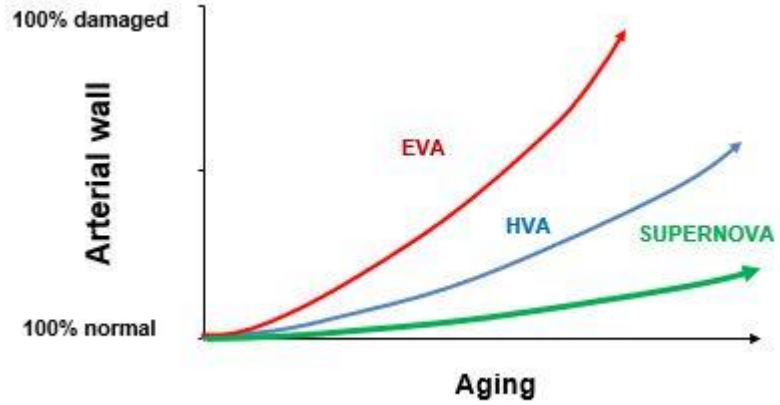
Arterial stiffness is a simple and robust parameter that is able to estimate vascular ageing, and particularly early vascular ageing (EVA). EVA is diagnosed in patients with an abnormally increased arterial stiffness for their age and sex. The ageing of the large artery wall is characterized by a progressive reduction in the elastin content, in parallel with an increased amount of collagen, and changes in cell-matrix interactions, leading to increased arterial stiffness. EVA represents an altered capacity for repairing arterial damage in response to aggressions like mechanical stress and metabolic/chemical/oxidative stresses. In other words, EVA-arterial stiffening is an integrator of all damage done to the arterial wall. It differs from the usual 'snapshot' that physicians get from their patients when they only measure blood pressure, cholesterol and glycemia. This is why EVA-arterial stiffness has a higher predictive value for cardiovascular (CV) events than classical CV risk scores. The epidemiological determinants of EVA are not only the classical risk factors, such as blood pressure, hyperglycaemia, insulin resistance/type 2 diabetes, obesity/abdominal fat, metabolic syndrome, dyslipidaemia, and smoking, but also sedentary behaviour, lack of physical activity, high salt intake, chronic low grade inflammation, oxidative stress, social deprivation, perceived stress, inadequate diet, alcohol consumption, and a number of genetic factors. EVA is a useful concept for primary CV prevention. Indeed, EVA can be easily detected by the non-invasive measurement of the carotid-femoral pulse wave velocity (cf-PWV). A cf-PWV that is abnormally high for a given age indicates extensive arteriosclerosis of the aortic pathway, a marker of cardiovascular risk. The higher the cf-PWV, the higher the risk of CV events, such as stroke, myocardial infarction and CV mortality. The measurement of cf-PWV is recommended by the 2013 ESH-ESC Guidelines for the management of hypertension, in order to better assess target organ damage (here, the arterial system), estimate the CV risk, and commence appropriate measures aimed at reducing the CV risk, such as antihypertensive treatment, cessation of smoking, hypolipemic agents and antidiabetic agents. *The Lancet* commission on hypertension (Olsen *et al. Lancet* 2016) integrated the concept of EVA in a life course strategy to address the global burden of high blood pressure. EVA is only one aspect of the entire spectrum of arterial ageing that spans from 'supra-normal' vascular aging (SUPERNOVA) to healthy vascular aging (HVA), and then to EVA. SUPERNOVA is the opposite of EVA, since it is diagnosed in patients with an abnormally low (i.e., below the 2.5^{th} percentile) arterial stiffness for their age and sex. The epidemiological determinants of SUPERNOVA include normal blood pressure, normal glycaemia, normal weight, normal lipids, low salt, calorie restriction, no smoking, intense physical activity, no perceived stress, no social deprivation, normal sleep pattern, normal prenatal fetal growth, no inflammation and insensitivity to oxidative stress. Searching for the molecular determinants of SUPERNOVA is of outmost importance, since it can be an effective way to discover pharmacological means to retard arterial aging. Animal models, such as the naked mole rat, that has a maximum lifespan potential of more than 30 years and a constitutive upregulation of numerous anti-oxidants, detoxicants, molecular chaperons and proteasome components, may help to better understand how to identify the most effective molecules to retard the

arterial ageing process.



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British and Irish Hypertension Society Invited Speaker

The relationship between aortic stiffness and cardiac remodelling in younger adults with type 2 diabetes

William Hunt

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Background: Heart failure is now the most common and most deadly complication of type 2 diabetes (T2D). Diabetic cardiomyopathy is well recognized, but the main aetiological causes are uncertain. Aortic stiffness (AoS) is frequently observed in patients with T2D and is associated with adverse cardiovascular events. Cardiovascular magnetic resonance (CMR) imaging can quantify AoS directly as aortic distensibility (AD), or indirectly with aortic pulse-wave velocity (aPWV). We hypothesized that AoS would be independently associated with cardiac remodelling in younger adults with T2D.
range
Methods: Eighty patients with uncomplicated T2D (median age 44 years (32–57)) and no prior cardiovascular disease underwent comprehensive CMR scanning. Blinded scans were analysed for ascending AD (AAD), descending AD (DAD), aPWV and LV remodelling (LVmass/volume and LV mass index (LVMI)). Multivariate linear regression assessed whether AoS independently predicted LV remodelling.

Results: We show for the first time that, when adjusted for age, systolic BP, BMI, heart rate, diabetes duration and HbA1c, AAD and DAD, but not aPWV, independently predicted LVMI and LVM/volume (Table 1).

Conclusions: AD is independently associated with cardiac remodelling in T2D. This suggests that ventricular/arterial interactions may play a significant role in cardiac risk in T2D. AoS may be a potential therapeutic target, independent of blood pressure control, to prevent heart failure in T2D.

LVM/volume	Univariate	Multivariate	LVMI	Univariate	Multivariate
AAD ($x10mmHg^{-3}$)	r=-0.417, p<0.001	β=-0.344, p=0.003	**AAD ($x10mmHg^{-3}$)**	r=-0.424, p<0.001	β=-0.264, p<0.001
DAD ($x10mmHg^{-3}$)	r=-0.425, p<0.001	β=-0.349, p=0.005	**DAD ($x10mmHg^{-3}$)**	r=-0.437, p<0.001	β=-0.281, p<0.001

Table 1: Pearson correlations and multivariate regressions

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American Heart Association Invited Speaker
Heme redox switches and blood pressure control

Adam Straub

University of Pittsburgh, Pittsburgh, PA, USA

ABSTRACT ---- PLEASE INSERT

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HBPRCA Austin Doyle Lecture

A view into human kidney morphogenesis using stem cells

Melissa Little

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The capacity to generate a pluripotent stem cell from any somatic cell type has revolutionized stem cell biology. The development of protocols for the stepwise differentiation of such pluripotent cells, not only to specific cellular endpoints but complex 3D organoids representative of developing human tissues, completely changes the future prospects of stem cell medicine. It is hoped that such stem cell-derived human tissue will drive personalised disease modelling, toxicity and screening, cell therapy and even tissue bioengineering. It is also hoped that this will provide a window into human development not previously available and potentially allow the dissection of the biophysical requirements for tissue self-organization. All of this will depend upon how reliably these models mirror normal human development at the level of cellular identity, multicellular complexity and functional maturation. We have developed a protocol for the generation of kidney organoids (Takasato *et al*., *Nature* 2015) from human pluripotent stem cells. This protocol relies upon the stepwise recapitulation of morphogenetic events previously characterized during normal kidney development in the mouse. Hence, the validity of the model remains to be investigated. Using CRISPR-Cas9 editing, we have developed a suite of reporter lines that is now allowing us to query the accuracy of patterning within the organoids, the lineage relationships during organoid formation and the transcriptional (bulk and single cell) profiles of individual cell types. We are also applying CRISPR-Cas9 gene editing to patient stem cell lines to test the capacity of organoids to model human kidney disease. Finally, the use of fluorescent reporter lines is facilitating real-time imaging after *in vivo* transplantation to assess the degree to which we can mature such stem cell-derived tissue for renal replacement

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Colin I Johnston Lecture

Blood pressure measurement accuracy –through shades of grey where are we going?

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Measurement of blood pressure is a cornerstone method in medical practice. Being able to accurately identify chronically raised blood pressure is important because blood pressure can be treated with medication or lifestyle intervention to not only lower blood pressure but reduce the risk for cardiovascular events. The auscultatory and oscillometric cuff blood pressure methods used in clinical practice are based on measurement principles more than a century old, with little change to improve precision. Currently, there are about 3,000 commercially available cuff blood pressure devices, for which less than 20% have publicly accessible information on performance with respect to accuracy testing according to expected scientific standards. Indeed, when directly compared against invasive (intra-arterial) blood pressure, many cuff devices are inaccurate within the systolic blood pressure range of 120 to 160 mmHg (with both under- and over-estimation) – the range pertaining to most people worldwide. The reasons underlying such measurement imprecision are multifactorial, and span factors ranging from regulatory loopholes that allow sale of devices with uncertain accuracy to individual clinical characteristics associated with systematic and random bias. A multitude of new technologies have emerged in recent years to measure blood pressure with cuffless sensors and continuous monitoring using a variety of recording methods over durations that may extend to weeks or months. These technologies present opportunities to improve hypertension detection and control, as well as to advance systems of healthcare delivery. Conversely, various challenges are created for issues such as clinical validity, integration, safety and utility. Despite all the uncertainty, this rapidly evolving field appears set for moving towards better and more accurate blood pressure measurement.

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Aetiology of essential hypertension: A possible unifying hypothesis

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Background: The aetiology of essential hypertension is poorly understood. Studies of the physiological control of blood pressure have not provided an explanation. The circulation represents a closed loop. The pressure within a loop must reflect the pressure generated by a pump (heart), resistance to outflow, volume of fluid within the loop and stiffness of the wall.

Aim: To understand the cause(s) of hypertension in order to explain it to the layperson.

Methods: The hypothesis presented is the result of an extensive review of the medical literature.

Results: Increased cardiac output cannot be the cause of hypertension as left ventricular hypertrophy only develops after long-standing hypertension. Resistance to outflow cannot be the explanation either. It reflects the Bayliss phenomena and resolves with treatment of hypertension. Increased stiffness of the arterial wall due to arteriosclerosis with superimposed atherosclerosis fulfils Koch's 1st postulate and is the principle cause of essential hypertension. It commences decades before the onset of hypertension and increases in severity with age, as does the incidence of essential hypertension. Increased intravascular blood volume (as much as 2–3 litres) with obesity and a smaller contribution from excess salt consumption and/or increased peripheral resistance as a result of increased blood viscosity related to an elevated LDL exacerbate the severity of essential hypertension.

Conclusions: Essential hypertension is secondary to and not the primary cause of arteriosclerosis with secondarily superimposed atherosclerosis.

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Superior performance of seated versus recumbent saline suppression testing for the diagnosis of primary aldosteronism 3

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Background: Failure of plasma aldosterone (aldo) to suppress during fludrocortisone (FST) or saline (SST) suppression testing confirms primary aldosteronism (PA). Aldo can be higher upright (e.g., seated) than in recumbent PA; upright levels are used for FST. We hypothesized that seated SST (SSST) is more sensitive than recumbent (RSST). In a pilot study of 24 patients with confirmed PA, 23 tested positive by SSST vs. 8 by RSST (*J Clin Endocrinol Metab* 2014;99:2745). Numbers were too small, however, to determine if this was the case for the unilateral, surgically curable form of PA, or to compare specificity of SSST vs RSST.

Aim: To (1) validate results of our pilot study and compare SSST with RSST in terms of sensitivity for detecting both unilateral and bilateral forms of PA and specificity, using an expanded cohort, and (2) determine optimal diagnostic criteria for SSST as a reliable and more convenient alternative to FST in confirmatory testing for PA.

Methods: The current validation study involved 100 patients who underwent FST, RSST and SSST, eight before and after unilateral adrenalectomy. Of the 108 FSTs, 73 confirmed and 18 excluded PA. Four patients with inconclusive FST lateralized on adrenal venous sampling making a total of 77 with PA.

Results: The area under the receiver-operating characteristic (ROC) curve was greater for SSST than RSST (0.96 vs. 0.80; $P < 0.01$). ROC analysis predicted optimal cut-off aldosterone levels of 162 pmol/L for SSST and 106 pmol/L for RSST. At these cut-offs, SSST showed high sensitivity for PA (87%) that markedly exceeded that for RSST (38%; $P < 0.001$), but similar specificity (94 vs. 94%; NS). SSST was more sensitive than RSST in detecting both unilateral (n = 28; 93 vs. 68%; $P < 0.05$) and bilateral (n = 40; 85 vs. 20%; $P < 0.001$) forms of PA. Only three SSST (vs. 9 RSST and 17 FST) results were inconclusive.

Conclusions: SSST is highly sensitive and superior to RSST in identifying both unilateral and bilateral forms of PA and has a low rate of false positives and inconclusive results. It therefore offers a reliable and much less complicated and expensive alternative to FST for the confirmation of PA.

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Novel CIC-2 chloride channel mutations cause familial hyperaldosteronism type II

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Background: Primary aldosteronism (PA), the most common cause of secondary endocrine hypertension, exists in both familial and apparently non-familial forms. While the genetic bases of familial hyperaldosteronism type I (FH-I), FH-III, FH-IV and FH-V have already been established, the pathophysiology of FH-II [Stowasser *et al*., *CEPP* 1992;19:319]) remains unknown.

Aim: To identify genetic mutations responsible for FH-II.

Methods: Exome sequencing of an extended Australian family followed by Sanger sequencing of 80 additional kindreds diagnosed with early-onset PA revealed five different mutations in the gene *CLCN2* encoding the chloride channel ClC-2: Met22Lys, Tyr26Asn, Arg172Gln, Lys362del, and Ser865Arg. Among these, Arg172Gln was present in 13 individuals from four independent kindreds. Met22Lys and Arg172Gln in one kindred occurred *de novo*.

Results: Of the 8 members of the Australian family who were mutation carriers, 5 (63%) were female, 4 (50%) had hypertension diagnosed before the age of 25y (the other 4 being normotensive when last assessed, one at 49 years and the other 3 before 20 years), 3 (38%) were hypokalemic, 7 (88%) had borderline (n=1) or frankly elevated plasma aldosterone/renin ratios, and of the 5 who underwent further assessment, all demonstrated failure of plasma aldosterone to respond to upright posture or to suppress normally during 4 days administration of oral fludrocortisone administration and salt loading. Computed tomography of the adrenals (n=4) revealed either no abnormality, or mild bulkiness or nodularity. Adrenal venous sampling (n=3) demonstrated bilateral adrenal production of aldosterone as expected. Electrophysiology demonstrated increased relative open probabilities of all mutant channels at the glomerulosa resting potential of –80 mV. Because intracellular glomerulosa chloride concentrations are high, these effects cause depolarization of the cell membrane. Expression of ClC-2 could be detected in the zona glomerulosa of human adrenal glands via immunohistochemistry. RT-qPCR investigations showed an increased expression of the aldosterone synthase gene *CYP11B2* after transfection of all mutant *CLCN2*-encoding CIC-2 channels compared to the transfection of the wild-type channel.

Conclusions: Our findings establish germline gain-of-function *CLCN2* mutations as a cause of FH-II and for the first time implicate an anion channel in adrenal aldosterone production and hypertension. The underlying pathophysiology is increased chloride permeability, depolarization and voltage-gated calcium influx, followed by *CYP11B2* upregulation. In

practice, this enables the genetic diagnosis of affected patients and family members.

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A novel catecholamine-sparing strategy to protect the renal microcirculation in septic acute kidney injury

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Background: In septic shock, excessive sympathetic activity can lead to catecholamine-refractory hypotension and acute kidney injury (AKI) leading to increased mortality. High doses of noradrenaline are required in such cases to attain target blood pressure.

Aims: To (1) examine the effects of noradrenaline on the renal macro- and microcirculation in ovine septic AKI, and (2) to determine the effects of the alpha2-adrenoreceptor agonist, clonidine, on renal sympathetic nerve activity (RSNA) and pressor responsiveness to phenylephrine.

Methods: We implanted a renal artery flow probe, nerve recording electrodes and laser-Doppler/oxygen-sensing probes in the renal cortex and medulla in sheep. We infused *Escherichia coli* to induce septic AKI in conscious sheep. Noradrenaline (0.4–0.8 μg/kg/min), clonidine (1 μg/kg/h) or vehicle-saline were infused (24–32h of sepsis) (all n=8). Pressor responses to phenylephrine were measured at baseline, and at 24 and 32 h of sepsis.

