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Citation for final published version:

Warnert, Esther A. H., Rodrigues, Jonathan C. L., Burchell, Amy E., Neumann, Sandra, Ratcliffe, Laura E. K., Manghat, Nathan E., Harris, Ashley D., Adams, Zoe, Nightingale, Angus K., Wise, Richard G. , Paton, Julian F. R. and Hart, Emma C. 2016. Is high blood pressure self-protection for the brain? *Circulation Research* 119 (12) , e140-e151. 10.1161/CIRCRESAHA.116.309493

Publishers page: <http://dx.doi.org/10.1161/CIRCRESAHA.116.309493>

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1 **Is high blood pressure self-protection for the brain?**

2

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29

30 **Total word count:** 9412

31

32 **Subject codes:** Hypertension, Physiology, Cerebrovascular Disease/Stroke, Clinical Studies
33 Magnetic Resonance Imaging (MRI)

34

1 **Abstract**

2 **Rationale:** Data from animal models of hypertension indicate that high blood pressure may
3 develop as a vital mechanism to maintain adequate blood flow to the brain. We propose that
4 congenital vascular abnormalities of the *posterior* cerebral circulation and cerebral
5 hypoperfusion could partially explain the etiology of essential hypertension, which remains
6 enigmatic in 95% of patients.

7
8 **Objective:** To evaluate the role of the cerebral circulation in the pathophysiology of
9 hypertension.

10
11 **Methods and Results:** We completed a series of retrospective and mechanistic case-control
12 magnetic resonance imaging and physiological studies, in normotensive and hypertensive
13 humans (n=259). Interestingly, in humans with hypertension, we report a higher prevalence of
14 congenital cerebrovascular variants; vertebral artery hypoplasia and an incomplete posterior
15 circle of Willis, which were coupled with increased cerebral vascular resistance, reduced
16 cerebral blood flow and a higher incidence of lacunar type infarcts. Causally, cerebral vascular
17 resistance was elevated *before* the onset of hypertension and elevated sympathetic nerve
18 activity (n=126). Interestingly, untreated hypertensive patients (n=20) had a cerebral blood flow
19 similar to age-matched controls (n=28). However, participants receiving anti-hypertensive
20 therapy (with blood pressure controlled below target levels) had reduced cerebral perfusion
21 (n=19). Finally, elevated cerebral vascular resistance was a predictor of hypertension
22 suggesting it may be a novel prognostic and/or diagnostic marker (n=126).

23
24 **Conclusions:** Our data indicate that congenital cerebrovascular variants in the posterior
25 circulation and the associated cerebral hypoperfusion may be a factor in triggering
26 hypertension. Therefore lowering blood pressure may worsen cerebral perfusion in susceptible
27 individuals.

28
29
30 **Key words:** Hypertension, vertebral artery hypoplasia, cerebral blood flow, sympathetic nerve
31 activity, and magnetic resonance imaging

1 **Abbreviations**

2

3 ANCOVA; analysis of covariance

4 BMI; body mass index

5 BOLD; blood oxygen level dependant

6 BP; blood pressure

7 DBP; diastolic blood pressure

8 CoW; circle of Willis

9 MRI; magnetic resonance imaging

10 MRA; magnetic resonance angiography

11 MSNA; Muscle sympathetic nerve activity

12 NHS; National Health Service

13 SBP; systolic blood pressure

14 SNA; sympathetic nerve activity

15 PCASL; pseudo continuous arterial spin labelling

16 RVLM; rostral ventrolateral medulla

17 TE; echo time

18 TR; repetition time

19 VAH; vertebral artery hypoplasia

20

1 Introduction

2 High blood pressure (blood pressure) affects ~25% of the world's population and is the largest
3 single contributor to global mortality¹. Hypertension represents a significant economic burden to
4 public healthcare providers, where the global cost of non-optimal BP is estimated to be US\$370
5 billion (10% of healthcare expenditure)². Remarkably, despite the availability of many
6 pharmacological treatments, BP is poorly controlled with a recent report stating that only 53% of
7 patients prescribed anti-hypertensive medication have BP controlled³. This reflects the well-
8 known heterogeneity of the syndrome including epigenetic and inherited factors contributing to
9 the unknown causes in 95% of patients⁴.

10

11 Despite the devastating consequences of hypertension (e.g. stroke, kidney failure, coronary
12 heart disease, death^{1,2}), the mechanisms that lead to the onset of hypertension in humans are
13 poorly understood. It is well established that elevated sympathetic nerve activity (SNA)
14 contributes to the development of hypertension in most humans⁵⁻⁷ but what initiates this
15 remains unclear. Experimental data from hypertensive rats and observations in post-mortem
16 human studies suggest that blood flow to the brain might be important in setting the operating
17 level of SNA and thus systemic arterial pressure^{8,9}. Evidence from Dickinson¹⁰ showed that
18 the vertebral arteries in hypertensive patients were narrower than those observed in
19 normotensive individuals. Dickinson and Thomson⁹ demonstrated that high vertebral artery
20 resistance correlated with higher blood pressure; importantly, a weaker relationship was found
21 in other arteries including femoral, renal and internal carotid arteries. They proposed that
22 narrowing of the vertebral arteries with subsequent brainstem hypoperfusion might be a *cause*
23 of hypertension, rather than being a *consequence*, but had no evidence to support causality.
24 This has been termed "Cushing's mechanism" or "the selfish brain hypothesis" of hypertension
25¹¹. The mechanism may trigger elevations in SNA and BP thereby maintaining cerebral blood
26 flow^{8,12}. Evidence from spontaneously hypertensive rats at a pre-hypertensive age supports
27 this notion: Cates et al.⁸ demonstrated that vertebrobasilar artery hypertrophy occurred *before*
28 the onset of hypertension in these animals. The authors also showed that brainstem ischemia
29 caused by bilateral vertebral artery clamping, generated a greater increase in SNA in pre-
30 hypertensive spontaneously hypertensive rats compared to age-matched normotensive
31 animals⁸. Additionally, the brainstem of hypertensive rats is hypoxic and this is accentuated
32 when BP is normalised¹³.

33

34 We have addressed the issue of whether "Cushing's mechanism" is involved in the development
35 of hypertension in humans. This may have a significant impact on the diagnosis and treatment
36 of hypertension, whilst potentially aiding prevention of early onset vascular dementia in
37 hypertensive humans¹⁴. Thus, we have evaluated the temporal relationship of changes in
38 cerebral vascular structure and cerebral blood flow with both the onset of hypertension and
39 raised SNA in humans. We performed a series of retrospective *and* mechanistic case-control
40 studies in a range of participants with different levels of BP and classifications of hypertension.
41 Uniquely, we show that congenital cerebral vascular variants, vascular resistance and blood
42 flow are tightly coupled to the development of hypertension in humans.

43

44 Methods

45 **Retrospective study**

46 We first measured whether there were anatomical differences in the cerebral circulation of
47 hypertensive patients compared to controls. We specifically focused on vertebral artery
48 hypoplasia (VAH; a congenital anatomical variant of the posterior circulation that occurs in the
49 general population), which is associated with lower posterior cerebral territory blood flow¹⁵, and
50 variations in the anatomy of the circle of Willis (CoW). We hypothesised that the occurrence of

1 anatomical variants in the vertebral arteries and CoW would be higher in the hypertensive
2 population compared to that reported for healthy controls.

3 4 *Study population*

5 133 patients with *essential* hypertension referred to the Bristol Heart Institute tertiary
6 hypertension clinic between February 2012 and April 2015 were included in the retrospective
7 analyses (secondary causes of hypertension had been excluded in clinic). The local Research
8 Ethics committee confirmed that the study conformed to the governance arrangements for
9 research ethics committees. All patients provided written informed consent. Supplementary
10 Table 1 shows patient characteristics. Cases included were from consecutive referrals by the
11 hypertension clinic to the Cardiovascular Magnetic Resonance Unit in the NIHR Bristol
12 Cardiovascular Biomedical Research Unit in the Bristol Heart Institute.

13 14 *BP measurements*

15 Average office systolic (SBP) and diastolic BP (DBP) were measured from both arms after
16 seated rest, using standard automated sphygmomanometry with an appropriate sized cuff ¹⁶. In
17 a subgroup of patients (n= 84), 24 hour ambulatory BP monitoring was completed ¹⁷
18 (Supplementary Table 1).

19 20 *MRI procedures*

21 3D time-of-flight MR angiography (MRA) at 1.5T (Avanto, Siemens, Erlangen, Germany) with a
22 dedicated head coil was used to measure arterial anatomy (TR = 38ms, TE= 5.28ms, flip angle
23 = 25 degrees, voxel size = 0.7 x 0.5 x 0.8mm, field of view = 200mm, covering major arteries
24 feeding into the CoW). See *supplementary material* for further information regarding angiogram
25 analyses.

26
27 Briefly, vertebral artery hypoplasia (VAH) was defined as a diameter <2 mm uniformly
28 throughout the vessel ¹⁵. Anterior and posterior CoW anatomy was reviewed as previously
29 described ¹⁸. VAH was compared to data previously reported from 306 healthy controls ¹⁵. CoW
30 morphology was classified according to normal reference standards ¹⁸.

31 32 **Case-control study**

33 *Participants*

34 Following approval by NHS Research Ethics Committee (11/SW/0207) and local R&D approval,
35 142 participants were prospectively recruited and enrolled at a single site (University Hospitals
36 Bristol NHS Foundation Trust). Participants gave their written informed consent to participate in
37 this study. 16 volunteers were excluded due to screen failure and/or early termination of MRI
38 scan due to discomfort or unforeseen technical difficulties. See *supplementary material* for
39 inclusion and exclusion criteria. Table 1 outlines participant characteristics and the number and
40 classes of anti-hypertensive medications being taken. One patient in this study had received
41 renal denervation, which was successful in treating their hypertension.

42
43 Six specific BP subgroups were *prospectively* recruited: young normotensive (age <35 years;
44 Table 2 for characteristics), older normotensive (age >35 years), borderline/pre-hypertensive,
45 untreated hypertensive, treated-controlled hypertensive (taking anti-hypertensive medication
46 and BP controlled), and treated-uncontrolled hypertensive groups (taking anti-hypertensive
47 medications, but BP uncontrolled). Borderline hypertension was defined as an office BP 135-
48 140/85-90 mmHg and a daytime ambulatory BP 130-135/80-85 mmHg.

49 50 *Screening BP*

1 Participants attended a screening session, where office BP was measured using an automated
2 cuff (Omron, The Netherlands), in line with the European Society of Hypertension guidelines¹⁹.
3 Participants were fitted with an ambulatory BP monitor (Spacelabs, OSI Systems Company,
4 USA). Their 24-hour BP was measured twice per hour during the daytime and once per hour
5 during the night.

6 *Microneurography*

7 Peroneal microneurography was completed to measure multi-unit muscle sympathetic nerve
8 activity (MSNA). For full methods, see *supplementary material*. Following instrumentation, 5-10
9 minutes of baseline data were collected in all patients. Heart rate, BP and MSNA were
10 measured and recorded continuously using a data acquisition program on a study laptop
11 (LabChart, AD instruments).
12

13 *MRI acquisition*

14 All study participants were scanned using 3T MRI (GE HDx, Milwaukee, Wisconsin, USA). The
15 protocol consisted of a high resolution T₁-weighted fast spoiled gradient echo (3D-FSPGR)
16 structural scan, 3D time of flight angiography to measure arterial anatomy, phase contrast pulse
17 sequences to measure blood flow in the internal carotid and basilar arteries at baseline and in
18 response to 5% CO₂, and pseudo-continuous arterial spin labelling (PCASL) to measure
19 regional cerebral blood flow. BP (automated cuff), heart rate (pulse oximeter), and end tidal CO₂
20 (capnograph) were monitored throughout all acquisitions. See *supplementary information* for
21 imaging parameters.
22

23
24 Since poor cerebral vascular reactivity is linked to the risk of developing hypertension, we
25 hypothesised that the hypertensive group would have impaired cerebral vascular reactivity. In a
26 subgroup of participants, cerebral vascular reactivity to isoxic hypercapnia (5% CO₂) and to a
27 strong visual stimulus (flashing checkerboard²⁰, using a dual echo blood oxygen level
28 dependent; BOLD and ASL MRI acquisition) was measured (supplementary material for MRI
29 parameters).
30

31 *MRI analyses*

32 All data analyses were blinded and completed by separate investigators. Please see
33 *supplementary material* for details regarding methodology for MRI analyses. In short, to
34 measure blood flow in the right and left internal carotid and basilar arteries, phase contrast
35 images were analysed using Segment (version 1.9, Medviso, Sweden)²¹. Total cerebral blood
36 flow was estimated as the sum of blood flow in these vessels and scaled for parenchymal tissue
37 volumes. Cerebral vascular resistance was calculated as the brachial mean arterial pressure
38 (measured during the phase contrast acquisition) divided by average flow in each vessel. This
39 method assumes that intra-cranial pressure and venous pressure is normal and similar between
40 groups, and therefore that mean arterial pressure is an accurate estimation of cerebral perfusion
41 pressure in different groups. The method has been used in multiple studies to calculate cerebral
42 vascular resistance^{22, 23}. Regional cerebral perfusion was measured from the PCASL images
43 using the standard Buxton model²⁴. Cerebral vascular reactivity to hypercapnia (5% CO₂) was
44 calculated as the change in total cerebral blood flow (calculated as the sum of blood flow in the
45 internal carotid and basilar arteries, measured using phase contrast MRI) from the normocapnic
46 condition. Blood flow was scaled for changes in end tidal CO₂ and blood pressure. Finally,
47 positive and negative changes in cerebral blood flow and BOLD signal, in response to the
48 flashing checkerboard stimulus, were measured in the visual cortex.
49

50 *Statistical analyses*

1 All data analysis was blinded. An unpaired Students T-test was used to test for differences in
2 participant's characteristics/demographics between normotensive and hypertensive groups. A
3 one-way ANCOVA was used to test for differences in total cerebral blood flow, regional cerebral
4 blood flow and MSNA between hypertensive and normotensive groups, using BMI as a
5 covariate. Binary logistic regression (enter method) was used to test for differences in the
6 prevalence of anatomical variations (VAH, incomplete posterior CoW or VAH *with* an incomplete
7 posterior CoW) between hypertensive and normotensive groups. To test for differences in
8 cerebral blood flow and cerebral vascular resistance, between hypertensive and normotensive
9 participants with and without anatomical variants, a one-way ANCOVA (BMI as a covariate) was
10 used with a Bonferroni test for multiple comparisons. Participants sub-grouped into specific
11 normotensive and hypertensive groups; a one-way ANCOVA (BMI as covariate) with a
12 Bonferroni test for multiple comparisons was used to test for differences in demographics, BP ,
13 cerebral blood flow, cerebral vascular resistance and MSNA.