Results: Septic AKI was characterized by hypotension (~20%) and reduced creatinine clearance (~60%). Despite global renal and cortical hyper-perfusion, medullary perfusion and oxygenation decreased (both ~50%). Restoring blood pressure with noradrenaline further reduced medullary perfusion (~70%) and oxygenation (~80%). Sepsis was associated with increased RSNA (~75%) and blunted pressor responses to phenylephrine (~50%). Clonidine-treatment substantially reduced RSNA and fully restored pressor responsiveness to phenylephrine.

Conclusions: Renal medullary hypoxia due to intra-renal shunting of microvascular perfusion may contribute to septic AKI. Resuscitation with noradrenaline further worsened the underlying medullary hypoxia in septic AKI. Reducing noradrenaline requirements with alpha2-adrenoreceptor agonists may minimize the harmful effects of excessive catecholamines on the renal microcirculation and mitigate the progression of septic AKI.

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Sex differences in the association between aortic stiffness and orthostatic blood pressure changes

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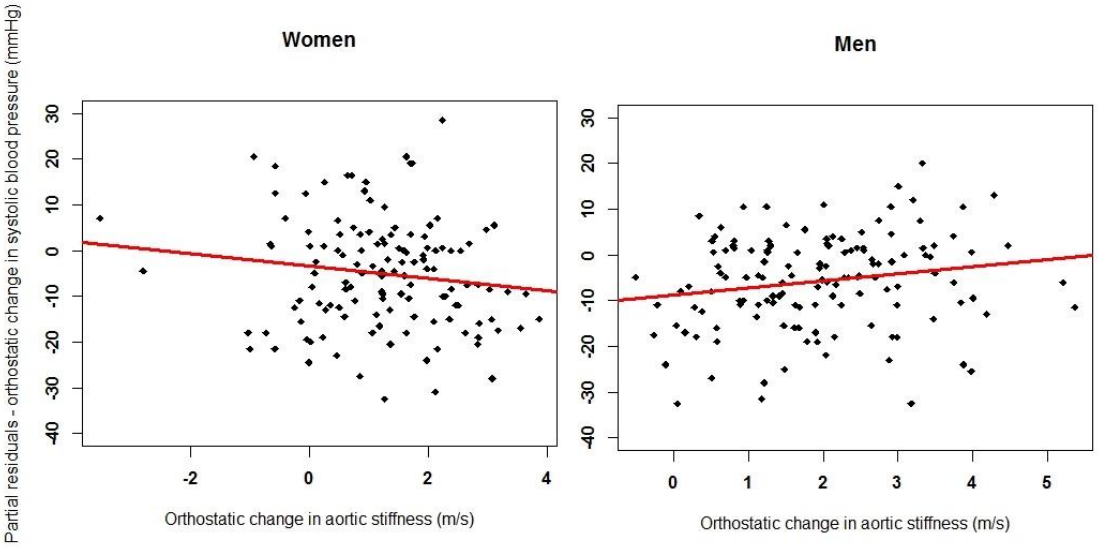
Background: Orthostatic blood pressure (BP) changes are associated with cardiovascular disease. Aortic stiffness could affect BP responses to postural changes, but the influence of sex differences on the pressure dependency of arterial stiffness is unclear.

Aim: To investigate the relationship between aortic stiffness and orthostatic-BP changes, as well as the influence of sex, which is a moderator of aortic stiffness.

Methods: Duplicate BP and aortic stiffness measures were recorded whilst supine and after 2-minutes standing in 271 patients with uncomplicated hypertension (50% female; aged 60 [range 23–73] years). Orthostatic-BP and aortic stiffness changes were determined as the differences from supine to standing. BP was measured by a validated oscillometric device and aortic stiffness was measured by carotid-to-femoral pulse-wave-velocity (XCEL, AtCor Medical, Australia).

Results: Orthostatic-systolic BP (SBP) changes averaged –5.4±11.0 (mean±SD) mmHg, with no differences between sexes. However, the orthostatic change in aortic stiffness was higher in men compared with women (1.9±1.2 vs. 1.3±1.2 m/s; $P < 0$ .05). There were only weak or non-significant associations between supine aortic stiffness and changes in BP for women and men. However, in multivariate analyses, orthostatic change in aortic stiffness was negatively associated with orthostatic-BP change in women, but positively associated in men (B=–1.97 [95%CI: –3.57, –0.37], P=0.02 and B=1.71 [95%CI: 0.34, 3.07], P=0.01, respectively) (Figure).

Conclusions: Orthostatic change in aortic stiffness is associated with orthostatic change in SBP among patients with uncomplicated hypertension. However, the direction of this association differs by sex, suggesting that the underlying pressure-dependent mechanisms of arterial stiffness may also differ. A better understanding of these interactions may have relevance to the new approaches of BP treatment and arterial stiffness as a marker of cardiovascular disease.


Women
Men
Partial residuals - orthostatic change in systolic blood pressure (mmHg)
30
20
10
0
-10
-20
-30
-40
-2
0
2
4
1
3
5
Orthostatic change in aortic stiffness (m/s)
Orthostatic change in aortic stiffness (m/s)

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Endothelial dysfunction and reduced volume compliance in Schlager hypertensive (BPH/2J) mice.

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Background: The BPH/2J mouse is a genetic model of hypertension that has been researched for over 20 years. The hypertension in BPH/2J mice has been well-characterized and is associated with an overactive sympathetic nervous system. Less is known about the vascular pathophysiology of BPH/2J mice.

Aim: To examine vascular function and remodelling in systemic vessels from hypertensive BPH/2J mice and normotensive BPN/3J mice.

Methods: Blood pressure was measured in 14-week-old BPH/2J and BPN/3J mice via radiotelemetry. Wire and pressure myography were used to analyse vascular function and passive mechanical wall properties of larger conduit (abdominal aorta and femoral) and smaller resistance-type (mesenteric) arteries.

Results: BPH/2J mice were hypertensive compared to BPN/3J mice (Table). In BPH/2J mice, relaxation to acetylcholine was blunted in the aorta and mesenteric arteries, indicating endothelial dysfunction. In the mesenteric arteries, this was underpinned by a significant reduction in the contribution of the nitric oxide and endothelium-derived hyperpolarization. In contrast, the contribution of prostanoids to endothelium-dependent relaxation was significantly reduced in the hypertensive aorta. Interestingly, vasoconstriction to angiotensin II, phenylephrine and the thromboxane mimetic U46619 were all increased in mesenteric arteries from BPH/2J mice (Table). Structural abnormalities suggestive of hypertrophic inward remodelling were also observed in the arteries of BPH/2J mice (increased wall thickness and reduced inner and outer diameters). Conversely, hypertension did not affect femoral artery wall thickness or vessel diameter. Despite this, both mesenteric and femoral arteries had reduced volume compliance in BPH/2J mice.

Conclusions: This comprehensive study in BPH/2J mice confirms that this strain is a robust model of hypertension-induced vascular dysfunction and adverse remodelling, and that it may be a suitable mouse model for testing new vascular therapies for hypertension.

RESULTS:	BPN/3J	BPH/2J
Mean arterial pressure (mmHg)	107 ± 1	128 ± 3*
Heart rate (bpm)	447 ± 11	599 ± 22*
Mesenteric artery function		
Acetylcholine pEC_{50}	8.55 ± 0.32	5.13 ± 0.80*
Sodium nitroprusside pEC_{50}	8.09 ± 0.23	8.21 ± 0.22
Iloprost pEC_{50}	8.79 ± 0.24	8.20 ± 0.11*
Angiotensin II E_{max}	32.1 ± 8.92	96.59 ± 5.13*
Phenylephrine pEC_{50}	6.06 ± 0.18	6.70 ± 0.09*
U4119 pEC_{50}	8.34 ± 0.12	8.72 ± 0.07*
Aortic function		
Acetylcholine pEC_{50}	7.55 ± 0.10	6.55 ± 0.19*
Sodium nitroprusside pEC_{50}	8.07 ± 0.10	8.25 ± 0.12
Phenylephrine pEC_{50}	5.68 ± 0.03	7.14 ± 0.17*

*P<0.05 significantly different to BPN/3J (unpaired student's t-test).
pEC_{50} = sensitivity (−log (half-maximal effective concentration));
E_{max} = maximum response.

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Identifying adolescents at high risk of cardiometabolic disorders

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Background: Although cardiovascular disease manifests in adulthood, atherosclerosis begins in childhood. Identifying children most at risk has relied on individual risk factors or estimation of their cumulative effects in the 'metabolic syndrome'. This metric relies on cut-points for several risk factors and may miss individuals at high risk of adult cardiovascular disease.

Aim: To compare the prevalence, stability and estimated cardiovascular risk in a population of 17 and 20 year-olds defined either by clustering of cardiometabolic risk factors or by the metabolic syndrome.

Methods: Anthropometry, blood pressure and fasting bloods were obtained from participants attending the 17-year (n=1048) and 20-year (n=1120) surveys of the West Australian Pregnancy Cohort (Raine) Study. Cluster analysis at 17 and 20 years used BMI, systolic BP, triglycerides and insulin resistance to define high– and low- risk clusters. Cluster membership stability was assessed in 806 participants measured at both time points. Lifetime cardiovascular risk (Q-Risk) and Framingham 30-year risk were compared in the low-risk cluster and in the high-risk cluster with and without the metabolic syndrome.

Results: The high-risk cluster comprised 17.9% and 21.3% of the cohort at 17 and 20 years, respectively. Seventy-two percent of participants in the high-risk cluster at 17 years remained in that cluster at 20 years, and had higher BMI, waist circumference and CVD risk scores than the low-risk cluster. The metabolic syndrome was identified in only 1.2% and 3.4% of participants at 17 and 20 years, respectively. Compared with the low-risk cluster, Q-risk and Framingham risk at 20 years was increased by 17–23% ($P < 0.001$), in the high-risk cluster participants without the metabolic syndrome and by 47–119% ($P < 0.001$) in those with the metabolic syndrome.

Conclusions: We have shown that, even in the absence of the metabolic syndrome, a large number of individuals are at substantially increased risk of CVD. Therefore, the use of continuous risk scores rather than categorical metabolic syndrome cut-points should be used to define CVD risk in adolescents and young adults.

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Hemoglobin and blood pressure in a Chinese community-dwelling population

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Background: Studies showing associations of increased levels of haemoglobin (Hb) and erythropoietin with elevated blood pressure have been mainly conducted in patient cohorts. The few reports for the normal population are restricted to healthy voluntary blood donors.

Aim: To investigate the association between Hb levels and systolic (SBP) and diastolic (DBP) blood pressure in a large community-dwelling cohort with normal glucose metabolism.

Methods: The study population comprised 9181 (3888 male) subjects (age 29–95 years) with normal glucose tolerance from the Xuhui District community of Shanghai. Hb, fasting plasma glucose, glycated haemoglobin A1c (HbA1c), hepatic and renal function, lipids, electrolytes and anthropometric parameters were measured. Normal glucose tolerance was defined as plasma glucose level ≤ 126 mg/dl and HbA1 < 6.5%.

Results: Hb level was found to be positively but weakly correlated with SBP (r=0.075, P <0.001) and more strongly correlated with DBP (r=0.272, $P < 0.001$) in the cohort. The relationship was not affected by age, body mass index (BMI), serum creatinine (Cr) nor low density lipoprotein (LDL) in both males and females. Multivariate stepwise regression analysis showed age (β=0.556, $P < 0.001$), BMI (β =1.107, $P < 0.001$), Hb (β=0.082; $P <$ 0.001), Cr (r= –0.032, $P < 0.001$), and LDL (r=1.023, $P < 0.001$) were independent predictors for SBP and Hb (β=0.168, $P < 0.001$), BMI (β=0.519, P=0.001), and LDL (β =0.331, $P <$ 0.001) predictors for DBP.

Conclusions: In a Chinese community-dwelling population with normal glucose metabolism, although Hb level is positively associated with both SBP and DBP, it has a much stronger association with DBP.

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Osteocalcin is negatively associated with C-reactive protein and positively associated with systolic blood pressure in Chinese women

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Background: Inflammation exacerbates age-related diseases such as osteoporosis, type 2 diabetes and atherosclerosis. Osteocalcin (OCN), a bone formation marker, can suppress inflammation to improve bone and glucose metabolism. Increase in osteoblast activity is also associated with vascular calcification, which in turn contributes to vascular stiffness and elevated systolic blood pressure (SBP).

Aim: To investigate the association of OCN with the inflammation marker C-reactive protein (CRP) and with SBP.

Methods: The study subjects comprised 160 women (age 21–81 years) with normal glucose tolerance (NGT) and normal blood pressure (NBP). Serum OCN, fasting plasma glucose, and 2 h post-challenge glucose levels during oral glucose tolerance test, fasting insulin, glycated hemoglobin A1c (HbA1c), hepatic and renal functions, electrolytes, CRP, SBP and diastolic pressure were measured.

Results: Serum OCN was negatively associated with CRP (r=–0.107, *P*=0.001) and positively associated with SBP after adjustment for confounding factors (r=0.23, *P*=0.003). Age (r=0.094, *P*=0.005), body mass index (r=–0.498, *P*=0.005) and SBP (r=0.132, *P*=0.029) were the major determinants of the variations of OCN (adjusted R^2 = 0.608, *P*=0.01). When SBP was used as a dependent variable, age (β =0.344, *P*=0.001), body weight (r=0.303, *P*=0.001), fasting plasma glucose OCN (r=0.209, *P*=0.049), entered the regression model (adjusted R^2 = 0.420, *P*=0.028). Compared with the lowest SBP group, there was an increase in OCN between the groups (*P*=0.001), and the highest OCN levels were observed in subjects in the highest SBP group, even when multiple confounders were adjusted (*P*=0.015).

Conclusions: The bone formation marker, serum OCN, was negatively associated with CRP and positively associated with SBP in NGT and NBP women. Whether the increased OCN level in NGT and NBP subjects is an early marker predicting the subtle rise in blood pressure and the risk of occurrence of hypertension requires further study.

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Development of algorithms to predict cardiovascular health in renal transplant patients: The role of CMV

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Background: Predictive algorithms are needed to assist physicians in reducing future cardiovascular outcomes and prolonging lifespan of the transplant. Cytomegalovirus (CMV) has been implicated with accelerated cardiovascular changes in renal transplant recipients (RTR) and may warrant inclusion.

Aim: To investigate whether markers of CMV burden, systemic, vascular and inflammatory biomarkers can provide a predictive algorithm of vascular assessments in the future to reduce cardiovascular events.

Methods: RTR (n=46) who have been stable for several years after transplantation and age-matched controls (n=58) were recruited in 2014, and retested in 2017.nPlasma proteins linked with inflammation (sIFNaR2, sTNFR1, sCD14, CRP) or vasculopathy (p-selectin, ICAM-1, VCAM-1), and metrics of the burden of CMV assessed in 2014 were evaluated as predictors of the vascular health assessed in 2017 using brachial artery flow mediated dilatation (FMD) to assess peripheral vessels and pulse wave analysis [augmented index corrected for heart rate of 75 bpm (Aix@75)] to assess central vessels.nThe burden of CMV was assessed using antibody reactive with CMV lysate, gB or IE-1 (by ELISA), CMV DNA in saliva (by quantitative PCR) and T-cell IFN gamma responses to CMV antigens (by ELISpot).

Results: In a multivariable regression model adjusted for age, sex and BMI, CMV gB antibody and saliva CMV DNA associated with higher FMD values in RTR (adjusted R^2 = 0.421), with gB antibody associated with protection (*P*=0.015) and CMV DNA with risk (*P*=0.012). In contrast, p-selectin (*P*=0.03) and ICAM-1 (*P*=0.003) influenced FMD values in controls (adjusted R^2=0.274). With the same adjustments, (R^2 = 0.380), worsened Aix75 was optimally predicted by CMV IE-1 antibody (*P*=0.097) and sIFNa R^2 (*P*=0.03) in RTR, whilst ICAM-1 (*P*=0.008) influenced Aix75 in controls (R^2=0.406) with marginal effects of CMV IE-1 antibody and sTNFR1.

Conclusions: Overall measures of a high burden of CMV predicted surrogate markers of vascular health in RTR several years after assessment with more potency than was achieved with plasma proteins considered to mark systemic and vascular inflammation. These markers were more potent than metrics of CMV in control subjects. Antibody reactive with CMV gB may be protective.

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Human renin promoter interactions with gene neighbours and loci genome-wide

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Background: Transcriptional control of expression of the human renin gene (*REN*) promoter has been elucidated by the first author's Lab and by others. In recent times, there has been considerable interest in the role that genome-wide interactions play in gene action. These interactions have physiological and pathophysiological implications.