14
15 To predict which variables might be better predictors of hypertension (i.e. is cerebral vascular
16 resistance a stronger predictor of hypertension than BMI?), conditional forward binary logistic
17 regression was completed, where diagnosis of hypertension was the dependent variable. The
18 independent variables were age, BMI, cerebral blood flow, cerebral vascular resistance, VAH
19 plus an incomplete posterior CoW and MSNA. All statistical tests were two-tailed. Alpha was set
20 at 0.05. Where appropriate data are reported as mean \pm SEM, median with interquartile range
21 or as percentage with 95% confidence intervals.

22 23 **Results**

24 ***Retrospective study***

25 *Anatomical variations in the cerebral vasculature*

26 Patient characteristics are outlined in the Supplementary Table 1. Fishers exact test showed
27 that VAH and an incomplete *posterior* CoW were highly prevalent in the hypertensive population
28 (hypertensive vs. normotensive^{15, 18}: 53% vs. 27% and 64% vs. 36% respectively; $P < 0.0001$,
29 Figure 1). The odds ratios indicated that individuals with VAH or those with an incomplete
30 posterior CoW were 2.8 (95% CI; 1.8 to 4.3) and 3.1 (95% CI; 1.6 to 6.1) times more likely to
31 have hypertension. There were no differences in the prevalence of an incomplete *anterior* CoW
32 between our hypertensive cohort and that reported in a healthy control population¹⁸ (32% vs.
33 25%, respectively, $P = 0.26$).

34
35 During the retrospective analysis we noted that there was also a high prevalence of VAH *with*
36 an incomplete posterior CoW (27%). The prevalence of having both variants has not been
37 compared in healthy controls previously. We were interested in whether the prevalence was
38 higher in the hypertensive patients compared to controls, since having both may present further
39 challenges to perfuse the posterior regions of the brain. These results prompted a case-control
40 study where we assessed whether the anatomical variations in the posterior cerebral
41 vasculature related functionally to differences in cerebral perfusion and vascular resistance in
42 hypertensive patients

43 44 ***Case-control study***

45 *Participant characteristics*

46 The hypertensive (n=77) and normotensive groups (n=49) were similar in age and height
47 ($P = 0.12$); however, body mass index (BMI) and body mass were lower in the normotensive
48 group ($P = 0.02$, Students T-test, Table 1). Office BP, day-/night-time ambulatory BP and MSNA
49 were higher in the hypertensive compared to the normotensive group ($P < 0.0001$, ANCOVA,
50 Table 1). Hypertensive patients had a higher incidence of lacunar infarcts (14%) compared to
51 normotensive patients (4%, $P = 0.03$), but the number of subcortical and cortical infarcts were

1 similar between groups (3% vs. 2%; $P=0.680$, and 1% vs. 1%; $P=0.831$, respectively, Fishers
2 Exact Test).

3
4 *Anatomical variants in the posterior cerebral vasculature are more prevalent in humans with*
5 *hypertension*

6 We observed that VAH, an incomplete posterior CoW and VAH *with* an incomplete posterior
7 CoW were higher in hypertensive (57%, 60%, and 42%; analysed using MR angiography by
8 blinded radiologist) compared to normotensive participants (Figure 1; 30%; $P=0.006$, 37%;
9 $P=0.028$ and 19%; $P=0.006$; respectively, binary logistic regression; enter method). The odds
10 ratio indicated that if VAH, an incomplete posterior CoW or VAH *with* an incomplete posterior
11 CoW were present, then individuals were 3.0 (95% CI: 1.4 – 6.3), 2.6 (95% CI: 1.2 – 5.6) and
12 3.2 (95% CI: 1.4-7.6) times more likely to have hypertension, respectively. Conditional forward
13 binary logistic regression selected VAH as the strongest predictor of having a diagnosis of
14 hypertension, when both VAH and an incomplete posterior CoW were inserted into the model
15 (odds ratio= 2.8; 95% CI: 1.2-6.2, $P=0.017$ vs. odds ratio 2.5; 95% CI: 1.1-5.6, $P=0.020$)
16 respectively). Importantly, there was no difference in the prevalence of an incomplete *anterior*
17 CoW between hypertensive (25%) and normotensive (32%) groups ($P=0.46$). Missing anterior
18 communicating arteries were the main cause of an incomplete anterior CoW. The A1 segment
19 of the anterior cerebral artery was missing in only a small proportion of individuals (left A1; 1%
20 vs. 0%; $P=1.00$ and right A1; 4% vs. 7%; $P=0.45$ in hypertensives and normotensives
21 respectively). There was no difference in the prevalence of a combined incomplete posterior
22 and anterior CoW between hypertensive and normotensive groups (27% vs. 20%, $P=0.35$).
23 Finally, binary logistic regression indicated that there was no interaction between BMI and VAH
24 ($\beta= 0.016$; $P=0.234$) or VAH plus an incomplete CoW ($\beta= 0.018$; $P=0.77$).

25
26 Next, we determined whether these anatomical variants in the posterior cerebral circulation are
27 functionally important. *Total* arterial cerebral blood flow (measured using MR phase-contrast
28 imaging) was lower in the hypertensive compared to the normotensive group (Table 1,
29 $P<0.0001$; ANCOVA). Using region of interest analysis on cerebral perfusion maps (PCASL),
30 cerebral perfusion was lower in the hypertensive compared to normotensive group in all regions
31 studied (Table 3, $P<0.05$; ANCOVA). Moreover, total cerebral vascular resistance was higher in
32 hypertensive participants versus those with normotension ($P<0.0001$; ANCOVA, Table 1). We
33 hypothesised that VAH and/or an incomplete posterior CoW would be associated with lower
34 cerebral perfusion.

35
36 Participants were split into those with/without VAH ($n=56/68$, respectively) regardless of their BP
37 status. Those with VAH had a lower total arterial cerebral blood flow ($P<0.0001$, ANCOVA) and
38 a higher cerebral vascular resistance ($P<0.0001$) than those without these anatomical variants
39 (Figure 2). Data for both VAH and an incomplete posterior CoW showed similar differences and
40 are presented in Figure 2.

41
42 Interestingly, hypertensive participants with VAH ($n=39$) had a lower cerebral arterial blood flow
43 compared to hypertensives without VAH ($n=36$; Figure 2, $P=0.014$, one-way ANCOVA with
44 Bonferroni test for multiple comparisons). Additionally, the reported incidence of lacunar type
45 infarcts was greater in hypertensive patients with VAH versus those without VAH (22% vs. 3%,
46 $P=0.001$, Fishers exact test). Intriguingly, there were no differences in cerebral blood flow
47 ($P=0.750$) or cerebral vascular resistance ($P=0.333$) between the normotensive groups with and
48 without VAH (ANCOVA and Bonferroni post-hoc test). This suggests that: a) in normotensive
49 individuals, VAH was not associated with a higher cerebral vascular resistance and, b) that in
50 the presence of VAH, individuals with normal BP are able to maintain cerebral perfusion.
51 Importantly, we found that there was no difference in total cerebral blood flow and vascular

1 resistance in hypertensive people with and without an incomplete *anterior* CoW (Supplementary
 2 Table 2). Additionally, there was no difference in these variables in hypertensives with or without
 3 both an incomplete anterior and posterior CoW (Supplementary Table 2). Similar findings are
 4 reported for the normotensive group. These data suggest that variants in the anterior CoW do
 5 not impact cerebral hemodynamics.

6
 7 *The contralateral vertebral artery does not compensate for the hypoplastic artery in*
 8 *hypertensive patients*

9 Individuals with VAH usually have a larger contralateral vertebral artery, apparently
 10 compensating for the hypoplastic vessel¹⁵. To estimate whether the contralateral vessel
 11 normalized blood flowing into the posterior circulation, we measured blood flow in the basilar
 12 artery (all data analysed with BMI as a covariate). In normotensive participants, there was no
 13 difference in blood flow in the basilar artery between those with/without VAH (11.4 ± 0.9 vs. 13.9
 14 ± 0.9 mL/100mL/min, $P=0.151$; ANCOVA). In contrast, in the hypertensive patients there was a
 15 lower basilar blood flow with VAH compared to those without VAH (10.4 ± 0.9 vs. 13.4 ± 0.9
 16 mL/100mL/min, $P=0.002$). These data suggest that in participants with hypertension, the
 17 contralateral vertebral artery does not fully compensate for lower blood flow in the hypoplastic
 18 vertebral artery

19
 20 *Assessing cause and effect: Cerebral vascular resistance, blood flow and muscle sympathetic*
 21 *nerve activity*

22 We next attempted to assess causality between cerebral vascular variants, cerebral
 23 hypoperfusion and the **onset** of elevated SNA, a driver of hypertension. To assess the temporal
 24 relationship between cerebral hypoperfusion and the onset of both increased sympathetic
 25 activity and hypertension, 4 sub-groups of patients with differing classes of hypertension were
 26 recruited and compared to age- and sex-matched normotensive controls. These groups were:
 27 borderline, untreated, treated-controlled, and treated but poorly controlled hypertensive
 28 participants (Table 2). The borderline (or high normal) group did not have hypertension but had
 29 daytime ambulatory SBP of 130-135 mmHg (Figure 3) and a high incidence of self-reported
 30 family history of hypertension in first order relatives (Table 2). The prevalence of family history
 31 of essential hypertension in all hypertensive groups was higher than that in the normotensive
 32 groups (Chi-square test, $P<0.0001$). Interestingly, the prevalence of VAH with an incomplete
 33 CoW was higher in the borderline hypertensive group compared to normotensive controls
 34 (borderline hypertension; 61%, and older normotension; 31%, Chi-squared test; $P<0.05$).

35
 36 Figure 3 shows that cerebral vascular resistance was elevated in the borderline hypertensive
 37 group compared to young and older normotensive controls. However, in the borderline group
 38 MSNA was not elevated and similar to the older normotensive group (49 ± 5 vs. 47 ± 3
 39 bursts/100 heart beats; ANCOVA; $P=0.9$). This suggests that increased cerebral vascular
 40 resistance occurs *before* the onset of higher MSNA and is thus a putative trigger for subsequent
 41 elevation of MSNA and blood pressure. Additionally, total cerebral blood flow was lower in the
 42 borderline hypertensive group compared to older ($P=0.002$) and younger normotensive groups
 43 ($P=0.001$), but was similar to that in the uncontrolled hypertensive ($P=1.00$) and treated
 44 hypertensive groups ($P=1.00$). The total cerebral arterial blood flow in the untreated
 45 hypertensive group was similar to that in the older ($P=0.891$) and younger normotensive groups
 46 ($P=0.899$); suggesting that in the face of higher cerebral vascular resistance, the elevated
 47 resting BP was able to normalise perfusion in this group.

48
 49 *Is cerebral vascular resistance a good predictor of hypertension?*

50 Conditional forward binary logistic regression was completed to determine which variables were
 51 predictive of having a diagnosis of hypertension (n=126; treated controlled hypertensive group

1 were included in the hypertension category). Cerebral vascular resistance was the strongest
 2 predictor of a diagnosis of high BP (odds ratio 1.86, 95% CI: 1.44, 2.40, $P < 0.0001$), followed by
 3 BMI (odds ratio 1.53, 95%CI: 1.23-1.92, $P < 0.0001$), age (OR: 1.15, 95% CI: 1.04-1.27,
 4 $P = 0.009$) and total cerebral blood flow (OR: 1.23, 95%CI: 1.0-1.5, $P = 0.01$). Thus, high cerebral
 5 vascular resistance predicts hypertension.

6 *Cerebrovascular reactivity, hypertension and anatomical variants*

7 We found no difference in total cerebral vascular reactivity to CO₂ (expressed as per % rise in
 8 end tidal CO₂ and scaled for changes in mean arterial pressure; MAP) between the
 9 hypertensive (n=29) and normotensive groups (n = 22, 5.6 ± 0.6 vs. 4.5 ± 0.7
 10 mL/100mL/min/mmHg/%; $P = 0.21$, ANCOVA, Supplementary Figure 1). Additionally, when the
 11 groups were split into participants with (n=19) and without VAH plus an incomplete CoW (n =
 12 32; split regardless of hypertensive status), there was no difference in cerebral blood flow
 13 reactivity to CO₂ (4.7 ± 0.4 vs. 5.6 ± 0.7 mL/100mL/min/mmHg/%; $P = 0.41$, Supplementary
 14 Figure 1).
 15