Aim: To determine gene-gene interactions for the human *REN* proximal promoter locally and genome-wide.

Methods: The WashU Epigenome Browser public database and the Chromatin Space Interaction (CCSI) website were used to determine contact points for interactions. The CCSI database contains 91 sets of chromosomal three-dimensional (3D) data collected from published literature, the University of California, Santa Cruz (UCSC) database and the NCBI Gene Expression Omnibus (GEO) database, that has resulted in a total of 3,017,962 pairwise interactions.

Results: We found that the *REN* promoter was connected via RNA polymerase II binding to its 11 neighboring genes over a distance of 762,497 bp. These genes formed clusters bounded by CTCF-binding sites that insulate them from their gene neighbours. The genes formed 3 topologically associated domains: TAD1: *ZC3H11A*, *SNRPE*, *LINC00303*, *SOX13* ; TAD2: *ETNK2*, *REN*, *KISS1*, *GOLT1A*; TAD3: *PLEKHA6*, *LINC00628*, *PPP1R15B*, *PIK3C2B* and *MDM4*, indicating that they form 3 distinct domains that likely represent actively-regulated chromatin compartments. TAD1 and TAD3 genes were co-expressed in various tissues suggesting co-regulation. TADs 1 and 3 contained super-enhancers (which are regions with high densities of enhancers). One super-enhancer overlapped with the location of *SOX13*, while another overlapped the long intergenic noncoding RNA (lincRNA), *LINC00628*. These super-enhancers likely regulate their respective TADs. REN, via RNA polymerase II and CTCF binding sites, also makes inter-chromosomal contacts with 62 specific genes, including the angiotensin receptor gene, AGTR1, on 18 chromosomes, not including X and Y.

Conclusions: *REN* interacts with 11 neighbouring genes, that include two lncRNA genes, on chromosome 1q32.1, as well as with 62 other genes across the genome. Expression of these may be influenced by super-enhancers. Since CTCF insulators are known to break down with age, and distant genes within TADs typically become co-regulated with TAD-central super enhancers, these new data may foster understanding of *REN*-related pathways during the aging process that leads to cardiovascular disease, cancers and other diseases of ageing.

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Association between serotonin 2A receptor (HTR2A) gene and incident hypertension

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Background: Hypertension is a one of the risk factors for obesity-related cardiovascular diseases. Several studies have assessed an association between 5-hydroxytryptamine (serotonin) 2A receptor (5-HTR2A) gene (*HTR2A*) polymorphisms and an increased risk of hypertension.

Aim: To investigate the effect of genetic variations of *HTR2A* on elevated blood pressure.

Methods: This was a cross-sectional study of 6008 adults aged 40–70 years, who did not have hypertension in 2005–2008. We tested for association of six *HTR2A* polymorphisms, three intronic (*rs733636*, T102C (*rs6313*), and *rs4941573*) and three in flanking DNA (*rs136020*, rs4531630 and *rs1706983*) with an increased risk of hypertension.

Results: In the participants who developed hypertension, the baseline systolic blood pressure and body mass index were 142.1SD±15.96 mg/dl and 24.9SD±3.34 kg/m^2, respectively. These parameters were higher than in those who did not develop hypertension .

Conclusions: Elevated and decreased blood pressure are associated with polymorphisms in *HTR2A*.

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MicroRNA-132 is associated with blood pressure and liver steatosis in obese individuals

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Background: Obesity is associated with numerous comorbidities including cardiovascular disease, diabetes and non-alcoholic fatty liver disease (NAFLD). Obesity pathogenesis is complex and incompletely understood. Hence therapeutic options to address the global epidemic of obesity are lacking. In addition, NAFLD is strongly linked to cardiovascular disease. Our recent findings in experimental models have shown that microRNA miR-132 is an important regulator of liver homeostasis.

Aim: To assess miR-132 expression in liver and fat tissue of obese individuals and its association with blood pressure and hepatic steatosis.

Methods: The cohort consisted of 19 obese individuals (14 females and 5 males) undergoing bariatric surgery for weight management . They were aged 39±2SE years with a body mass index (BMI) of 42±1SE kg/m^2. Extensive clinical and demographic information was collected for each patient. Supine blood pressure was on average 127±4 mmHg (systolic) and 74±2 mmHg (diastolic) and heart rate was 67±24 beats/min. According to Adult Treatment Panel III, the participants had 2.2±0.3 metabolic abnormalities. Quantitative PCR was performed to determine tissue expression of miR-132 in liver and matched subcutaneous and visceral fat biopsies in these patients. Liver biopsies were read by a single hepatopathologist using a standardized pathological approach and graded in terms of steatosis, inflammation and fibrosis.

Results: Hepatic and visceral fat expression of miR-132 were strongly correlated (r=0.729, *P*=0.005). Hepatic miR-132 expression was also correlated with BMI (r=0.641, *P*=0.018), triglycerides (r=0.604, *P*=0.029), systolic blood pressure (r=0.577, *P*=0.039) and heart rate (r=0.694, *P*=0.009). Visceral fat miR-132 expression was associated with BMI (r=0.746, $P < 0.001$) and liver steatosis (r=0.533, *P*=0.33). There was no correlation between subcutaneous and visceral expression of miR-132 (*P*=0.21).

Conclusions: Our data supports miR-132 playing a causal role in cardiovascular and metabolic consequences of obesity in humans. Given the increasing public burden of obesity and associated comorbidities, novel therapeutic approaches are needed for prevention and treatment of these diseases. In addition, further targeted search for biomarkers in complex diseases such as obesity, cardiovascular disease and NAFLD are warranted.

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Transgenerational prevention of heart failure through maternal intake of high fibre

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Background: Emerging evidence suggests dietary intake of fibre protects against the development of cardiovascular disease (CVD) through the production of gut microbial metabolites. While maternal intake of macronutrients such as protein has been associated with blood pressure and CVD in the offspring, the intergenerational effect of fibre intake and gut microbiota composition has yet to be elucidated.

Aim: To determine if dietary intake of fibre during pregnancy can prevent the development of cardiac hypertrophy and heart failure through changes in the gut microbiota and metabolites using the angiotensin II (Ang II) model of hypertension.

Methods: C57BL/6 female mice were fed a diet without ('no fibre') or with high levels of resistant starches ('high fibre') during gestation. After weaning, all male offspring, independently of the mothers' diet, consumed a standard chow diet for the duration of the study. At 6-weeks of age, minipumps containing saline or Ang II (0.25 mg/kg/day) were implanted subcutaneously. No fibre sham (n=5), no fibre Ang II (n=7), high fibre sham (n=8), high fibre Ang II (n=8). Mice were followed for 4-weeks, at which point we determined cardiac weight, expression of key genes and gut microbiome composition (by 16S sequencing). 2-way ANOVAs with adjustment for multiple comparisons was performed and $P < 0$ .05 was considered statistically significant.

Results: Mothers fed diets without or with high levels of fibre had a different gut microbiome composition ($P = 0.001$). Pups born from mothers on a high fibre diet had distinct gut microbial colonisation ($P = 0.001$), irrespective of the presence of Ang II ($P = 0.013$), supporting a founder effect. Independently of the mothers' diet, Ang II mice had higher systolic and diastolic blood pressure, but no difference in body weight gain. However, Ang II pups whose mother had a high fibre diet had a significant decrease in heart to body weight ratio compared to those from no fibre mothers (4.84 vs 5.43 mg/g, $P = 0.034$). Furthermore, Ang II pups whose mothers received a high fibre diet had lower levels of markers of fibrosis such as Col1a1 ($P = 0.01$), TGF-beta ($P = 0.021$) and CTGF mRNA ($P = 0.005$) and lower mRNA levels of NPPB, a marker of cardiac remodelling and heart failure ($P = 0.002$).

Conclusions: High fibre intake during pregnancy protected the offspring against the development of cardiac fibrosis, remodelling and hypertrophy compared to those born from mothers who consumed no fibre. While the exact protective mechanism is unknown, our findings support the gut microbiota of the mothers being shaped by the intake of fibre during pregnancy and this had a lasting founding effect in the microbiota of their offspring.

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Modulation of the gut microbiota does not ameliorate heart failure in a genetic model

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Background: Dietary fibre reaches the colon mostly undigested, where the gut microbiota uses it as an energy source, releasing short-chain fatty acids (SCFAs) as a result of fibre fermentation. We have shown previously that fibre and the SCFA acetate were protective against the development of cardiovascular disease in the DOCA-salt model. However, whether this protection overrides genetic predisposition is yet to be determined.

Aim: To determine whether high fibre intake or acetate supplementation could override a genetic predisposition to heart failure.

Methods: Six-weeks old male transgenic Mst1 mice, which overexpress Mst1 in a cardiac-specific manner, and littermate wild-type mice were fed a control or high fibre diets, or received acetate in drinking water together with a control diet for six weeks (n=7–8/group). Cardiac function and remodelling (by cardiac catheter and echocardiogram), fibrosis (by qPCR and Masson's trichrome staining), inflammation (by qPCR), prevalence of T cells (by flow cytometry) and gut microbiome composition (by 16S sequencing) were assessed. Data were analysed by 2-way ANOVAs with adjustment for multiple comparisons and $P < 0.05$ was considered statistically significant.

Results: Wild-type and Mst1 mice had distinct composition of the gut microbiota that was attributed to diet, particularly the amount of fibre consumed, independently of their genotype. This was consistent with a significant increase in the number of T regulatory cells (Treg) in the spleen of Mst1 mice fed a high fibre diet in comparison to those fed the control diet (P=0.0017). Mst1 mice on a control diet had significantly increased heart to tibia ratio (P=0.0222) and lung to tibia ratio (P=0.0003), as well as lower systolic blood pressure ($P < 0.0001$) and diastolic blood pressure ($P < 0.0001$), left ventricular maximum pressure ($P < 0.0001$) and contractility ($P < 0.0001$) when compared to littermates. Treatment with fibre or acetate did not prevent the alterations in cardiac or lung weight, nor the changes in cardiac function or blood pressure. Mst1 mice on a control diet had increased cardiac levels of fibrotic markers, including Col1a1 mRNA (P=0.0180), and inflammatory markers including CTGF (P=0.0184), Il6 (P=0.0487) and Cd8 (P=0.0428) mRNA when compared to wild-type mice on the same diet, and these were not reduced by fibre or acetate

Conclusions: A diet rich in fibre or addition of the SCFA acetate modulated the gut microbiota of Mst1 and littermate wild-type mice, and was consistent with an increase in Treg cells, which are anti-inflammatory. These dietary interventions, however, were not able to prevent the development of heart failure in a genetic model where Mst1 gene is overexpressed in the heart. These results suggest that the gut microbiota could not override a strong genetic predisposition to the development of heart failure, especially after cardiomyocyte loss is established.

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Brachial and radial systolic blood pressure are not the same: potential implications for validation protocols including brachial cuff devices and wrist-based wearables

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Background: Radial intra-arterial blood pressure (BP) is sometimes used as the reference standard for validation of brachial cuff BP devices and there is an emerging 'wearables' market seeking to measure BP at the wrist. However, radial systolic BP may not be a good representation of the brachial systolic BP, and this could have implications for appropriate BP validation protocols.

Aim: To determine the difference between brachial and radial systolic BP.

Methods: Intra-arterial BP was measured consecutively at the brachial and radial arteries in 180 participants undergoing coronary angiography (aged 61±10years; 69% male). Intra-arterial BP recordings were made via fluid-filled catheter according to guideline recommendations.

Results: On average, brachial systolic BP was lower than radial systolic BP (137.1±20.4 vs. 142.5±22.2 mmHg respectively; $P<0.001$), and only 43% of participants had brachial systolic BP within ±5 mmHg of radial systolic BP. Additionally, brachial systolic BP was between 5 and 10 mmHg or 10 and 15 mmHg lower than radial systolic BP among 19% and 13% of participants, respectively. A further 14% of participants had brachial systolic BP >15 mmHg lower than radial systolic BP (142.4±20.5 vs. 163.9±22.0 mmHg; $P<0.001$) and 11% had >5 mmHg higher systolic BP at the brachial artery (143.9±26.5 vs. 133.3±26.6 mmHg; $P<0.001$).

Conclusions: Radial systolic BP is not representative of brachial systolic BP, with the majority of participants having brachial systolic BP >5 mmHg lower than radial. Therefore, validation testing of BP devices utilising intra-arterial BP as the reference standard should use intra-arterial BP measured at the same site as the brachial cuff or wrist-based wearable device.

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A prospective examination of exposure to passive smoking in pregnancy, infancy and childhood, and adult blood pressure in the Tasmanian Infant Health Study

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Background: Exposure to passive smoking in childhood may affect adult cardiovascular health. Few studies have repeated, prospective passive smoke exposure or long-term assessment of cardiovascular health.

Aim: To examine the influence of passive smoke exposure during pregnancy, infancy and childhood on central and peripheral blood pressure in young adults.

Methods: Data were collected from a 27 year follow-up of the Tasmanian Infant Health Study, a birth cohort from 1988–1990. Exposure to smoking during pregnancy, the postnatal period, childhood and early adulthood was ascertained with questionnaires. Exposure to passive smoke at each time point was summed to create a cumulative index ranging from 0 (no exposure) to 8 (exposed all periods). Outcomes were central and peripheral blood pressure measured with oscillometry (Mobil-O-Graph and Omron HEM907) in adulthood analysed with multivariable linear regression. Potential confounders were sex, maternal age at birth, socioeconomic status measures (education level, occupation and employment status), infant feeding choice and duration of breastfeeding.

Results: There were 96 participants (41.8% female, mean age 27.0 [SD 0.7] years). Exposure to maternal smoking during pregnancy, but not postnatally, during childhood or the cumulative index, was associated with greater central diastolic blood pressure (β =4.7; 95% CI 1.3-8.1) and greater central systolic blood pressure (β=4.4; 95% CI 0.2-8.6) compared to no exposure in adjusted analyses. There were similar associations with peripheral blood pressure outcomes.

Conclusions: Exposing children to tobacco smoke during pregnancy appears to have an adverse effect on their blood pressure in adulthood, suggesting a potential sensitive period for this exposure.

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Concordance between manual and automated blood pressure during incremental treadmill exercise among individuals with type 2 diabetes

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Background: Manual measurement of blood pressure (BP) during clinical exercise testing is recommended. Automated measurement of BP is often used during exercise testing in clinical settings, but there are little data comparing manual and automated BP in this setting.

Aim: To determine the concordance between manual and automated BP during a standard clinical treadmill exercise test in a population of patients with type 2 diabetes mellitus.

Methods: 46 participants (66±5 years; 54% male) with type 2 diabetes mellitus completed one Bruce treadmill exercise test at baseline and/or follow-up to a clinical trial. Manual and automated BP were measured simultaneously at each exercise test stage. Manual BP was measured by a technician blinded to automated BP measured by an automated device (Tango+, Suntech). Concordance between manual and automated BP was assessed using mean differences and intraclass-correlation (ICC).

Results: Manual and automated systolic BP had a small mean difference and high ICC at each stage, but variability in concordance increased with stage (pre-exercise: 2±10 mmHg, *P*=0.11; ICC=0.906; exercise stage 1: 3±11 mmHg, *P*=0.04; ICC=0.911; stage 2: 3±13 mmHg, *P*=0.11; ICC=0.927; and stage 3: 6±7 mmHg, *P*=0.04; ICC=0.963). Diastolic BP had a similar small mean difference, high ICC and increasing variability with each stage (pre-exercise: –1±6 mmHg, *P*=0.35; ICC=0.879; exercise stage 1: 1±10 mmHg, *P*=0.32; ICC=0.726; stage 2: 3±13 mmHg, *P*=0.21; ICC=0.746; and stage 3: 9±14 mmHg, *P*=0.09; ICC=0.729).

Conclusions: Manual and automated BP are concordant during a standard clinical exercise test. However, variability in concordance increases with exercise intensity

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Associations between reservoir pressure parameters and kidney function are dependent on the arterial measurement site

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Background: Reservoir pressure parameters derived from pressure waveforms predict adverse kidney function independently of conventional cuff blood pressure (BP). However, some reservoir pressure parameters differ throughout the arterial tree and it is unknown if associations with kidney function may differ depending on arterial site of measurement.

Aim: To determine the association of reservoir pressure parameters at different arterial sites with markers of kidney dysfunction.

Methods: Intra-arterial BP waveforms were measured via fluid filled catheter at the ascending aorta, brachial and radial arteries in 172 people undergoing coronary angiography (aged 60±13 years, 67% male). Customised Matlab software was used to derive reservoir pressure and associated parameters of excess pressure, diastolic and systolic rate constants at each arterial site. Kidney function was determined by estimated glomerular filtration rate (eGFR).

Results: Reservoir and excess pressure derived from BP waveforms measured at the aorta were associated with eGFR (r=-0.26, and r= –0.24; all $P = 0.07$). However, diastolic rate constants from BP waveforms at all arterial sites were associated with eGFR. These associations remained following adjustment for aortic systolic BP, heart rate, sex, and body mass index ($\beta = –0.34$, 95% CI –1.2, –425; $\beta = –0.26$, 95%CI –1222, –211.9; $\beta = –0.32$, 95% CI –1368, –423, respectively). Systolic rate constants were not associated with eGFR at any arterial site.

Conclusions: Associations between reservoir pressure parameters and kidney function may depend on site of waveform measurement, with the exception of the diastolic rate constant, which independently relates to kidney function irrespective of location. This is of clinical relevance since this variable can be derived from non-invasively recorded peripheral BP waveforms.

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Role of tissue plasminogen activator in the cardiovascular response to acute and chronic stress

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Background: Tissue plasminogen activator (tPA) is a key enzyme of the fibrinolytic pathway, but it is also an important modulator of synaptic plasticity in the central nervous system. tPA is highly expressed in the medial amygdala where it is an important mediator of stress-induced anxiogenic effects as well a stress-induced neuronal plasticity. The medial amygdala is a forebrain region known to regulate the pressor response to stress and to contribute to some forms of neurogenic hypertension. Given the role of tPA in stress-induced medial amygdala plasticity and behavioural effects, it is possible that tPA may also affect the cardiovascular response to stress.

Aim: To examine the role of tPA in mediating the cardiovascular response to acute and chronic stress exposure

Methods: Three groups of mice were assessed, including WT/C57Bl6 (n=11), thy-tPA TG mice, which overexpress tPA in neurons (n=10), and global tPA knockout (KO)mice (n=10). All mice were implanted with radiotelemetry probes to measure the blood pressure in conscious unrestrained mice. Mice were exposed to either chronic stress (1 h restraint, and 1 h dirty cage swap stress, 5 times/week) or no stress for 3 weeks, and the effect on 24 h average blood pressure, and cardiovascular response to acute stressors and novel stressors were examined. Fos immunohistochemistry was performed on brains of 2–3 mice per group collected following 1 h restraint stress.

Results: At baseline, 24 h mean arterial pressure (24 h MAP) was comparable between the three strains (WT, 105±0.4 mmHg, TG 103±0.7 mmHg, KO 101±0.6 mmHg, P=0.34). There was also no difference between the effect of chronic stress compared with no stress on 24 h MAP in any strain (P = 0.70). At baseline there was no difference in the pressor response to either dirty cage switch stress or restraint stress between strains (P >0.13) and chronic stress had no effect on the pressor responses to either of these stressors in any of the three strains. The pressor response to the novel shaker stress was lower in the KO compared with the WT mice exposed to chronic stress (10.5±1.9 vs. 19.1±2.6 mmHg respectively; P < 0 .001). Fos counts were lower in the medial amygdala of non-stress TG mice compared with WT mice (16±1 vs. 40±4 counts; P = 0.005). Following chronic stress, Fos counts were lower in WT mice only (12±3; P = 0.001), resulting in comparable counts between WT and TG (P = 1.0).

Conclusions: tPA has no overt effect on blood pressure nor the cardiovascular response to acute or chronic stress exposure despite tPA overexpression seeming to result in reduced neuronal activity in the medial amygdala.

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Antihypertensive treatment fails to inhibit exercise hypertension irrespective of blood pressure control in older adults from the Southall and Brent Revisited (SABRE) study

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Background: A hypertensive response to exercise (exercise hypertension) is associated with increased cardiovascular disease risk, irrespective of office blood pressure (BP). Whilst sustained antihypertensive treatment may provide office BP control, it is largely unknown if treatment dampens the exercise BP response and the prevalence of exercise hypertension.

Aim: To determine the influence of antihypertensive treatment and office BP control on exercise BP and the prevalence of exercise hypertension in older adults.

Methods: 678 participants (mean age 71±7 years, 56% male) from the Southall and Brent Revisited (SABRE) study completed a self-paced six-minute step-exercise test. Peak-exercise systolic BP was defined as the peak value attained from serial measurements during the exercise test. Exercise hypertension was defined as peak-exercise systolic BP ≥ 188 mmHg (the median exercise systolic BP value in this cohort). Self-reported treatment with at least one antihypertensive medication (any class) was considered treatment(+). Controlled/normal office BP was defined as BP < 140/90 mmHg from the average of three seated measurements.

Results: Pre-, peak- and delta- (pre-to-peak change) exercise systolic BP was similar between treatment(+) and treatment(–), in both those with controlled/normal office BP (mean difference 1 mmHg [95% CI –4, 2], 3 mmHg [95% CI –2, 9] and 4 mmHg [95% CI –1, 10], respectively) and in those with uncontrolled office BP (mean difference 0 mmHg [95% CI –4, 5], 4 mmHg [95% CI –3, 4] and 4 mmHg [95% CI –3, 10], respectively]. Prevalence of exercise hypertension did not differ between treatment(+) and treatment(–) (53% vs. 49%; *P* >0.05).

Conclusions: Irrespective of office BP control, current antihypertensive treatment does not mitigate the BP response to exercise in older adults, nor the prevalence of exercise hypertension. This suggests there may be some residual cardiovascular disease risk related to BP that is not improved with antihypertensive treatment or office BP control.

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The angiotensin type 2 receptor mediates the cardioprotective actions of relaxin in aged female SP-SHR

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Background: Females of reproductive age are protected against renal and cardiovascular diseases relative to age-matched males and post-menopausal women. This, in part, is accounted for by upregulation of the angiotensin type 2 receptor (AT2R) in young, adult females. With age, plasma relaxin levels decline in females, but expression levels of its target receptor, the relaxin-insulin like family peptide receptor 1 (RXFP1), remain unchanged. Recently, *in vitro* and *in vivo* studies have demonstrated that the renal and cardiovascular vasodilatory and anti-fibrotic actions of relaxin are mediated via an interaction between RXFP1 and AT2R. However, it is unclear whether the age-related reduction in relaxin is associated with loss of cardio-renal protection in aged, reproductively senescent females.

Aim: To determine whether relaxin infusion, via an AT2R-dependent mechanism, provides renal and cardiovascular protection in aged female stroke-prone spontaneously hypertensive rats (SP-SHR).

Methods: In young (6 months) and aged (15 months; reproductively senescent) female SP-SHR, arterial pressure, cardiac function, glomerular filtration rate (GFR) and proteinuria were measured before and after 4 weeks of treatment with vehicle (sodium acetate, s.c.), RLX (serelaxin; 0.5 mg/kg/day, s.c.) or RLX+PD123319 (AT2R antagonist; 3 mg/kg/day, s.c). In addition, aortic endothelium-dependent relaxation in response to acetylcholine and tissue fibrosis (renal, aortic and cardiac) were assessed at the end of treatment.

Results: Age-related reductions in GFR and vascular function as well as increases in arterial pressure, proteinuria and tissue fibrosis were observed in 15-month-old SP-SHRs (all P <0.05). In young SP-SHR, treatment with RLX enhanced GFR (~25% increase compared to basal GFR; $P < 0.001$), an effect that was abolished by co-infusion with PD123319 ($P <$ 0.05). However, RLX did not affect GFR in aged females. Endothelial dysfunction was apparent in aged, but not young, vehicle-treated female SP-SHR (~58% vs. ~87% maximal vasodilation, respectively; $P < 0.0001$). In aged animals, RLX markedly improved endothelial function (~30% increase in maximal vasodilation as compared to vehicle; $P <$ 0.001), but this was not modulated by PD123319. RLX reduced cortical renal (4.0±0.3 vs. 5.6±0.6 score; $P < 0.05$) and aortic (1.7±0.2 vs. 2.7±0.1 score; $P < 0.05$) fibrosis indices as compared to vehicle treatment. RLX+PD123319, as compared to RLX treatment alone, exacerbated cortical renal fibrosis in young (1.5±0.2 vs. 0.8±0.1 score; $P < 0.05$) and aged animals (5.7±0.4 vs. 4.0±0.3 score; $P < 0.01$), as well as aortic fibrosis in the aged females (3.0±0.1 vs. 1.7±0.2 score; $P < 0.001$).

Conclusions: Treatment with relaxin in a model of severe essential hypertension conferred renal and cardiovascular protection in aged females, and was in part due to a RXFP1-AT2R interaction. Understanding the mechanisms regulating the relaxin-RXFP1-AT2R cross-talk may introduce novel therapeutics for the treatment of renal and cardiovascular diseases, and associated end-organ damage in post-menopausal women.

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Effects of ganaloxone on blood pressure and stress in female BPH/2J genetically hypertensive mice

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Background: Dysfunctional forebrain gamma-aminobutyric-acid type-A receptors (GABAARs) have been suggested to contribute to neurogenic hypertension in Schlager BPH/2J mice. Ganaxolone is a synthetic-form of the progesterone metabolite, allopregnanolone, an allosteric modulator of GABAARs that has reduced blood pressure (BP) in male BPH/2J mice. However, it is unknown whether ganaxolone is suitable to treat hypertension in female mice due to it being structurally related to progesterone.

Aim: To determine the cardiovascular effects of ganaxolone treatment in female BPH/2J mice.

Methods: Female 12–13-week-old BPH/2J (n=20) and normotensive (BPN/3J; n=19) mice were implanted with a telemetry probe to record BP and heart rate. Cardiovascular responses to stress tests and pentolinium were measured before and after administering vehicle or ganaxolone (5 mg/kg/day via subcutaneous minipumps) for two weeks.

Results: Ganaxolone reduced BP by 9.9 mmHg (P <0.05))

Conclusions: Ganaxolone is effective in reducing hypertension and the cardiovascular response to stress in female BPH/2J mice. Therefore, targeting GABAARs with ganaxolone presents a novel treatment for stress-related hypertension.

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Effect of pulsatile blood pressure on fatigue and rupture of atherosclerotic plaques

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Background: The rupture of the fibrous cap overlying the lipid pool of atherosclerotic plaques is the leading cause of acute myocardial infarction. Plaque rupture often occurs at the location of stress concentration and in stress levels much lower than those required for plaque disruption with monotonic tension. Based on these observations, it has been hypothesized that mechanical fatigue caused by pulsatile blood pressure is the main mechanism underlying atherosclerotic plaque rupture.

Aim: To quantify the effect of mean and pulse pressure on the fatigue process and subsequent plaque rupture in realistic models of human coronary atherosclerotic plaques.

Methods: Eight samples of left anterior descending coronary artery with type V plaques were obtained by endarterectomy surgery. Based on histological examination, the different components of the atherosclerotic plaques were located (fibrous cap; lipid pool; calcification). The plaque geometry was constructed (Abaqus software) and the stiffness of different components of the atherosclerotic plaque was allocated based on published data. Pulsatile blood pressure was applied as the external load. Stress distribution within each model was estimated using finite element method. The initial crack was located at the highest stress concentration and its propagation was modelled in a stable way until it reached the lipid pool or arterial wall. The number of fatigue cycles required for plaque rupture was calculated for different pulse and mean pressures based on fracture mechanic rules.

Results: The effect of blood pressure was consistent for different models and various tissue properties tested. The location of initial crack formation and the direction of crack propagation were not affected by blood pressure variation. However, the rate of crack propagation changed significantly in response to alteration of pulse and mean pressure. For the same pulse pressure of 60 mmHg, decreasing the mean pressure from 120 to 100 mmHg (17% decrease) increased the cycles to rupture by 27±6% (1.6% increase per % decrease in mean pressure, or 1.4 %/mmHg). Decreasing the pulse pressure from 80 to 60 mmHg (25% decrease) increased the fatigue life by 154±18% (6.2% increase per % decrease in pulse pressure, or 7.7 %/mmHg). Further reduction of pulse pressure to 40 mmHg resulted in 275±29 % increase in fatigue life (5.5% increase per % decrease in pulse pressure, or 6.9 %/mmHg).

Conclusions: Modelling showed that pulse pressure has greater influence than mean pressure on the rate of crack propagation in atherosclerotic plaques. Reduced pulse pressure potentially prolongs time for plaque rupture.

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Hypertensive stimuli promote brain inflammation in a partially pressure-dependent manner

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Background: Hypertension increases the risk for stroke and cognitive impairment and is strongly associated with inflammation of the vasculature and kidneys, as well as cerebrovascular dysfunction and oxidative stress. However, it is unclear to what extent there is inflammation and immune cell infiltration in the brain during hypertension.

Aim: To test whether chronic administration of angiotensin II or aldosterone/salt causes brain inflammation and whether this is blood pressure-dependent.

Methods: Male C57Bl/6 mice were administered vehicle (saline; n=22) or angiotensin II (Ang II, 0.7 mg/kg/d, s.c.; n=23) for 14 d via osmotic minipumps. A subset of mice also received hydralazine hydrochloride (50 mg/kg; n=15) in their drinking water for 14 d after minipump implantation. Another cohort of mice were treated with vehicle (87% propylene glycol, 9% ethanol, 4% water; n=7) or aldosterone (0.72 mg/kg/d, s.c, plus 0.9% NaCl for drinking; n=8) for 14 d using osmotic minipumps. Systolic blood pressure was measured using tail-cuff plethysmography, immune cell numbers using flow cytometry and inflammatory markers using real-time PCR.

Results: Ang II infusion caused an increase in blood pressure and promoted accumulation of leukocytes in the brain (CD45+high), including neutrophils (CD11b+ Ly6G+), monocytes (CD11b+ Ly6C+high and Ly6C+low), T cells (CD3+) and B cells (CD19+), all of which were elevated by ~2.5-fold compared to vehicle-treated mice (n=6–8, $P < 0$ .05). Similarly, aldosterone/salt-induced hypertension was associated with increases in brain myeloid cells (CD11b+, ~3.5-fold) and T cells (CD3+, ~2-fold) (n=7–8, $P < 0$ .05). Co-administration of hydralazine prevented the pressor response to Ang II (163 ± 5 mmHg vs. Ang II + hydralazine, 121 ± 4 mmHg; n=7–8, $P < 0$ .05). Ang II-induced increases in brain neutrophils and monocytes were blunted by co-administration of hydralazine (n=7–8, $P < 0$ .05). However, hydralazine had no effect on T cell or B cell numbers (n=7–8). Ang II-induced increases in brain mRNA expression of chemokine (C-C motif) receptor 2 (CCR2), chemokine (C-C motif) ligand 2 (CCL2) and CCL8 were also blunted by co-administration of hydralazine (n=7–8, $P < 0$ .05).

Conclusions: Our data indicate that immune cell infiltration and inflammation occur in the brain during both the Ang II and aldosterone/salt models of hypertension. Furthermore, the Ang II-induced brain infiltration of myeloid cells, but not lymphoid cells, appears to be pressure-dependent. Chronic brain inflammation may be a contributing factor to the increased stroke risk and cognitive impairment during hypertension and may only partly be mitigated by blood pressure reduction.

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Novel AT2 receptor agonists for the treatment of cardiac and renal fibrosis

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Background: Targeting the angiotensin type 2 receptor (AT_2R) evokes anti-fibrotic effects in various organs. However, the lack of selective AT_2R ligands limits studying the function of AT_2R. We demonstrated that a single β-amino acid substitution to angiotensin III (β-Pro^7-Ang III) markedly improved the AT_2R: AT_1R selectivity over 20,000-fold (Del Borgo et al., Clin Sci 2015;129:505). More recently, we have found that tryptophan substitution to position 8 of β-Pro^7-Ang III (β-Pro^7-Trp^8-Ang III) further improved the AT_2R: AT_1R selectivity, while a D-arginine substitution or N-acetyl attachment to β-Pro^7-Trp^8-Ang III (D-Arg^2- β-Pro^7-Trp^8-Ang III and N-Ac- β-Pro^7-Trp^8-Ang III) increased in vitro plasma stability.

Aim: To determine and compare the anti-fibrotic effects of these novel AT_2R selective ligands in high salt (HS) diet-induced heart and kidney disease.

Methods: Male FVB/N mice were given HS (5% NaCl) chow to induce organ fibrosis. From weeks 5–8, sub-groups of mice (n=8–9/group) were treated with either β-Pro^7-Ang III (0.1 mg/kg/day) ± PD123319 (1 mg/kg/day), β-Pro^7-Trp^8-Ang III, D-Arg^2- β-Pro^7-Trp^8-Ang III or N-Ac- β-Pro^7-Trp^8-Ang III (all 0.1 mg/kg/day) via subcutaneous mini-pumps. Various markers of cardiac and renal inflammation, oxidative stress, fibrosis and collagen turnover were measured.