16
 17 We next assessed the cerebral vascular reactivity to a strong visual stimulus (Figure 4A shows
 18 example acquisition). The visual stimulus caused a similar increase in cerebral blood flow in
 19 normotensive (n=28) and hypertensive (n=36) subgroups in an activation mask within the
 20 occipital lobe, consisting of a union of significantly activated voxels in the BOLD and ASL time-
 21 series (Figure 4B). In all participants, negative BOLD and cerebral blood flow signals were also
 22 detected within the occipital lobe and surrounding the visual cortex (Figure 4, panel A for
 23 example of cerebral perfusion). Despite these similar changes in blood flow, the hypertensive
 24 group exhibited a greater increase in BP during the visual stimulus (figure 4B, $P = 0.02$,
 25 ANCOVA) suggesting that hypertensive men and women rely on increasing perfusion pressure
 26 to maintain cerebral blood flow than local vasodilatory mechanisms. In a group with both VAH
 27 and an incomplete CoW, however, data indicated a difference in cerebrovascular reactivity. We
 28 found a blunted increase in BOLD signal along with a trend towards a blunted increase in
 29 cerebral blood flow response to the visual stimulus (Figure 4C). Moreover, linear regression
 30 analyses suggested that for participants with both VAH and an incomplete posterior CoW, the
 31 positive and negative BOLD responses have a stronger inverse relationship than for participants
 32 without VAH and incomplete posterior CoW ($\beta_1 = -0.17$; $P < 0.05$ vs. $\beta_1 = 0.65$; $P < 0.05$,
 33 respectively; ANOVA, Supplementary Figure 2). This implies that for a larger positive increase
 34 in BOLD signal the hypertensive group rely on a blood flow steal from other adjacent tissue.
 35 However, this needs to be interpreted with caution since the BOLD response is a result of
 36 neurovascular coupling²⁵, which is a mechanism that does not solely depend on regional
 37 cerebral blood flow.
 38

39 **Discussion**

40 This is the first confirmation in conscious humans that the cerebral vasculature and cerebral
 41 hypoperfusion might be important in the development of hypertension. This is based on: 1) a
 42 higher prevalence of congenital anatomical variants; VAH and an incomplete posterior CoW, in
 43 hypertensive patients that were associated with reduced cerebral blood flow and increased
 44 cerebral vascular resistance. 2) The association of these anatomical variants with diminished
 45 cerebrovascular *reactivity* in the visual cortex. 3) The finding of elevated cerebral vascular
 46 resistance *before* the increase in MSNA and hypertension. This was consistent with the finding
 47 that cerebral vascular resistance was found to be the greatest predictor of hypertension status
 48 compared to body mass index and age. 4) The reliance on a systemic BP surge to increase
 49 cerebral blood flow, during a visual cortex stimulus, in the hypertensive cohort. Overall, these
 50 data support our contention that, in some cases, hypertension develops as 'self-protection for
 51 the brain'.

1
2 It is accepted that cerebral arteries and arterioles are remodelled in hypertension, thereby
3 increasing resistance to blood flow²⁶. Narrowing of the vessel lumen and an increased
4 wall/lumen ratio are typically demonstrated in animal models^{8, 27, 28} and humans with
5 hypertension^{9, 29}. Furthermore, cerebral blood flow is attenuated in elderly patients with
6 hypertension^{30, 31} and is related to white matter lesions³² and small vessel disease³³, a finding
7 which is contradictory to studies indicating that cerebral autoregulation is intact in hypertensive
8 patients³⁴. Our data are the first to show that in middle-aged hypertensive humans without
9 cerebral stenotic disease, *total* arterial cerebral blood flow (Table 1) and cerebral perfusion in all
10 brain regions measured (Table 3) are lower compared to age-matched normotensive
11 participants. This may help to explain why patients with hypertension have an increased risk of
12 developing vascular dementia¹⁴. Traditionally, cerebral vessel remodelling and cerebral
13 hypoperfusion were thought to be a *consequence* of high blood pressure. Evidence in animals
14 and humans now suggest that this theory may be incorrect with the reverse true; cerebral artery
15 remodelling and hypoperfusion may precede hypertension as found herein^{10, 11}.

16
17 Remarkably, in this study, we show that cerebral vascular resistance is increased *before* the
18 onset of sympathetic hyperactivity and hypertension in humans. Cerebral vascular resistance
19 was elevated in a group of participants with borderline-high BP (daytime SBP 130-135 mmHg),
20 as it was in all other hypertensive groups, whereas the level of SNA in the borderline population
21 was similar to aged matched controls. A potential caveat of this study is the cross-sectional
22 design; therefore we do not know whether the borderline hypertensive group will develop
23 hypertension. A longitudinal study is needed to confirm this. Another potential limitation of this
24 study is the indirect method used to calculate cerebral vascular resistance. Since measures of
25 intracranial pressure were not possible, the method does not take into account potential
26 variations in intracranial pressure between groups, and thus its influence on perfusion pressure
27 and resistance. It is reasonable to assume that there was no difference in intracranial pressure
28 between hypertensive and normotensive groups, since none of the participants showed
29 symptoms of intracranial hypertension or hydrocephalus, and patients with tumours were
30 removed from the study. Although many other studies have used this method of calculating
31 cerebral vascular resistance^{22, 23}, the method needs validating in both healthy controls and
32 patients with disease.

33
34 In the borderline hypertensive group, total arterial cerebral blood flow was lower than that in
35 aged matched controls and the untreated hypertensive group, indicating that their BP had not
36 corrected for the reduction in cerebral perfusion. Since these participants have a similar self-
37 reported family history to groups of hypertensive patients, they may represent a group of
38 patients who have a high probability of developing hypertension in later life. Interestingly, the
39 treated controlled hypertensive group had lower cerebral perfusion compared to the untreated
40 group. This supports previous data, where anti-hypertensive treatment (except for angiotensin
41 receptor blockers) was associated with a decline in cerebral blood flow and parenchymal tissue
42 volumes³⁵. Additionally, other studies indicate that in patients with hypertension, decreased
43 mean arterial pressure occurred concomitantly with cognitive decline and increased Tau related
44 neuro-degeneration³⁶. Therefore, although BP lowering confers a reduced risk of a
45 cardiovascular event³⁷, it may also lower cerebral perfusion especially when cerebral artery
46 hypoplasia and high cerebral vascular resistance exist. Our data emphasise the need to assess
47 cerebral artery architecture and resistance to ensure that cerebral blood flow is not
48 compromised when BP is lowered. A failure to do so may put patients at risk of developing
49 cognitive impairment and vascular dementia. This is critical to consider following the results of
50 the recent SPRINT trial, where intensive BP lowering (target <120 mmHg) was shown to provide
51 added protection against fatal and non-fatal cardiovascular events³⁸. Conversely, lower target

1 BP (<120 mmHg) was associated with adverse events, such as syncope and orthostatic
2 intolerance. Although trials, such as the SPRINT³⁸ and Secondary Prevention of Small
3 Subcortical Strokes³⁹ indicate decreased incidence stroke with lower BP targets (<120 and <130
4 mmHg, respectively), these changes were non-significant. The long-term effect of intensive BP
5 lowering on cognitive health and the rate of dementia has yet to be assessed.

6
7 If cerebral hypoperfusion causes sympathoexcitation and hypertension then the brain must
8 sense hypoxemia. The highly vascularized regions of the brainstem⁴⁰ that regulate the
9 autonomic control of BP could potentially be such sites. In rodents, neurons in areas including
10 the nucleus tractus solitarius and rostral ventrolateral medulla (RVLM) are directly sensitive to
11 hypoxia and cause sympathoexcitation and augmented BP^{41 42}. Moreover, Marina et al.¹³
12 showed that hypoxia-induced activation of the RVLM in spontaneously hypertensive rats could
13 be suppressed by adenosine triphosphate antagonists or a glycogenesis inhibitor. These data
14 indicate that metabolic by-products, which are increased during hypoxemia, can activate the
15 neurons directly controlling sympathetic outflow.

16
17 Exactly what causes elevated cerebral vascular resistance in hypertension is unclear. In the
18 cerebral circulation, larger arteries predominantly regulate cerebral vascular resistance to blood
19 flow, rather than the smaller arterioles^{43, 44}. Alterations in the structure of the large feeder
20 arteries and collateral vessels are, therefore, likely contributors to increased cerebral vascular
21 resistance predisposing individuals to hypertension. For the first time, we present interesting
22 evidence that the prevalence of congenital cerebral variants confined to the posterior circulation
23 (VAH and an incomplete posterior CoW) is greater in hypertensive patients compared to
24 controls. This supports the concept proposed by Dickinson⁹, that vertebral artery narrowing
25 triggers brainstem hypoperfusion and hypertension. We report that hypertensive participants
26 with VAH (and those with both VAH plus an incomplete posterior CoW) had lower cerebral
27 perfusion and elevated cerebral vascular resistance. VAH and an incomplete posterior CoW
28 have both been individually linked to increased risk of posterior territory stroke^{45 46} and may
29 provide an explanation as to why hypertension is a specific risk factor for posterior circulation
30 infarcts⁴⁷. We show that VAH is linked to a higher proportion of lacunar type infarcts in our
31 cohort of hypertensive patients. Additionally, congenital variants in the cerebral circulation may
32 help to explain a proportion of the estimated inheritance of hypertension (30-68%⁴). However, if
33 these variants are indeed congenital, then it is perplexing why hypertension develops with age
34 rather than during childhood development. Potentially, VAH and/or an incomplete posterior CoW
35 might predispose individuals to cerebrovascular disease, since these smaller vessels may be
36 prone to pro-thrombotic/atherosclerotic damage, increasing the risk of stenosis or occlusion in
37 the hypoplastic vessel¹⁵. However, this needs further research. Intriguingly, we show that
38 normotensive patients who exhibit these anatomical variants do not have elevated cerebral
39 vascular resistance, and have a normal cerebral perfusion suggesting adequate remodelling
40 has compensated. Exactly what prevents an increase in cerebral vascular resistance in these
41 patients is unclear but may include: compensation from the other vertebral artery, collateral
42 vessel formation to maintain cerebral perfusion and/or lower rates of cerebral atherosclerotic
43 disease. The exact mechanism(s) might provide therapeutic insight.

44
45 In hypertensive patients without VAH, cerebral blood flow remained lower than that measured in
46 aged matched normotensives with normal vertebral anatomy. This might be explained by the
47 increased incidence of cerebral small vessel disease in hypertension, which may develop before
48 the onset of high BP³³. Although basal blood flow is important, cerebral vascular reactivity to
49 changes in metabolic demand are also crucial for cerebral health and is impacted by cerebral
50 vessel disease. We used a visual task to assess regional changes in cerebral blood flow in
51 hypertensives and normotensives. Whilst there were no differences in blood flow responses

1 between groups in the occipital lobe, the hypertensives had a greater systemic BP response
 2 during the challenge. This suggests that the increased blood flow was driven by the elevation of
 3 BP in the hypertensive group. These data support our 'selfish brain hypothesis': generation of
 4 hypertension to satiate the brain.

5
 6 We propose that the level of cerebral arterial resistance could be used as a novel prognostic
 7 indicator of those who will become hypertensive, and might be a valuable diagnostic marker to
 8 stratify treatment. However, a longitudinal study is needed to confirm this. For example,
 9 borderline hypertensive patients with elevated cerebrovascular resistance may benefit from
 10 early treatment with specific anti-hypertensive therapies that prevent further vessel remodelling
 11 and are known to improve cerebral blood flow (e.g. angiotensin converting enzyme inhibitors ⁴⁸
 12 or angiotensin receptor blockers ³⁵), although this requires further investigation. Future research
 13 focused on screening for hypoplastic vertebral arteries (particularly genetic variants ⁴) may also
 14 be advantageous to better direct anti-hypertensive treatment, as VAH could add complication in
 15 treating high BP whilst preventing cerebral hypoperfusion and early onset dementia.

16
 17 In summary, we show that that congenital cerebrovascular variants in the posterior cerebral
 18 circulation and associated changes in cerebral blood flow and vascular resistance may be a
 19 factor in triggering essential hypertension. Due to the cross-sectional design of this study,
 20 further longitudinal based research is required to confirm that high cerebral vascular resistance
 21 and congenital cerebral vascular variants are *causal* in the onset of hypertension in humans.
 22 Once this mechanism is confirmed, cerebrovascular architecture should potentially be
 23 considered in the prognosis, diagnosis and treatment of hypertension. Early treatment to
 24 prevent further vascular remodelling might help to prevent both the progression of hypertension
 25 but also vascular dementia.

26 **Acknowledgements**

27 The authors would like to dedicate this work to Professor John Dickinson who sadly died on 30th
 28 December 2015. We remain in debt to him for the many discussions and his solitary work on
 29 Cushing's response as a mechanism for neurogenic hypertension, which greatly motivated us to
 30 perform this study.

31
 32
 33 The authors would like to thank Peter Hobden, Martin Stuart and John Evans for their help in
 34 designing the case-control study MR paradigms and acquiring the MR images. We would also
 35 like to thank Research Nurses; Rissa Calsena, Jenny Wilcox and Ruth Bowles for their help in
 36 recruiting and screening the participants. In addition, thank you to Lesley Stewart and Kim
 37 Connor for their help in piloting and co-ordinating the study. Finally, we would like to thank the
 38 volunteers for participating in this study.

39 **Funding and disclosures**

40 This study was funded by the BHF (IBSRF FS/11/1/28400, ECH). JFRP funded by the BHF
 41 RG/12/6/29670. AEB funded by University Hospitals Bristol NHS Foundation Trust Clinical
 42 Research Fellowship. Clinical CMR/MRA supported by the Bristol Cardiovascular Biomedical
 43 Research Unit. JCLR funded by Royal College of Radiologists Kodak Research Scholarship.
 44 NM, AKN and JCLR funded by the NIHR Bristol Cardiovascular Biomedical Research Unit. The
 45 James Tudor Foundation funded a Research Nurse for our work completed at CRIC-Bristol.

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1 **Table 1:** Characteristics of participants in the case-control study.