Results: Compared to mice fed with normal salt (NS) diet, HS increased cardiac and renal inflammation (monocyte chemoattractant protein-1 (MCP-1); phosphorylated-IkB; F4/80 levels) and oxidative stress (measured by DHE staining). Left ventricular interstitial fibrosis and renal interstitial fibrosis (picrosirius red-staining) both increased by ~1.5 fold and renal glomerulus fibrosis increased by ~2 fold due to HS diet which was confirmed by hydroxyproline analysis (all $P < 0$ .05 vs. NS group). These changes were associated with increased myofibroblast differentiation (α-smooth muscle actin) and inhibited collagen degradation (MMP-13). β -Pro^7-Ang III reversed HS-induced cardiac fibrosis, which was abolished by AT_2R antagonist PD123319. β -Pro^7-Trp^8-Ang III, -Arg^2- β-Pro^7-Trp^8-Ang III and N-Ac- β-Pro^7-Trp^8-Ang III all reversed HS-induced inflammation (MCP-1; phosphorylated-IkB; F4/80 levels) and fibrosis in heart and kidney (all $P < 0$ .05 vs. HS group). The anti-fibrotic effects caused by these AT2R selective agonists in the heart were associated with downregulated myofibroblasts differentiation (all $P < 0$ .05 vs. HS group). In addition, cardiac TIMP-1 expression was significantly inhibited by N-Ac- β-Pro^7-Trp^8-Ang III from HS ($P < 0$ .05 vs. HS group). Moreover, HS-induced cardiac and renal oxidative stress was reversed by N-Ac- β-Pro^7-Trp^8-Ang III, D-Arg^2- β-Pro^7-Trp^8-Ang III and N-Ac- β-Pro^7-Trp^8-Ang III (all $P < 0$ .05 vs. HS group).

Conclusions: This study has demonstrated that novel AT_2R -selective agonists reduced cardiac and renal end-organ damage, highlighting a potential therapeutic role of AT_2R in cardiovascular disease.

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Targeting NLRP3 inflammasome activity as a novel approach to treat cardiac fibrosis

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Background: The immune-modulatory NLRP3 inflammasome complex can promote cardiac inflammation and fibrosis in models of cardiomyopathy, with NLRP3 and RXFP1 (relaxin family peptide receptor 1) implicated in regulating pro-fibrotic TGF-β1-mediated NLRP3 inflammasome activity (pro-IL-1β and pro-IL-18), myofibroblast differentiation (α-SMA expression) and collagen-I production. The extent to which NLRP3 inflammasome activity in myofibroblasts can be targeted to attenuate cardiac fibrosis remains unknown.

Aim: To determine the extent to which targeting NLRP3 inflammasome activity would reduce cardiac fibrosis in TGF-β1-stimulated primary human cardiac myofibroblasts (HCMFs) in vitro and in mice subjected to isoproterenol (ISO)-induced fibrotic cardiomyopathy in vivo.

Methods: TGF-β1 (T; 5 ng/ml)-stimulated primary HCMFs (ScienCell, USA; 1.5–2 x 10^5 cells/ml) were additionally treated with LPS (L; 100 ng/ml) + ATP (A; 5 mM) (T+L+A) to determine the effects of L+A on NLRP3 inflammasome activation. T– and T+L+A-stimulated HCMFs were also treated with relaxin (RLX; RXFP1 agonist; 16.8 nM/100ng/ml) to determine the extent to which inhibition of NLRP3 inflammasome activity at 8 h and 72 h would lead to reduced myofibroblast differentiation and collagen-I deposition at 72 h (by Western blotting and densitometry of the relevant bands; n=4–6 experiments). Subgroups of male 129 sv/ev mice (n=5–6/group) administered with ISO (25 mg/kg; s.c.) for 5 consecutive days *in vivo*, were then left untreated (injury control) or treated with RLX (0.5 mg/kg/d) ± MCC (10 mg/kg/d) from days 7–14. Changes in pro-IL-1β and pro-IL-18, TLR4, α-SMA and collagen-I were measured, while correlative changes in blood pressure (BP) were measured at days 0, 7 and 14 by tail-cuff plethysmography.

Results: T+L+A-stimulation of HCMFs significantly increased pro-IL-1β and pro-IL-18 activity at 8 h, and TLR4 and α-SMA expression at 72 h (all by 25–35%; all $P < 0.05$ vs. T alone). These measures of inflammasome activity and fibrosis also increased in the left ventricle of ISO-injured mice (by 25–105%), in the absence of any changes in BP, at day 14 post-injury. RLX significantly decreased expression of pro-IL-1β, pro-IL-18, α-SMA and collagen-I *in vitro* and *in vivo* (all $P < 0.05$ vs. T+L+A or ISO). MCC950 alone significantly reduced inflammasome activity without affecting fibrosis. Combining the two therapies negated the effects of RLX.

Conclusions: RLX appears to reduce NLRP3 inflammasome activity as part of its anti-fibrotic effects. Hence, targeting RXFP1 on myofibroblasts may offer a novel approach to treat NLRP3-induced cardiac fibrosis.

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Circular RNAs Hrcr and cTtn are upregulated in the hypertrophic heart independent of blood pressure

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Background: Cardiac hypertrophy (CH) is the main risk factor for cardiovascular disease after age. Circular RNAs (circRNA), a novel RNA type, are created by the back-splicing of pre-mRNA and have been proposed to regulate gene expression post-transcriptionally.

Aim: To investigate the expression of circRNAs in the hypertrophic heart. We used the hypertrophic heart rat (HHR), a unique normotensive polygenic model of cardiac hypertrophy and heart failure, and its genetic control strain, the normal heart rat (NHR).

Methods: We used quantitative real-time PCR to measure the expression of heart-related circular RNA (Hrcr) and circular titin (cTtn) RNA (originating from the Titin gene) in left ventricles of HHR and NHR at 5 ages (2 days old, 4-, 13-, 33- and 50-weeks old).

Results: We found that Hrcr and cTtn circular RNAs are upregulated in the HHR at 13-, 33- and 50-weeks old (FC=2.77–3.57; $P < 0.05$). The regulation mechanisms and targets of circRNA remain largely unknown. However, Hrcr was shown to be downregulated in mice with induced CH caused by chronic infusion of isoproterenol.

Conclusions: Our findings indicate that circRNA expression is associated with changes in the hypertrophic heart and may be a potential molecular contributor to cardiac hypertrophy and heart failure. We believe that circRNAs deserve more attention as possible gene expression regulators.

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Circular RNA expression is reset by brief antihypertensive treatment in spontaneously hypertensive rats (SHR)

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Background: The 'legacy effect' of persistently lower blood pressure in SHR is observed after short-term treatment with angiotensin converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) antihypertensive drugs and is associated with changes in renal function. This presumably involves resetting of the genetic program leading to hypertension in SHR. Circular RNAs (circRNA) are novel non-coding RNAs that regulate mRNA expression post-transcriptionally and might be relevant to the legacy effect.

Aim: To study circRNA expression in the SHR after antihypertensive treatment.

Methods: We treated male SHR with an ACEi (perindopril), an angiotensin II receptor blocker (losartan) or a vasodilator (hydralazine) from 10 to 14 weeks of age. Renal cortex and cardiac left ventricular tissues were collected at 20-weeks of age (n=3–5 per group). We measured the expression of a heart-related circular RNA (Hrcr), circular titin (cTtn) RNA (originating from the Titin gene) and circular forkhead box O3 (cFoxo3) RNA (originating from the FoxO3 gene) using quantitative real-time PCR. These circRNAs have been implicated in cardiac hypertrophy and heart failure in mice. Statistical analysis was performed using one-way ANOVA and significance was set as $P < 0.05$.

Results: Hrcr and cFoxo3 RNAs were downregulated in renal cortex at 20-weeks when compared with vehicle after all antihypertensive treatments ($P < 0.05$).

Conclusions: Early antihypertensive treatment in SHR resets circRNA expression in renal cortices, but not in the heart, of SHR. This indicates tissue-specific regulation of circRNA expression might be important in reprogramming genetic hypertension by early renin-angiotensin system blocking drugs in SHR.

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Use of HealthStats BPro cuffless blood pressure watch in an ambulatory setting: comparison with conventional brachial cuff sphygmomanometry

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Background: There is increasing interest in obtaining improved out-of-clinic blood pressure (BP) measurement using unobtrusive devices, particularly devices that do not require a cuff placed on the upper arm, so as to improve convenience of use for ambulatory BP measurement in clinical practice. The HealthStats BPro watch is such a device. Although the HealthStats technology has been in use for nearly 20 years and is in clinical use for ambulatory BP, there is limited published data on comparison with cuff-based techniques for ambulatory BP monitoring.

Aim: To quantify the degree of agreement between BP determined using the BPro device and that by conventional cuff-based device in the ambulatory setting.

Methods: 14 participants aged 52±15 (range 34–75) years (4 female) wore both a conventional brachial cuff-based sphygmomanometric device (Petr Telegin BPLab or Microlife WatchBP03) and the BPro watch for a 24-hour period. The cuff-based device was programmed to take measurements every 20 minutes during the day and every 30 minutes at night. The BPro device is factory set to take measurements every 15 minutes – hence comparison is essentially asynchronous. BP values and number of measurements were compared over the 24-hour period; the day-time period (excluding 2 hours before bed and 3 hours after waking), and the night-time period (excluding 2 hours after going to bed and 1 hour before waking). All measurements of systolic (SBP) and diastolic (DBP) BP were averaged for each hour before averaging to obtain the result for the 24-hour/day-time/night-time period.

Results: The cuff-based device returned results for all 14 participants. The BPro device gave an initial reading, but no subsequent readings over the 24-hour period for 1 participant. Results across the remaining 13 participants are summarized in the Table. Despite the higher frequency of attempted readings, the BPro had fewer successful readings for both SBP and DBP than the cuff-device during the day. According to the guideline, the cuff-based device gave sufficient readings for a diagnosis for the 24-hour, the day-time and the night-time period in 14, 14 and 13 of the participants, respectively. The BPro device provided adequate number of readings for 7, 4 and 11 participants respectively. Diagnosis of presence/absence of hypertension agreed between the devices in 9 of the 13 participants. Both average day-time SBP and DBP were in relatively good agreement with cuff-based BP, but with a relatively large scatter. The BPro device tended to report higher nocturnal DBP with increased variability in difference from cuff-based measures for both SBP and DBP.

Conclusions: These preliminary results in a relatively small cohort suggest that the BPro device may have utility in population-based studies for day-time BP measurement. The large variability from cuff-based BP and the offset in night-time DBP suggests further

investigations are required to ascertain if the source of the variability in the clinical ambulatory setting is patient specific.

	24-hour period	day-time	night-time
Number of BP readings (cuff / BPro)	69±9 / 42±16***	41±13 / 18±16***	10±2 / 13±5
Difference in systolic BP (mmHg)	-3±14*	3±13**	7±23
Difference in diastolic BP (mmHg)	3±11*	2±11	10±16***

* p<0.05, ** p<0.01, *** p<0.001 compared to cuff-based device

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Validation and acceptability of a cuffless continuous wearable blood pressure monitoring device

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Background: High blood pressure (BP) is an important modifiable cardiovascular risk factor. Wearable cuffless BP monitoring devices have potential to improve BP measurement and control. However, little is known about the validity of wearable devices, and their acceptability among users and healthcare providers.

Aim: To validate a cuffless wearable device for continuous BP measurements and determine its acceptability among participants and healthcare professionals.

Methods: This feasibility study compared BP measured with a wearable BP device (T2 Tmart), an ambulatory BP measurement (ABPM) and home BP device in 20 participants with normal BP. BP was measured simultaneously for 24 hours using wearable and ABPM device (recorded every 30–60 minutes) and for 7 days using the wearable device (hourly) and home BP device (3 readings/day). Agreement between devices was assessed using Bland-Altman plots. Reliability was estimated by Pearson's product-moment correlation coefficient to compare the degree of association and intraclass correlation coefficient (ICC). Semi-structured interviews were conducted with participants and 10 healthcare professionals to determine the facilitators and barriers of using the wearable BP device. Data were audio recorded, transcribed verbatim and a thematic analysis was performed.

Results: The mean age of participants was 20.3±5.4 years; 50% were females. The mean±SD BP (SBP/DBP) measures using the home (7 days), wearable (7 days) and ABPM (overall 24-hours) devices were 112±12/71.5±9.8 mmHg, 125±5/77±3mmHg and 125±10/71±8 mmHg, respectively. Bias and precision between the wearable and ABPM devices for the 24 hour period was 0.5 (limits of agreement [LoA]: –10.1 to 11.1) mmHg for SBP and 2.24 (LoA: –17.6 to 13.1) mmHg for DBP. The bias and precision between the wearable and home device for 7 days was –12.7 (LoA: –28.7 to 3.4) mmHg for SBP and –5.6 (LoA: –20.5 to 9.2) mmHg for DBP. The wearable BP device was generally well accepted by participants and healthcare providers, and both groups could see value in wearable devices for future practice.

Conclusions: BP data obtained using the wearable device compared well with the ABPM and home BP device. Wearable BP devices have potential for clinical utility, but require further evaluation in larger studies.

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Modelling the impact of reduced salt intake on blood pressure and cardiovascular disease burden in a sub-Saharan African country

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Background: Reduction in salt (sodium) intake is a key population strategy recommended to tackle high blood pressure and cardiovascular disease.

Aim: To assess the impact of a modest reduction in population salt intake on the burden of cardiovascular disease and premature mortality in adult Cameroonians.

Methods: Proportional multistate lifetable model was used to estimate the potential impact of achieving the 30% relative reduction in salt intake as recommended by the World Health Organization. Blood pressure data were obtained from a national survey, while disease burden (incidence and mortality) estimates were obtained from the Global Burden of Disease 2016 study. Probabilistic (Monte Carlo simulations) analyses were performed to assess the uncertainty in our estimates.

Results: Our model predicted that reducing current salt intake by 30% (i.e., by ~1.7 g/day for men and 1.5 g/day for women) will, over the remaining lifetime, decrease the incidence of ischaemic heart disease by 5.2%, decrease the incidence of haemorrhagic strokes by 6.6%, ischemic strokes by 4.8%, and incident hypertensive heart disease by 12.9%. In addition, mortality over the lifetime is projected to be reduced by 5.1% for ischemic heart disease, by 6.9% for haemorrhagic stroke, by 4.5% for ischaemic stroke, and 13.3% for hypertensive heart disease. Overall, approximately 776,411 (95% UI: 712,555–841,220) health-adjusted life years would be gained.

Conclusions: Reducing salt intake could considerably decrease the burden of cardiovascular disease in Cameroon. Salt reduction interventions have the potential to produce substantial health gains in this population.

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Non-invasive assessment of aortic flow and pressure waves in the arterial system using cardiac magnetic resonance imaging and arterial tonometry

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Background: Favourable elastic properties of the thoracic aorta cushion, rectify and smooth pulsatile flow from the left ventricle with each beat.

Aim: To use cardiac magnetic resonance (CMR) and central aortic pressure (CAP) to assess haemodynamics in the proximal aorta.

Methods: Data were collected from 37 healthy volunteers (mean age 43 years; 24 male and 13 female) with no known cardiovascular diseases. CMR data were acquired using a GE 750w 3T MRI (Milwaukee, WI, USA). 4D-flow CMR datasets were acquired at 2.5 mm isotropic resolution using a velocity encoding of 150–170 cm/s. Simultaneous radial tonometry was performed using a CMR-compatible wrist tonometer with continuous recording during scan. Radial waves were converted offline to aortic pressure using SphygmoCor 8.1 (AtCor Medical, Sydney) and calibrated using brachial cuff values.

Results: Left ventricular (LV) load was quantified from pressure/flow data in the frequency domain as characteristic impedance (Zc). Zc is determined as average modulus of pressure ÷ flow from the first six harmonics of pressure and flow waves. Impedance modulus was higher in older subjects by up to 3 Hz, reflecting higher peripheral resistance (SVR) in older subjects (mean 7444.7±1661 dyne.s.cm^{-3}). Values of Zc (mean 651.7±201.7 dyne.s.cm^{-3}) fell within the normal estimated range for a realistic model of the arterial system between age 20 and 80 years (O'Rourke & Avolio, *Circ Res* 1980;46:363-72). Mean helicity, mean vorticity and fluid shear strain rate (SSR) were derived from the 4D-flow vector fields and all showed a strong negative association with the mean and pulsatile pressure/flow relationship (Table). Significant linear associations were also detected between 4D-flow parameters and the pressure wave reflection index (aortic augmentation index) (helicity: $y=48.6–0.69x$, $r^2 = 0.083$; vorticity: $y=106–0.79x$, $r^2 = 0.132$; SSR: $y=91.9–0.74x$, $r^2 = 0.176$), as well as with the mean and pulsatile pressure/flow relationship (Table).

Conclusions: 4D-flow MRI measurements of flow structure correlate strongly with central arterial pressure derived from tonometry, and may have an important role to better characterise the haemodynamic consequences of aortic stiffening in the central arteries.

Table. Association between hemodynamic (pressure and flow) indices in the ascending aorta
CC = correlation coefficient, SVR = systemic vascular resistance

	Helicity	Vorticity	SSR
SVR (dyne.s.cm-3)	CC = -0.453 p = 0.005 y=108-0.09x r^2 = 0.205	CC = -0.643 p < 0.001 y=183-0.01x r^2 = 0.414	CC = -0.663 p < 0.001 y=157-0.01 r^2 = 0.439
Zc (dyne.s.cm-3)	CC = -0.464 p = 0.004 y=90.2-0.08x r^2 = 0.215	CC = -0.498 p = 0.002 y=145-0.08x r^2 = 0.248	CC = -0.530 p = 0.001 y=125-0.07x r^2 = 0.281

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A qualitative difference in the initial cardiac output response to standing in healthy adults is associated with altered cardiovascular autonomic activity

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Background: We have reported that one third of healthy adults show an early transient fall (COF) rather than the normal rise (COR) in cardiac output (CO) on active standing. Associated changes in systolic blood pressure (SBP) and heart rate (HR) on standing suggest autonomic reflex dysfunction.

Aim: To investigate the autonomic characteristics associated with COF.

Methods: Finometer beat-to-beat measures of SBP and inter-beat interval (IBI) from 460 medical students (mean age 21 y, 162 COF, 298 COR) were analysed for autonomic parameters. Autonomic analyses were made for supine, on-standing and standing periods. Time-frequency analyses were performed on IBI and SBP series to compute a time-varying power spectrum with focus on low (LF) and high frequency (HF) bands. The HF power of IBI represents parasympathetic modulation of HR and the LF power of SBP describes vascular sympathetic tone. Baroreflex sensitivity (BRS) was assessed by the transfer function method and time-varying BRS (xBRS) by the time course BRS method. Comparisons and mean values between COR and COF subjects were adjusted for age, sex, height, weight and Asian/non-Asian race. Non-normal values were log-transformed prior to analyses.

Results: Compared with COR subjects, COF subjects had significantly ($P < 0.0001$) lower SBP and higher HR when lying (114 vs. 123 mmHg and 74 vs. 70 beats/min) and standing (107 vs. 116 mmHg and 88 vs. 83 beats/min). On standing, COF subjects experienced a significantly ($P < 0.0001$) lower nadir in SBP (65 vs. 88 mmHg), but little difference in peak HR (107 vs. 104 beats/min; $P=0.05$). In all periods, COF subjects had significantly lower power associated with IBI HF, consistent with reduced parasympathetic modulation of HR. In COF subjects the power associated with SBP LF was not different when lying or standing, but transiently higher than COR subjects during the on-standing period ($P < 0.0001$). BRS was significantly reduced in COF subjects when standing (1.83 vs. 1.94; $P=0.005$), but not different when lying. xBRS during the 30 s on-standing period was also significantly reduced in the COF subjects (4.27 vs. 5.08; $P=0.007$).

Conclusions: The dichotomous haemodynamic characteristics between COR and COF subjects appear to be associated with underlying differences in BRS, parasympathetic modulation of HR and sympathetic vascular activity on standing. These qualitative differences in healthy subjects might have a major genetic basis.

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CCL18 as a potential mediator of the pro-fibrotic actions of M2 macrophages in the vessel wall during hypertension

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Background: M2 macrophages contribute to vascular fibrosis and stiffening in hypertension. A potential mediator of these actions is the macrophage-derived pro-fibrotic chemokine, CCL18. However, the role of CCL18 and its cognate receptor, CCR8, in hypertension and vascular fibrosis has not been investigated. We hypothesized that CCL18 contributes to hypertension-associated fibrosis via targeting CCR8 on aortic adventitial fibroblasts.

Aim: To determine if CCL18 promotes vascular fibrosis by targeting human aortic adventitial fibroblasts, and whether CCL18 produces pro-fibrotic effects via the CCR8 receptor.

Methods: Human aortic adventitial fibroblasts were treated with the pro-fibrotic agent TGF-β (10 ng/ml) or CCL18 (3-300 ng/ml) for 3-72h. mRNA expression of type I, III, and V collagen and α-smooth muscle actin were detected via qRT-PCR, and pro-collagen I, mature collagen I, α-smooth muscle actin and CCR8 were measured by Western blotting. The ability of CCL18 (300 ng/ml for 72 h) to promote the differentiation of human aortic adventitial fibroblasts to myofibroblasts, was assessed via a collagen gel contraction assay, in the absence or presence of the CCR8 antagonist, R243 (5 μM).

Results: TGF-β increased mRNA expression of collagen I (1.7-fold), collagen V (2.5-fold) and α-smooth muscle actin (5.8-fold) in human aortic adventitial fibroblasts at 24 h ($P <$ 0.01, n=5–6), which translated to an ~2-fold increase in protein expression of collagen I (at 24 h; $P < 0$ .01) and α-smooth muscle actin (at 24-72 h; $P < 0$ .05). CCL18 (300 ng/ml) did not change the expression of α-smooth muscle actin, but increased the protein expression of pro-collagen I by 2-fold at 24 h ($P < 0$ .01; n=7), and elevated mature collagen I levels at 72 h in a concentration-dependent manner (by up to 4-fold; n=4). In preliminary studies, collagen gels that contained CCL18-treated human aortic adventitial fibroblasts were contracted by ~89%, an effect that was abolished by the CCR8 antagonist, R243 (n=1).

Conclusions: CCL18 targets human adventitial aortic fibroblasts to promote collagen synthesis and augment extracellular matrix contraction. These effects of CCL18 may be mediated via CCR8. Thus, CCL18 and its receptor CCR8, may serve as potential targets for the treatment of vascular fibrosis during hypertension.

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Obstructive sleep apnoea and cardiometabolic risk factors in young adults

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Background: Obstructive sleep apnoea (OSA) has been linked to increased risk of cardiometabolic disease and increased cardiovascular morbidity. The majority of previous studies have been conducted in middle-aged and older adults. Very few have focused on this relationship in young adults.

Aim: To investigate the association between high risk for OSA and cardiometabolic risk factors in a community sample of young adults.

Methods: : Measurements of OSA risk and cardiometabolic risk were obtained in 850 young adult (22±0.5 y) participants of the Western Australian Pregnancy Cohort (Raine) Study. High risk for OSA was determined from the Berlin Questionnaire. A range of cardiometabolic risk factors were measured, including body weight, blood pressure, insulin, HOMA-IR as a measure of insulin resistance, serum lipids and hs-CRP. Regression and sensitivity analyses were used to examine associations between measures.

Results: The prevalence of high risk for OSA was 14.7% (13.8% in females and 15.5% in males). Those at high risk for OSA were more likely to be overweight/obese or have central obesity. A positive association was found between high risk for OSA and systolic blood pressure, triglycerides, hs-CRP and a negative association with high density lipoprotein cholesterol (HDL-C) (all associations remained before and after adjustment for gender and lifestyle factors). However, none of these associations were significant when accounting for BMI.

Conclusions: In young adults, increased cardiometabolic risk is associated with high risk for OSA. However this relationship is most likely mediated by the increased obesity seen in those at high risk of OSA.

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Transcranial Colour Duplex and Central Aortic Pressure Measurements in the Management of Cerebral Arteriovenous Malformations: A Pilot Study Using Non-Invasive Measures

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Background: Following removal of an arteriovenous malformation of the brain (bAVM) the redistribution of blood can impose several clinically challenging issues including intracranial haemorrhage and arteriovenous capillary hypertensive syndrome. The underlying mechanism of such complications remains controversial, although control of blood pressure has been recognised as an integral component in haemorrhage prevention. Serial daily non-invasive monitoring for patients in this instance would be beneficial in improving management. Transcranial colour duplex (TCD) is a potential technique for providing pressure measurements and real-time, dynamic, haemodynamic spectra.

Aim: To establish whether blood outflow velocity in the middle cerebral vein (MCV) can be quantified in the days following bAVM resection and whether values differ from other types of intracranial surgery.

Methods: Blood pressure and TCD of 13 patients (aged 46±19 y, 7 female) having bAVMs resected and 7 patients having other intracranial surgeries (control group, aged 48±15 y, 6 female) were studied for days 1 to 3 following surgery. Ultrasound via the transtemporal window was used to obtain diameter, as well as peak and end-diastolic velocity of the MCV. Brachial blood pressure was also obtained using an automatic oscillometric blood pressure monitor.

Results: Systolic (bAVM 96±2 mmHg, control 89±10 mmHg; P=0.68) and diastolic blood pressure (bAVM 55±2 mmHg, control 48±7 mmHg; P=0.92) did not differ between the groups. MCV peak systolic velocity was greater in the bAVM group (34±20 cm/s, controls 20±9 cm/s; P=0.049). The control group had peak systolic velocities ranging from 9 to 32 cm/s. Peak systolic velocity in the bAVM group varied from 9 to 98 cm/s. End diastolic velocity (bAVM 13±11 cm/s, control 13±6 cm/s; P=0.89) and diameters (bAVM 37±19 mm, control 26±7 mm; P=0.16) did not differ between the groups. Two of the bAVM patients that had sustained high MCV peak velocities had a post-operative haemorrhage.

Conclusions: Unusually elevated blood flow velocities and diameters were observed in the MCV of patients following bAVM resection. Findings on this small data set provide insight into plausible vessel remodelling and elucidate a post-operative time frame when vessels may have impaired autoregulation of cerebral blood flow.

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Post-stroke administration of relaxin improves stroke outcomes

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Background: H2-relaxin is a peptide hormone known for its pleiotropic properties, including anti-inflammatory and anti-apoptotic effects. It may therefore provide neuroprotection following stroke. Administration of H2-relaxin 30 min prior to stroke has been shown to decrease cerebral infarct size in rats. However, it remains unclear if post-stroke administration of relaxin is neuroprotective.

Aim: To investigate whether post-stroke administration of H2-relaxin reduces infarct size and improves functional outcomes, and to identify the mechanisms by which H2-relaxin provides neuroprotection.
M male C57BL6 mice aged 8–12-weeks were anaesthetized via isoflurane inhalation (2.0–2.5% in O_2) and subjected to photothrombotic stroke or sham surgery (n=8). Mice were administered vehicle (sodium acetate; n=10) or recombinant H2-relaxin (0.5 µg, n=8 or 5 µg, n=7) i.v. at 6, 24 and 48 h post-stroke. Asymmetry in forelimb use and grip strength was assessed prior to surgery and at 24 and 72 h post-stroke using the cylinder and hanging wire test, respectively. At 72 h post-stroke, brain infarct volume was examined using thionin staining and neutrophil infiltration was measured via myeloperoxidase (MPO) immunofluorescence.

Results: Stroke-induced impairment to forelimb contact during the cylinder test was abolished in mice treated with 0.5 µg ($P < 0.05$) or 5 µg relaxin ($P < 0.05$). In the hanging wire test, mice treated with 0.5 µg or 5 µg relaxin held on to the wire for 19.9 % or 45.0 % longer, respectively. However, these data did not differ significantly compared to vehicle-treated mice. Surprisingly, cerebral infarct size was similar between vehicle and both relaxin therapy groups. Despite this, fewer MPO-positive neutrophils were observed in the ischaemic hemisphere of mice treated with 5 µg relaxin (79.1±9.3 neutrophils) compared to vehicle (115.6±14.9 neutrophils; $P < 0.05$).

Conclusions: The findings from this study suggest that post-stroke relaxin therapy may provide functional recovery and reduce infiltrating neutrophils in the ischaemic brain, although it does not reduce infarct size. Thus, relaxin may be a potential therapeutic option for stoke patients, particularly as it may aid functional recovery.

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Delayed post-stroke administration of stem cell-derived exosomes improves ischaemic stroke outcome

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Background: Nano-sized packages, termed 'exosomes', released by stem cells contain signalling molecules that can initiate repair and regeneration, have anti-inflammatory properties and possess fewer limitations than their parent cell. Acute (1.5 h) post-stroke administration of stem cell-derived exosomes has been shown to improve outcomes in mice. Whether a delayed post-stroke injection of these exosomes is also neuroprotective is not known.

Aim: To test the long-term benefits of delayed post-stroke administration of stem cell-derived exosomes following ischaemic stroke.

Methods: C57BL6 male mice (aged 8–12 weeks) were anaesthetized by isoflurane inhalation (2.0–2.5% in O_2) and subjected to either sham (n=8) or photothrombotic stroke surgery. At 24 h and 14 d post-stroke, mice were intravenously administered with saline (vehicle, n=11) or 10 mg of stem cell-derived exosomes (n=6). Functional tests assessing motor and sensory function were conducted pre-surgery and 1, 3, 7, 14, 21 and 28 d post-surgery. Infarct volume analysis and von Willebrand Factor (vWF), a marker of blood vessels, immunofluorescence were performed on brain tissue 28 d post-surgery.

Results: Exosome-treated mice were able to hang on to a wire for 76% longer at day 7 post-stroke compared to vehicle-treated mice ($P < 0$ .05). Between days 14 and 28, whilst the hanging wire times for exosome-treated mice were not significantly different from vehicle-treated mice, they were normalized to those of sham animals. Conversely, exosome treatment did not improve forelimb use in the cylinder test or provide faster adhesive removal. Histologically, there was no significant difference in infarct volume between exosome and vehicle treatment (1.5±0.2 vs. 1.7±0.2 mm^3, respectively; P=0.78). However, more vWF-positive microvessels within the ischaemic regions of the brain were observed in mice treated with exosomes (43.9±4.0 micro-vessels) compared to vehicle (37.0±1.5 micro-vessels), but these differences were non-significant (P=0.09).

Conclusions: These data suggest that delayed post-stroke exosome treatment may improve long-term functional and histological outcomes, and hence may be a viable therapy for stroke patients.

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Targeting the NLRP3 inflammasome for the treatment of pulmonary hypertension

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Background: Pulmonary hypertension (PH) is characterized by increased pulmonary arterial pressure, vascular remodelling and right ventricular (RV) hypertrophy; the prognosis is poor and a cure elusive (Baliga *et al*., *Br J Pharmacol* 2014;171:3463-75). Macrophages are key contributors to PH pathogenesis. These cells express an NLRP3 inflammasome complex, which releases pro-inflammatory cytokines interleukin (IL)-1β and IL-18. Since the NLRP3 inflammasome is implicated in other cardiovascular diseases (Coll *et al*., *Nat Med* 2015; 21:248-55), we hypothesized that NLRP3 activation similarly contributes to PH and that pharmacological targeting of this pathway prevents disease progression.

Aim: To investigate whether the NLRP3 inflammasome plays a role in PH pathogenesis using a selective inhibitor in experimental models of PH, and examining the effects on markers of PH severity.

Methods: Male C57BL/6 mice (20–25g) were exposed to hypoxia (10% O_2, 5-weeks, plus vascular endothelial growth factor inhibitor SU5416, 20 mg/kg, s.c.) to induce PH. Mice were randomly assigned to 1 of 5 groups: normoxia control, or SU5416/hypoxia (SuHx) plus selective NLRP3 inflammasome inhibitor MCC950 (10 mg/kg/day, s.c.) (Krishnan *et al*., *Br J Pharmacol* 2016;173:752-65), existing PH therapy sildenafil (30 mg/kg/day, drinking water), both MCC950 and sildenafil, or MCC950 vehicle (saline). MCC950 was delivered via osmotic mini-pump implanted at day 14. A second model, bleomycin (2 mg/kg, i.t., 2-weeks)-induced pulmonary fibrosis with secondary PH was utilized, with MCC950 delivered from day 7. Indices of disease progression assessed at endpoint included: right ventricular systolic pressure (RVSP; Millar Mikro-Tip catheterization under 2% isoflurane), RV hypertrophy by Fulton's index (RV/LV+S), lung weight (LW) to bodyweight (BW) ratio and immunohistochemistry to assess pulmonary fibrosis and pulmonary vascular muscularization. Data are presented as mean±SE and analysed by one-way ANOVA with Tukey's post-test.