		Normotensive (n=49)	Hypertensive (n=77)
Female sex (%)		57	58
Age (years)		52 ± 2	57 ± 2
Height (cm)		171 ± 1	172 ± 1
Weight (kg)		71 ± 2	82 ± 2
Body mass index (kg/m ²)		25.2 ± 0.8	27.7 ± 0.5 ***
Office	SBP (mmHg)	122 ± 2	148 ± 2 ****
	DBP	75 ± 1	89 ± 2 ****
	MBP	91 ± 1	109 ± 2 ****
	HR (beats/min)	65 ± 2	66 ± 1
ABPM daytime	SBP (mmHg)	119 ± 2	139 ± 2 ****
	DBP	76 ± 1	85 ± 2 ****
	MBP	90 ± 1	101 ± 2 ****
	HR (beats/min)	75 ± 2	74 ± 1
ABPM night	SBP (mmHg)	107 ± 2	122 ± 2 ****
	DBP	64 ± 1	72 ± 1 ****
	MBP	79 ± 1	89 ± 1 ****
	HR (beats/min)	65 ± 2	64 ± 1
Anti-hypertensive medications (#)		0	1 (0 – 6)
ACEi (%)		0	23
ARB (%)		0	15
CCB (%)		0	20
Diuretic (%)		0	19
β-blocker (%)		0	8
α-blocker (%)		0	2
I ₁ -blocker (%)		0	2
Family history of hypertension (%)		17	48 ^{†††}
Brain volumes			
<i>White matter (%)</i>		38.61	38.33
<i>Grey matter (%)</i>		40.49	41.74 **
<i>Grey/white matter ratio</i>		1.05	1.09 **
Total CBF (ml/min/100 mL tissue)		54.4 ± 1.1	61.8 ± 1.4 ****
Total CVR (ml/min/100mL/mmHg)		1.91 ± 0.05	1.28 ± 0.03 ****

2 SBP; systolic blood pressure, DBP; diastolic BP, MBP; mean blood pressure, HR; heart rate,
3 ABPM; ambulatory blood pressure monitoring, ACEi; angiotensin converting enzyme inhibitor,
4 ARB; angiotensin receptor blocker, CCB; calcium channel blocker, CBF; cerebral blood flow,
5 CVR; cerebral vascular resistance. Family history of hypertension in first order relatives is self-
6 reported. Data are mean ± SEM or median (IQR). *** $P < 0.001$ (unpaired Students T-test), **
7 $P < 0.01$ **** $P < 0.0001$ (One-way ANCOVA, BMI as covariate). ††† $P < 0.001$; Fisher's exact test.

8

Table 2: Characteristics of normotensive (NTN) and hypertensive (HTN) sub-groups.

	Young-NTN (n=20)	Older-NTN (n=28)	Borderline-HTN (n=20)	Untreated-HTN (n=20)	Treated-HTN (n=19)	Uncontrolled-HTN (n=18)
Age (years)	28 ± 0.8	52 ± 2 *	51 ± 3 *	56 ± 2 *	58 ± 2 *	59 ± 2 *
Sex (% women)	50	50	45	50	55	46
BMI (kg/m ²)	24.0 ± 0.8	24.5 ± 0.6	28.3 ± 1.1 * †	28.0 ± 1.2	28.7 ± 1.0 * †	31.0 ± 0.9 * †
Office						
SBP (mmHg)	121 ± 3	123 ± 2	138 ± 2*	169 ± 5 *†‡§	138 ± 3	163 ± 5 *†‡§
DBP	73 ± 2	76 ± 1	84 ± 2	99 ± 3*†‡§	82 ± 2	93 ± 2 *†‡§
MBP	89 ± 2	92 ± 1	103 ± 1	122 ± 4 *†‡§	102 ± 2	116 ± 3 *†‡§
HR (beats/min)	67 ± 3	64 ± 2	64 ± 2	67 ± 2	68 ± 3	68 ± 3
ABPM daytime						
SBP (mmHg)	121 ± 2	118 ± 2	132 ± 2 * †	150 ± 4 *†‡§	127 ± 2	146 ± 2 *†‡§
DBP	78 ± 2	76 ± 1	82 ± 1 †	93 ± 3 *†‡§	80 ± 2	88 ± 2 *†‡§
MBP	90 ± 2	90 ± 1	97 ± 2* †	111 ± 3 *†‡§	95 ± 1	106 ± 2 *†‡§
HR (beats/min)	77 ± 3	74 ± 2	72 ± 2	76 ± 2	76 ± 2	70 ± 3
ABPM night						
SBP (mmHg)	114 ± 3	105 ± 2	118 ± 2* †	126 ± 3*†‡§	115 ± 2	128 ± 3 *†‡§
DBP	66 ± 3	63 ± 1	70 ± 2 †	76 ± 2* †	70 ± 2	74 ± 2 †
MBP	82 ± 3	78 ± 1	86 ± 2 †	93 ± 2* †	84 ± 2	90 ± 4* †
HR (beats/min)	68 ± 4	64 ± 2	64 ± 2	65 ± 2	76 ± 2	63 ± 3
Anti-hypertensive medications (#)	0	0	0	0	2.0 (1.0-2.0)	3.0 (1.5 – 2.5)
ACEi (%)	0	0	0	0	42	63
ARB (%)	0	0	0	0	32	37
CCB (%)	0	0	0	0	26	63
Diuretic (%)	0	0	0	0	42	47
β-blocker (%)	0	0	0	0	16	21
α-blocker (%)	0	0	0	0	0	11
I ₁ -blocker (%)	0	0	0	0	5	5
Family history HTN (%)	5	22	55 †	59 †	58 †	56 †

See Table 1 for abbreviations. Data are mean \pm SEM or median (IQR). * $P < 0.05$ vs. young-NTN, † $P < 0.05$ vs. older-NTN, ‡ $P < 0.05$ vs. borderline-HTN, § $P < 0.05$ vs. treated-HTN (One-way ANCOVA with Bonferroni test for multiple comparisons, or chi-square test where appropriate).

Table 3: Regional (bi-lateral) cerebral perfusion in hypertensive compared to normotensive humans included in the *case-control study*

Regional perfusion (mL/100g/min)	Hypertension	Normotension	P-value
Brainstem	25.7 ± 0.7	29.1 ± 0.9	0.003
Cerebellum	34.1 ± 1.1	42.2 ± 1.3	<0.0001
Pons	25.3 ± 0.7	27.9 ± 0.9	0.022
Medulla	25.9 ± 1.0	22.7 ± 0.7	0.006
Midbrain	28.9 ± 1.0	34.8 ± 1.3	0.001
Insula	46.1 ± 1.2	54.4 ± 1.2	<0.0001
Thalamus	39.6 ± 1.2	46.7 ± 1.2	<0.0001
Occipital pole	37.3 ± 1.7	50.0 ± 2.1	<0.0001
Frontal pole	38.1 ± 1.2	45.6 ± 1.5	<0.0001
Precentral gyrus	37.7 ± 1.1	44.7 ± 1.4	<0.0001
Anterior cingulate cortex	49.2 ± 1.1	57.2 ± 1.6	<0.0001
Temporal pole	34.6 ± 1.0	40.6 ± 1.2	<0.0001

P-values represent one-way analysis of covariance with body mass index as a covariate