Results: RVSP, RV/LV+S and LW/BW ratios were significantly increased in SuHx and bleomycin-treated mice compared to control animals (Tables 1 and 2), confirming development of PH. MCC950 alone did not affect RVSP in either model, but significantly reduced RVSP in combination with sildenafil (Table 1). Treatment with MCC950 significantly decreased RV/LV+S ratio, more effectively than sildenafil in SuHx mice compared to controls (Table 1), with a similar trend in bleomycin-treated animals (Table 2). Finally, LW/BW ratio decreased in mice treated with bleomycin and MCC950 compared to

bleomycin alone (Table 2). Martius, Scarlet and Blue (MSB) staining of the lung further revealed that mice treated with bleomycin and MCC950 had a reduced degree of fibrotic lung tissue compared to bleomycin alone.

Table 1. Effect of MCC950 treatment on hypoxia-induced pulmonary hypertension

	Control	SuHx	SuHx +MCC950	SuHx +Sildenafil	SuHx +both
RVSP (mmHg)	27.3 ± 0.4 (16)	44.2 ± 1.0** (22)	43.4 ± 1.0** (20)	40.1 ± 1.1**$ (13)	38.7 ± 0.9**$$## (15)
RV/LV+S	0.25 ± 0.004 (14)	0.36 ± 0.007** (20)	0.32 ± 0.009**$$ (18)	0.33 ± 0.007**$ (17)	0.33 ± 0.006**$$ (16)
LW/BW	0.467 ± 0.0069 (12)	0.714 ± 0.0159* (13)	0.698 ± 0.0223* (9)	0.679 ± 0.0158** (8)	0.671 ± 0.0198** (6)

****P<0.01 vs. Control; $P<0.05, $$P<0.01 vs. SuHx; ##P<0.01 vs. SuHx+MCC950, (n) animals**

Table 2. Effect of MCC950 treatment on bleomycin-induced pulmonary hypertension

	Control	Bleomycin	Bleomycin+MCC950
RVSP (mmHg)	28.4 ± 0.8 (10)	35.4 ± 0.9* (10)	33.4 ± 0.9* (8)
RV/LV+S	0.25 ± 0.008 (6)	0.29 ± 0.01* (12)	0.263 ± 0.01$ (11)
LW/BW	0.46 ± 0.023 (3)	1.68 ± 0.177** (7)	1.20 ± 0.093*# (7)

***P<0.05, **P<0.01 vs. Control; $P=0.0855 vs. Bleomycin; #P=0.0519 vs. Bleomycin, (n) animals**

Conclusions: These data demonstrate that MCC950 treatment reverses RV hypertrophy and lung fibrotic burden in experimental models of PH, independently of pulmonary artery pressure. Ongoing studies will confirm whether MCC950 alters pulmonary vascular remodelling. Therefore, a combination of MCC950 with pulmonary dilators (current therapy) may provide a novel therapeutic strategy for PH.

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Cuff blood pressure is progressively more biased with increasing age: individual participant level analysis from the INSPECT consortium

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(On behalf of the INSPECT consortium)

Background: Accurate blood pressure (BP) measurement is critical for appropriate hypertension diagnosis and management. Aortic BP represents pressure loading on vital organs and this can be approximated using upper arm cuff BP. With advancing age, cuff systolic BP (SBP) increases and diastolic BP (DBP) decreases (widening pulse pressure [PP]), but the influence of age on cuff-measured BP compared with invasive BP is unknown.

Aim: To determine the influence of age on cuff-measured BP compared with invasive BP.

Methods: Cuff BP was measured simultaneously, or near-simultaneously, with invasive aortic BP during catheterization in 1689 individuals within the INSPECT consortium (an international collaboration comprising data from 31 studies and 19 different cuff BP devices [17 oscillometric, 2 mercury sphygmomanometry]). Differences in cuff and invasive BP were assessed using mixed models.

Results: Subjects were aged 63±11 years and 32% were female. Cuff SBP overestimated invasive aortic SBP in those aged 40–49, but with increasing age there was a progressive increase in the underestimation of aortic SBP (Table). Conversely, cuff DBP systematically overestimated aortic DBP, increasingly with age. Thus, there was a progressively higher error (underestimation) in cuff PP with older age. Adjusting models for sex, mean arterial pressure, heart rate, body mass index and catheter type did not alter the findings, and no interactions between these parameters and age were found.

Age category	n	Cuff – invasive systolic BP	Cuff – invasive diastolic BP	Cuff – invasive pulse pressure
40–49 years	169	3.4 (0.5 to 6.6)	3.8 (1., 6.1)	–0.5 (–3.6, 2.9)
50–59 years	406	1.2 (–1.3, 3.7)	5.4 (3.4, 7.4)	–4.2 (–7.0, –1.4)
60–69 years	555	–0.7 (–3.1, 1.8)	6.1 (4.1, 8.0)	–6.7 (–9.4, –4.0)
70–79 years	453	–2.7 (–5.1, –0.2)	7.9 (5.9, 10.0)	–10.7 (–13.4, –7.9)
80–89 years	106	–3.7 (–7.0, –0.4)	9.9 (7.4, 12.5)	–13.6 (–17.2, –10.)
Data are mean (95% confidence interval). BP, blood pressure.				

Conclusions: Cuff BP is progressively more biased with increasing age, exposing older people to greater chance for misdiagnosis of risk related to BP. The findings highlight the

need to improve cuff BP methods to ensure all people receive appropriate diagnosis and management of hypertension.

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Inhibition of insulin-regulated aminopeptidase prevents renal cellular senescence and tissue injury

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Background: The incidence of chronic kidney disease (CKD) in Australia is increasing at an alarming rate in association with an ageing population and growing prevalence of hypertension. Current best treatment (renin-angiotensin system blockade) delays progression of CKD but the effects are imperfect. Thus, improved treatments are required urgently.

Aim: To determine whether insulin-regulated aminopeptidase (IRAP), a little-understood component of the renin-angiotensin system, contributes to the loss of renal function and increase in arterial pressure observed in ageing.

Methods: Mean arterial pressure (MAP) was measured via telemetry in male wild-type (WT) and IRAP knockout (KO) mice at 4, 15 and 23 months of age. Glomerular filtration rate (GFR) was measured via transcutaneous decay of FITC-sinistrin, and albumin excretion was examined via 24 h metabolic cages. Kidneys were fixed for assessment of senescence-associated β-galactosidase (SA-β–gal, a marker of cellular senescence), tubulointerstitial fibrosis and glomerulosclerosis. Frozen kidney tissue was used to examine gene expression of cellular senescence markers.

Results: GFR declined by ~25% and MAP increased by ~8 mmHg (both $P < 0.01$) in WT mice between 4 to 23 months of age. The reduction in GFR in the WT mice was associated with a marked increase in albumin excretion, glomerulosclerosis, tubulointerstitial fibrosis and accumulation of senescent cells in the proximal tubules and podocytes of the kidney (all $P < 0.05$; n=6–12/group). By contrast, GFR in IRAP KO mice did not decline with age ($P < 0.01$ vs. aged-matched WT). Renal fibrosis was significantly attenuated (~58% reduction, $P=0.0006$) in IRAP KO mice compared to age-matched WT mice, coinciding with lower albumin excretion ($P < 0.01$) and reduced expression of cellular senescence markers in the kidney (SA-β-gal staining, mRNA expression of p53, p21, $p16^{INK4a}$). These effects were independent of arterial pressure, which increased to similar levels in both WT and IRAP KO mice with age.

Conclusions: IRAP KO mice are completely protected from the age-related decline in GFR and corresponding renal injury. However, arterial pressure increased with age similar to WT mice. IRAP may therefore have a role in promoting renal fibrosis and cellular senescence. Thus, IRAP inhibition has excellent therapeutic potential to attenuate age-related decline in renal function, CKD progression and cardiovascular sequelae.

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General applicability of a recently developed arterial path length formula for carotid-femoral pulse wave velocity measurements

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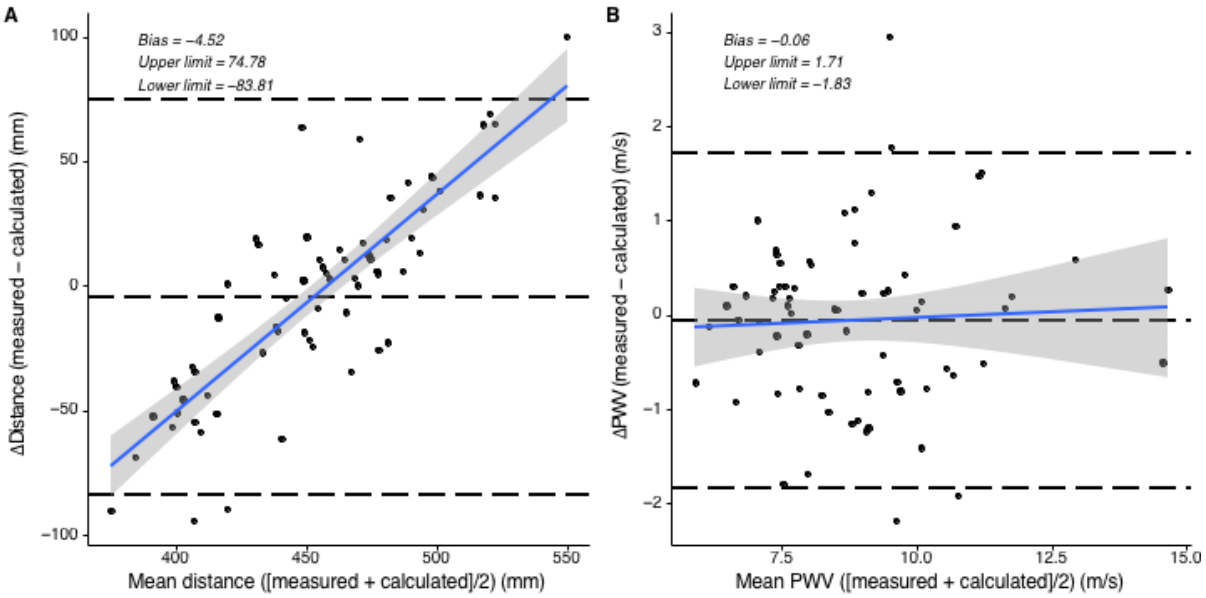
Background: Carotid-femoral pulse wave velocity (PWV), an index of large artery stiffening, is a significant prognostic marker for hypertension. Despite its additive value beyond traditional cardiovascular risk factors, the measurement of PWV in clinical practice is relatively limited due, in part, to practical aspects of measurement. In particular, accuracy of PWV is dependent on the arterial path length measurement, which is most commonly calculated from body surface measurements and subject to inter- and intra-observer variability. A regression formula for calculating carotid-femoral path length was developed recently (Weir-McCall *et al*., *Hypertension* 2018;71:937–45) and validated in two European cohorts, but its general applicability in other populations has yet to be investigated.

Aim: To investigate the general applicability of the carotid-femoral path length formula in a heterogenous Australian population.

Methods: The formula was used to calculate carotid-femoral PWV distance (distform) in 70 participants (aged 65±12 years (range 29–86), 24 female, 20 Asian, 50 Caucasian) who previously had PWV measured using the 3-point subtraction method for distance measurement. PWV was recalculated using the transit time (TT) previously recorded (PWVform = distform/TT). The formula-calculated values were then compared to the actual measured distance (distmeas) and PWV (PWVmeas) values, and their differences were compared to the differences observed in the validation study (distdiff_val, PWVdiff_val).

Results: The mean difference in measured and calculated distances (distmeas – distform) was –4.5±40.4 mm (P = 0.35), and the mean difference between measured and calculated PWV (PWVmeas – PWVform) was –0.06±0.90 m/s (P = 0.59). These differences were comparable to the validation study results for distance (distdiff_val = –7.8±24.9 mm; P = 0.53) but not for PWV (PWVdiff_val = 0.87±0.93 m/s; P < 0 .001). Using Bland-Altman analysis, a proportional bias was observed in the formula calculated distances, whereby the formula overestimated short distances but underestimated long distances.

Conclusions: Although the formula for calculating carotid-femoral path length overestimates short distances and underestimates long distance, the resulting calculated PWV values had a reasonable agreement with actual measured values, indicating the formula was generally applicable in this heterogenous Australian cohort. Further studies are required to investigate the applicability of the formula in other populations and age groups as well as accuracy in terms of estimating true arterial path-length.


A
Bias = −4.52
Upper limit = 74.78
Lower limit = −83.81
ΔDistance (measured − calculated) (mm)
Mean distance ([measured + calculated]/2) (mm)
B
Bias = −0.06
Upper limit = 1.71
Lower limit = −1.83
ΔPWV (measured − calculated) (m/s)
Mean PWV ([measured + calculated]/2) (m/s)

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Ultrasound ablation of the carotid body for treatment of resistant hypertension: a multi-centre safety and proof-of-principle cohort study

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Background: The carotid body (CB), a chemoreceptor located at the carotid bifurcation, is considered a therapeutic target in diseases mediated by the sympathetic nervous system. Surgical resection of the CB has demonstrated possible benefits in patients with resistant hypertension.

Aim: To establish the safety and to assess the effectiveness of a catheter-based system to ablate the carotid body and reduce blood pressure (BP) in patients with resistant hypertension and to confirm sustainability of the treatment benefits.

Methods: Inclusion criteria for this single-arm multicenter prospective study included stable prescription of 3 or more antihypertensive medications for at least 6 weeks prior to the procedure, office systolic BP ≥160 mmHg, confirmed presence of the right CB by CT angiography, and confirmation of resistant hypertension with daytime systolic ambulatory BP ≥135 mmHg on two consecutive occasions during the screening period. The primary safety endpoint was the combined rate of death, hospitalization for hypertensive crisis, and device- or procedure-related serious adverse events (SAE) at one-month post-treatment. The primary efficacy endpoint was defined as the change in 24-h systolic ambulatory BP between baseline and 1, 3- and 6-months post-treatment. Carotid body ablation was performed using a proprietary ablation catheter system delivering therapeutic ultrasound energy via the jugular vein under intravascular imaging guidance.

Results: A total of 39 patients were enrolled with 6-months follow up data being available from 27 patients. The study population consisted of hypertensive patients with a mean age of 63±11 years and BMI of 30.4±4.4 kg/m^2; 62% were male and 23% had diabetes. Patients were taking an average of 4.5±1.4 antihypertensive medications. Baseline mean systolic and diastolic 24-h ABPM was 154±13/94±13 mmHg and 44% of patients had isolated systolic hypertension at baseline (defined as office systolic BP ≥160mmHg and diastolic BP < 90 mmHg). At 6 months, the following SAEs had occurred: one TIA likely due to very high procedural BP, one elective angiogram, one episode of hyperkalaemia, one hypotensive episode, one episode of pneumonia, one groin closure complication, and one episode of chest pain. The 24-h ambulatory BP was reduced by an average of 9.1±13.5/6.7±8.7 mmHg at 6 months post-procedure, with similar reductions having been observed already at 1 and 3 months follow up. Six-month data for all 39 patients will be presented at the time of the meeting.

Conclusions: Transvenous catheter-based ablation of the carotid body appears to be a safe therapeutic approach and causes substantial and sustained BP reduction in patients with resistant hypertension. Prospective randomized clinical trials are needed to investigate the

usefulness of carotid body ablation in the treatment of resistant hypertension.

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Renal denervation 2018: update on recent studies and future implications

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Background: Several studies and registries have demonstrated sustained reductions in blood pressure (BP) after renal denervation (RDN). The long-term safety and efficacy after RDN in real-world patients with uncontrolled hypertension, however, remains unknown.

Aim: To assess the long-term safety and efficacy of RDN, including its effects on renal function.

Methods: The Global SYMPLICITY Registry is a prospective, open-label registry conducted at 247 sites worldwide in hypertensive patients receiving RDN treatment. Among 2,237 patients enrolled, 2,151 and 1,742 have been followed for 2 and 3 years, respectively.

Results: Baseline office and 24-h ambulatory systolic BP were 166±25 and 154±18 mm Hg, respectively. Systolic BP reduction after RDN was sustained over 3 years, including decreases in both office (–16.5±28.6 mmHg; $P < 0$ .001) and 24-h ambulatory systolic BP (–8.0±20.0 mmHg; $P < 0$ .001). Twenty-one percent of patients had a baseline estimated glomerular filtration rate (eGFR)of < 6 0 ml/min/1.73 m². Between baseline and 3 years, renal function declined within the expected range by 7.1 ml/min/1.73 m^2 in patients without chronic kidney disease (CKD; eGFR ≥ 60 ml/min/1.73 m^2; baseline eGFR 87±17 ml/min/1.73 m^2) and by 3.7 ml/min/1.73 m^2 in patients with CKD (eGFR < 6 0 ml/min/1.73 m²; baseline 47±11 ml/min/1.73 m^2). No long-term safety concerns were observed following the RDN procedure.

Conclusions: Long term data from the Global SYMPLICITY Registry, representing the largest available cohort of hypertensive patients receiving RDN in a real-world clinical setting, demonstrated both the safety and efficacy of the procedure, together with significant and sustained ambulatory BP reductions up to 3 years.

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The effects of moxonidine on the kidney of hypertensive mice

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Background: Moxonidine is a centrally acting antihypertensive drug. The kidney plays an important role in blood pressure regulation. The effect of moxonidine on the kidney is not clear.

Aim: To investigate the effect of moxonidine on kidneys of hypertensive mice.

Methods: Two groups (n=10 in each group) of apolipoprotein E-deficient mice were used. These mice were treated with (18 mg/kg body weight per day) or without moxonidine via drinking water throughout the experiment. Three days after the initiation of moxonidine treatment, hypertension was induced by subcutaneous infusion of angiotensin II (1 μg/kg body weight per min) for 28 days. Blood pressure (BP) was measured by the tail-cuff method. Kidneys were collected at the end of angiotensin infusion. Gene expression in the kidney was assessed by quantitative PCR.

Results: Angiotensin II infusion significantly increased BP and this increase was blunted by moxonidine treatment. Moxonidine treatment decreased wet kidney weight, but it did not change the size or area of either kidney tubules or glomeruli (P >0.05). Moxonidine significantly increased the expression of apoptosis marker caspase 3 (P=0.025). However, it did not change the renal expression of inflammatory markers. Both moxonidine receptors (imidazoline 1 and alpha-2 adrenergic receptors) were found to be expressed in kidney tissue. Moxonidine treatment did not change the mRNA expression level of its two receptors. However, it significantly increased the mRNA expression of prostaglandin E2 receptor E-prostanoid receptor 3 (EP3R) (P=0.025). Increased EP3R has been reported to be associated with promotion of diuresis and natriuresis and thus decreasing BP.

Conclusions: The present study suggests that moxonidine may lower BP partially through unrecognized non-central pathways, such as via regulating the prostaglandin E2 pathway in the kidney.

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Skeletal muscle microvascular perfusion abnormalities: A distinct phenotype of impaired exercise capacity in type 2 diabetes?

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Background: Left-ventricular dysfunction and abnormal skeletal muscle capillary blood flow (CBF) are each implicated in exercise impairment due to type 2 diabetes (T2D).

Aim: To identify whether there are distinct phenotypes of T2D-related exercise impairment based on differential associations of muscle CBF with exercise capacity according to the presence and type of left-ventricular dysfunction.

Methods: Individuals with T2D (n=132; otherwise healthy) performed a treadmill exercise test for maximal oxygen uptake (VO_2 peak), with pre-/post-exercise echocardiography and contrast-enhanced ultrasound of the quadriceps (for CBF; product of capillary blood volume × velocity). Left-ventricular diastolic dysfunction was defined by E/e' >10 (ratio of early diastolic filling/annular velocities), while systolic function was differentiated by tertiles of pre-/post-exercise change in systolic tissue velocity (s'index).

Results: Proportions with exercise impairment (VO_2 peak 0.10). However, when examined according to s'index, lower values of capillary blood velocity and CBF (P < 0 .05) with exercise impairment were restricted to the highest tertile only (P interaction = 0.043 and 0.19 for the high vs. middle and high vs. low tertiles, respectively).

Conclusions: Peak CBF is reduced in the setting of exercise impairment, irrespective of concurrent left-ventricular dysfunction (indeed, possibly more-so when systolic function is well-preserved). This supports the concept of a muscle angiopathy phenotype of exercise impairment in T2D.

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Biochemical and histological comparison between posture-responsive and unresponsive aldosterone-producing adenomas

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Background: Unilateral aldosterone-producing adenoma (APA) and bilateral adrenal hyperplasia account for approximately 30% and 65% of primary aldosteronism (PA), respectively. Based on responses of peripheral aldosterone concentration (PAC) to upright posture, APA can be subdivided into posture-responsive (-R) and -unresponsive (-U) subtypes. Cortisol normally synthesized mainly in zona fasciculata (ZF) cells, when exposed to aldosterone synthase that is normally expressed only in zona glomerulosa (ZG) cells, can be converted into 18-hydroxycortisol (18-HC) and 18-oxocortisol (18-OC), levels of which have been reported previously to be elevated in posture-U (but not -R) APA.

Aim: To compare biochemical and histological characterization between posture-R and -U APAs.

Methods: Forty-one patients with PA, who displayed lateralization of aldosterone production to one adrenal by adrenal venous sampling (AVS) and consented to undergo unilateral adrenalectomy (ADX), were recruited. Recumbent and upright PAC were measured to assess posture responsiveness (defined as a rise in PAC by at least 50% over basal, 3 h after assuming upright posture following overnight recumbency). Plasma and urinary aldosterone (PAC and UAC), 18-HC and 18-OC were measured by LC-MS/MS, while direct renin concentration (DRC) was quantified by CLIA. Pre- and post-ADX results were also compared.

Results: Before ADX, posture-U (n=26) patients had higher level of recumbent PAC than posture-R (n=15) patients (median, 830 vs. 357 pmol/l; $P < 0.01$), but similar upright PAC (641 vs. 684 pmol/l; NS) and DRC (recumbent 2.0 vs. 2.0 mU/l, upright 3.0 vs. 3.6 mU/l; NS). The changes in PAC and DRC associated with upright posture in both groups were all significant ($P < 0.01$). During AVS, posture-U patients showed more significant contralateral suppression of aldosterone secretion than posture-R patients (contralateral suppression index: 0.25 vs. 0.50; $P < 0.05$), while there was no significant difference in lateralization index (9.9 vs. 11.8; NS). Plasma 18-OC ($P < 0.01$), 18-HC ($P < 0.01$), and urinary 18-OC ($P < 0.05$) in the posture-U group (0.80, 4.44, 21.3 nmol/l) were higher than that in the posture-R group (0.11, 1.64, 3.8 nmol/l), but no significant differences were observed in UAC and urinary 18-HC. After ADX, plasma 18-OC and 18-HC declined ($P < 0.05$) in the posture-U group and were no longer significantly different from those of the posture-R group. The adenoma size in the posture-U group was larger than that in the posture-R group (median diameter, 17.5 vs. 9.0 mm; $P < 0.01$). Histologically, 96.2% of posture-U APAs demonstrated predominantly ZF-like cellular composition (n=25), while one case showed ZG-ZF mixed cellular features. In contrast, 73.3% of posture-R APAs demonstrated predominantly ZG-like cellular

composition (n=11), while 4 cases showed ZG-ZF mixed cellular features. The proportions differed significantly ($P < 0\ .01$).

Conclusions: Compared to posture-R APAs, posture-U APAs lack responsiveness of PAC to upright posture, were associated with higher levels of 18-OC, 18-HC and recumbent PAC and a greater degree of contralateral suppression of aldosterone production, were larger and were more often predominately comprised of fasciculata-type cells.

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Establishing ANZACT - the ANZ Alliance for Cardiovascular Trial Network

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(On behalf of ANZACT Executive Team)

Background: Randomized controlled clinical trials provide the evidence base for the implementation of effective therapies into clinical practice. Australia has a long history in cardiovascular clinical trials including leading the landmark LIPID and ANBP2 trials in the 1990's. Despite pockets of excellence across the country, participation in cardiovascular trials and contribution from Australia sites is at a low. With the Medical Research Future Fund highlighting the importance of established clinical trials networks, we have set out to increase the engagement of Australian and New Zealand investigators in cardiovascular trials by establishing a facilitating network for the promotion of cardiovascular clinical trials across the spectrum of cardiovascular disorders.

Aim: To establish the Australia New Zealand Alliance for Cardiovascular Trials (ANZACT Network) to facilitate and promote engagement of investigators with clinical trials and registries.

Methods: The Clinical Trials Council of the Cardiac Society of Australia and New Zealand (CSANZ) and the NHMRC Centre of Research Excellence in Cardiovascular Outcomes Improvements organised two workshops in February 2017 and February 2018. An Interim Steering Committee was established to set up a governance structure and develop Terms of Reference for the Steering and Scientific Advisory Committees. A website presence was established to fill the new Committee roles, and formally recruit members.

Results: The workshops recommended that ANZACT be: (i) a facilitating network; (ii) independent from any sole organisation; (iii) committed to engage with other cardiovascular research societies to ensure maximum collaborative opportunities; (iv) a vehicle for investigators to present ideas for clinical trials for support by network members; (v) a body that will include researchers from basic science, nursing and allied health; and (vi) a vehicle for promotion of centres of excellence for cardiovascular research across Australia and New Zealand

Conclusions: Cardiology in Australia and New Zealand now has an official network to promote investigator-initiated clinical trials. The rapid uptake of ANZACT membership (200 members within 6 months) demonstrates a previously unmet need is being addressed. Future

initiatives will include concept development and peer review workshops, and fostering a collaborative approach to conducting large, multi-site trials.

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Do cardiac massage or ECMO effectively perfuse the brain after a cardiac arrest?

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Background: Cardiac arrest is a common and catastrophic event associated with a high morbidity and mortality. Cardiopulmonary resuscitation aims to provide adequate perfusion to vital organs during cardiac arrest, especially the heart and the brain. The brain, however, may not receive adequate perfusion despite technically optimal cardiopulmonary resuscitation. This notion is supported by the observation that, despite cardiopulmonary resuscitation, most patients successfully resuscitated from cardiac arrest have debilitating neurological injury, and many dice.

Aim: To determine the ability of cardiopulmonary resuscitation or extracorporeal membrane oxygenation (ECMO) of the anterior cerebral circulation to maintain cerebral perfusion and oxygenation following a cardiac arrest.

Methods: Studies were performed on anaesthetised sheep with fibre-optic probes implanted in the left and right cerebral cortex to continuously monitor tissue PO_2, tissue perfusion and temperature. The right carotid artery was cannulated for antegrade perfusion and the right atrium, via the right jugular vein, for drainage. Cardiac arrest was induced, and after 2 min open-chest cardiac massage was performed for 10 min. After cardiac massage, ECMO-based direct cerebral perfusion (300 mL/min at 36ºC) with oxygenated blood with a high CO_2 concentration was provided. Further studies, following a similar protocol, used perfusion MRI to determine the effects of cardiac arrest, cardiac massage and cerebral ECMO on cerebral perfusion.

Results: Cardiac arrest markedly decreased cerebral tissue perfusion (from 700 to 49 blood perfusion units (BPU)) and PO_2 (from 54 to 0 mmHg), and these levels were only mildly improved by open-chest cardiac massage (perfusion: 199 BPU and PO_2 10 mmHg). ECMO-based antegrade cerebral perfusion and cooling increased cerebral oxygenation levels to pre-arrest or higher levels. MRI perfusion indicated that cardiac arrest abolished cerebral perfusion and this was not improved by open-chest cardiac massage. Subsequent ECMO increased perfusion on the right side of the brain to nearly normal levels. Perfusion on the left side was improved but remained significantly below the normal level.

Conclusions: Experimental cardiac arrest caused large decreases in cerebral tissue perfusion and oxygenation, which were only minimally improved by open-chest cardiac massage. Anterior cerebral perfusion with ECMO restored cerebral oxygenation to normal levels and although it improved perfusion, measured by MRI, on the side ipsilateral to the infusion cannula, the improvement was less on the contralateral side. These findings suggest that cerebral ECMO increases cerebral perfusion during cardiac arrest and thus reduce neurological damage.

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Central Blood Pressure Assessment during Atrial Fibrillation

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Background: Central haemodynamics are being increasingly recognized in the development of atrial fibrillation (AF). However, no studies have been performed to validate their non-invasive assessment during AF.

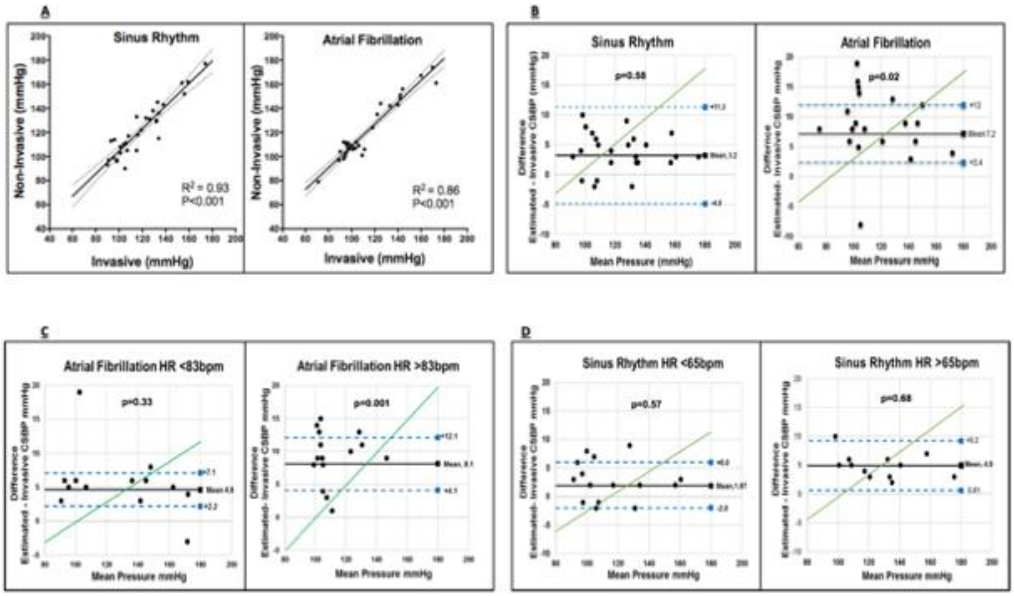
Aim: To validate a standardized non-invasive device, SphygmoCor XCEL (AtCor Medical, Australia) to estimate central blood pressure (CBP) against an invasive assessment of aortic root pressure during AF.

Methods: Simultaneous invasive and non-invasive CBP waveforms were recorded and averaged over 20 seconds in 31 consecutive patients (mean age 64±6 years, 57% male) undergoing AF ablation at our center, with a 4F pigtail catheter positioned in aortic root and through SphygmoCor XCEL, respectively. Correlation analysis was performed, and Bland Altman plots were employed to determine the agreement between non-invasive and invasive CBP.

Results: As shown in the Figure, a strong correlation was found between invasive and non-invasive estimates of CBP during SR (R^2 = 0.93, p 83 bpm). Similar analysis by using median HR of 65 bpm during SR did not uncover any significant difference between invasive and non-invasive CBP measurements. (Figure 1D- right and left panel respectively).

Conclusions: Our study is the first to demonstrate that CBP assessment can be reliably performed during rate-controlled AF. This can help improve risk profiling of our patients at risk of hypertension induced cardiovascular remodelling leading to AF.

Figure 1: Central Systolic BP during Sinus Rhythm and Atrial Fibrillation



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Aortic stiffness in atrial fibrillation: A systematic review and meta-analysis

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Background: Aortic stiffness is increasingly recognized to portend worse cardiovascular outcomes and the development of new onset atrial fibrillation (AF).

Aim: To perform a systematic review and meta-analysis of longitudinal studies reporting the risk of mortality and incidence of new onset atrial fibrillation (AF) in participants according to their aortic stiffness profile.

Methods: PubMed and EMBASE searches of the English scientific literature were performed to 30 August 2017 for prospective cohort studies reporting outcomes according to the aortic conformity profile determined by pulse pressure (PP) or pulse wave velocity (PWV). The search strategy is shown in the flow chart (Figure). We included studies with at least 50 participants and one year of follow-up. Data were analyzed by a random-effects meta-analysis technique.

Results: Twenty-five longitudinal studies (n=53,482 participants, mean age 58.3±5.6 years, 54% males) were included in the analysis. Aortic stiffness as determined by high aortic PWV (>10.7±1.6 m/s) was associated with 57% higher risk of all-cause mortality (OR 1.57; 95% CI: 1.20–2.06; *P*=0.001) and more than two-fold higher risk of cardiovascular mortality (OR 2.34; 95% CI: 1.81–3.02; *P*<0.001). Further, each m/s amplification in aortic PWV was independently associated with increased cardiovascular (OR 1.25, 95% CI: 1.16-1.34, p<0.001) and all-cause mortality (OR 1.16, 95% CI: 1.08-1.25, p<0.001). Aortic stiffness determined by elevated pulse pressure (>60±16 mmHg) was significantly associated with an increased risk of new-onset AF (OR 1.38; 95% CI: 1.15–1.64; *P*=0.0004).

Conclusions: Aortic stiffness is an independent predictor for the development of new-onset AF and is significantly associated with increased cardiovascular and all-cause mortality.

Figure 1: Study Selection Flow Diagram