Figure legends

Figure 1: Congenital variants of the posterior cerebral circulation are more prevalent in people with hypertension compared to normotensive controls. A and B: examples vertebral artery hypoplasia (VAH; right image) and an incomplete posterior circle of Willis (iCoW; no posterior communicating arteries; pCoA; right image). **C:** (**retrospective study**, n=133) prevalence of VAH and iCoW is higher in patients with hypertension compared to the prevalence in controls. There were no differences in age (51 ± 2 vs. 51 ± 2 years, $p=0.93$), sex (males; 56% vs. 50%, $p=0.50$), systolic blood pressure (SBP; 169 ± 3 vs. 170.1 ± 3 mmHg, $p=0.87$) or diastolic blood pressure (DBP; 97 ± 2 vs. 96 ± 5 mmHg, $p=0.72$) between hypertensive patients with VAH and those without this anatomical variant. **D:** (**case-control study**, n=136) prevalence of VAH and VAH with an incomplete posterior CoW in hypertensives and normotensive controls. The retrospective study is compared to data previously described by Park et al¹⁵. ** $P=0.006$ (binary logistic regression), **** $P<0.0001$ (Fishers exact test).

Figure 2: vertebral artery hypoplasia (VAH) or VAH that co-exists with an incomplete circle of Willis (iCoW) are linked with lower cerebral blood flow (CBF) and elevated cerebral vascular resistance (CVR). A and B: total CBF and CVR estimated via phase contrast imaging in participants with (n=56) and without (n=68) VAH. **C and D:** total CBF and CVR in participants with VAH plus an incomplete posterior circle of Willis (VAH+iCoW; n=42) or without this anatomical variant (n=82). **E and F:** CBF and CVR in those with/without VAH split in hypertensive (HTN) or normotensive (NTN) groups. **G and H:** similar data to E and F but grouped by incidence of VAH+iCoW. Groups with VAH or VAH+iCoW had a higher CVR and a lower CBF compared to those without these variants. Data are mean \pm SEM. **** $P<0.0001$ (one-way ANCOVA with BMI as covariate and Bonferroni for multiple comparisons), * $P<0.05$, *** $P<0.001$ (one-way ANCOVA with BMI as covariate and Bonferroni for multiple comparisons). **I to L:** examples of 3-D blood velocity pixel maps in a cross section of the left and right vertebral arteries (LVA; RVA), from a normotensive and hypertensive volunteer without VAH (NoVAH) and with VAH (+VAH). Each large square represents a time point in the cardiac cycle starting with peak systole. Velocity maps for nine successive time points within a cardiac cycle are shown in participants. In these examples, a negative velocity (blue to orange) represents blood travelling in a direction towards the brain (anterograde flow). Flow velocity is clearly lower in hypoplastic vessels, but in hypertensive patients the contralateral vessel does not correct for this as it does in normotensive controls.

Figure 3: Cerebral vascular resistance (CVR) is elevated before increased muscle sympathetic nerve (MSNA) activity in patients with borderline hypertension. A: total CVR and muscle MSNA in young normotensive (yNTN), older NTN (oNTN), borderline hypertensive (bHTN), untreated HTN (uHTN), treated but poorly controlled HTN (pCHTN) and treated controlled HTN (tHTN) participants. **B:** total cerebral blood flow (CBF) in the 6 groups. **C:** examples of multi-unit MSNA recordings in the 6 groups. Blue recordings represent integrated bursts of MSNA measured directly from the peroneal nerve, which are cardiac synchronous and coupled to the arterial pressure waveform shown below in pink. * $P<0.05$ vs. young NTN, † $P<0.05$ vs. older NTN (one-way ANCOVA with BMI as covariate and Bonferroni for multiple comparisons).

Figure 4: Cerebrovascular reactivity in the visual cortex is maintained in patients with hypertension due to a systemic pressor response, which does not occur in normotensive controls. A: example BOLD signal change during a visual (flashing

checker-board) stimulus in a patient with a normal posterior cerebral circulation (**left**) and patient with vertebral artery hypoplasia (VAH) plus an incomplete posterior circle of Willis (iCoW, **right**). **B**: average positive and negative BOLD (left), cerebral blood flow (CBF; middle), and mean arterial pressure (MAP; right) responses to visual stimulus (flashing checker-board) in participants with normotension and hypertension. There was no difference in cerebral reactivity to the visual stimulus in hypertensive and normotensive patients; however, the hypertensive group had a greater blood pressure (BP) response to the stimulus (ANCOVA, BMI as covariate). **C**: CBF and BOLD responses to the visual stimulus in patients grouped by posterior anatomical variants (those with or without VAH+iCoW). Participants with VAH+iCoW had a lower cerebral vascular reactivity (lower BOLD signal change) than those without VAH+iCoW. In the VAH+iCoW group there was only a trend towards a greater BP response to the visual stimulus (Mann-Whitney test). All participants had a negative BOLD and cerebral blood flow response to visual stimulus in some brain voxels, which is associated with a blood flow steal to increase flow to more metabolic active regions ⁴⁹. In the hypertensive participants, stealing blood flow from tissue that is already hypoperfused may put this tissue at risk of becoming ischemic.

Novelty and significance

What is known?

- Cerebral arterial remodelling occurs in humans with hypertension and animal models of hypertension.
- Experimental animal models of hypertension indicate that cerebral vascular remodelling occurs before the onset of hypertension.

What new information does this article contribute?

- Hypertension is more common in people with congenital cerebrovascular anatomical variants (i.e. vertebral artery hypoplasia).
- These anatomical variants were associated with lower cerebral perfusion, especially in hypertensive patients.
- Vertebral artery hypoplasia was more prevalent in people with high-normal blood pressure (who had an elevated family history of hypertension) compared to a normotensive cohort.
- A cross sectional study indicated that cerebral hypoperfusion occurs before the onset of elevated sympathetic nerve activity and hypertension, and thus may be causal in the onset of the disease.

Summary

Data from animal models of hypertension indicate that hypertension may develop as a vital mechanism to maintain adequate blood flow to the brain. In this study we investigated whether this mechanism is involved in the aetiology of human hypertension. Using magnetic resonance imaging we reveal that there is a higher prevalence of congenital cerebral vascular variants in patients with hypertension compared to healthy controls. We found that the majority of hypertensive patients exhibited vertebral artery hypoplasia and missing or hypoplastic posterior communicating arteries. This resulted in increased cerebrovascular resistance and hypoperfusion of the brain. This novel finding became more revealing when, surprisingly; we found that the cerebral artery variants, high cerebrovascular resistance and cerebral hypoperfusion were already present in patients with high-normal blood pressure (but with a strong family history of hypertension). This suggests that they were not caused by high blood pressure and may be causal in the development of hypertension. Additionally, untreated hypertensive patients had normal cerebral blood flow, but those on treatment (with normal blood pressure) had reduced cerebral perfusion. Our data may have novel prognostic and diagnostic importance; potentially patients with congenital cerebral hypoplasia are at risk of developing hypertension. Moreover, the data caution against aggressive lowering of blood pressure without checking cerebral perfusion adequacy. Longitudinal studies are needed to confirm this.