Is high blood pressure self-protection for the brain?

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Short title: Hypertension and cerebral perfusion

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Abstract

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

Objective: To evaluate the role of the cerebral circulation in the pathophysiology of hypertension.

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

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

Key words: Hypertension, vertebral artery hypoplasia, cerebral blood flow, sympathetic nerve activity, and magnetic resonance imaging

Abbreviations

ANCOVA; analysis of covariance
BMI; body mass index
BOLD; blood oxygen level dependant
BP; blood pressure
DBP; diastolic blood pressure
CoW; circle of Willis
MRI; magnetic resonance imaging
MRA; magnetic resonance angiography
MSNA; Muscle sympathetic nerve activity
NHS; National Health Service
SBP; systolic blood pressure
SNA; sympathetic nerve activity
PCASL; pseudo continuous arterial spin labelling
RVLM; rostral ventrolateral medulla
TE; echo time
TR; repetition time
VAH; vertebral artery hypoplasia

Introduction

High blood pressure (blood pressure) affects ~25% of the world's population and is the largest single contributor to global mortality [1]. Hypertension represents a significant economic burden to public healthcare providers, where the global cost of non-optimal BP is estimated to be US$370 billion (10% of healthcare expenditure) [2]. Remarkably, despite the availability of many pharmacological treatments, BP is poorly controlled with a recent report stating that only 53% of patients prescribed anti-hypertensive medication have BP controlled [3]. This reflects the well-known heterogeneity of the syndrome including epigenetic and inherited factors contributing to the unknown causes in 95% of patients [4].

Despite the devastating consequences of hypertension (e.g. stroke, kidney failure, coronary heart disease, death [1, 2]), the mechanisms that lead to the onset of hypertension in humans are poorly understood. It is well established that elevated sympathetic nerve activity (SNA) contributes to the development of hypertension in most humans [5-7] but what initiates this remains unclear. Experimental data from hypertensive rats and observations in post-mortem human studies suggest that blood flow to the brain might be important in setting the operating level of SNA and thus systemic arterial pressure [8, 9]. Evidence from Dickinson [10] showed that the vertebral arteries in hypertensive patients were narrower than those observed in normotensive individuals. Dickinson and Thomson [9] demonstrated that high vertebral artery resistance correlated with higher blood pressure; importantly, a weaker relationship was found in other arteries including femoral, renal and internal carotid arteries. They proposed that narrowing of the vertebral arteries with subsequent brainstem hypoperfusion might be a *cause* of hypertension, rather than being a *consequence*, but had no evidence to support causality. This has been termed "Cushing's mechanism" or "the selfish brain hypothesis" of hypertension [11]. The mechanism may trigger elevations in SNA and BP thereby maintaining cerebral blood flow [8, 12]. Evidence from spontaneously hypertensive rats at a pre-hypertensive age supports this notion: Cates et al. [8] demonstrated that vertebrobasilar artery hypertrophy occurred *before* the onset of hypertension in these animals. The authors also showed that brainstem ischemia caused by bilateral vertebral artery clamping, generated a greater increase in SNA in pre-hypertensive spontaneously hypertensive rats compared to age-matched normotensive animals[8]. Additionally, the brainstem of hypertensive rats is hypoxic and this is accentuated when BP is normalised [13].

We have addressed the issue of whether "Cushing's mechanism" is involved in the development of hypertension in humans. This may have a significant impact on the diagnosis and treatment of hypertension, whilst potentially aiding prevention of early onset vascular dementia in hypertensive humans[14]. Thus, we have evaluated the temporal relationship of changes in cerebral vascular structure and cerebral blood flow with both the onset of hypertension and raised SNA in humans. We performed a series of retrospective *and* mechanistic case-control studies in a range of participants with different levels of BP and classifications of hypertension. Uniquely, we show that congenital cerebral vascular variants, vascular resistance and blood flow are tightly coupled to the development of hypertension in humans.

Methods

Retrospective study

We first measured whether there were anatomical differences in the cerebral circulation of hypertensive patients compared to controls. We specifically focused on vertebral artery hypoplasia (VAH; a congenital anatomical variant of the posterior circulation that occurs in the general population), which is associated with lower posterior cerebral territory blood flow [15], and variations in the anatomy of the circle of Willis (CoW). We hypothesised that the occurrence of

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

Study population

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

BP measurements

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

MRI procedures

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

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

Case-control study

Participants

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

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

Screening BP

Participants attended a screening session, where office BP was measured using an automated cuff (Omron, The Netherlands), in line with the European Society of Hypertension guidelines [19]. Participants were fitted with an ambulatory BP monitor (Spacelabs, OSI Systems Company, USA). Their 24-hour BP was measured twice per hour during the daytime and once per hour during the night.

Microneurography

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

MRI acquisition

All study participants were scanned using 3T MRI (GE HDx, Milwaukee, Wisconsin, USA). The protocol consisted of a high resolution T_1-weighted fast spoiled gradient echo (3D-FSPGR) structural scan, 3D time of flight angiography to measure arterial anatomy, phase contrast pulse sequences to measure blood flow in the internal carotid and basilar arteries at baseline and in response to 5% CO_2, and pseudo-continuous arterial spin labelling (PCASL) to measure regional cerebral blood flow. BP (automated cuff), heart rate (pulse oximeter), and end tidal CO_2 (capnograph) were monitored throughout all acquisitions. See *supplementary information* for imaging parameters.

Since poor cerebral vascular reactivity is linked to the risk of developing hypertension, we hypothesised that the hypertensive group would have impaired cerebral vascular reactivity. In a subgroup of participants, cerebral vascular reactivity to isoxic hypercapnia (5% CO_2) and to a strong visual stimulus (flashing checkerboard[20], using a dual echo blood oxygen level dependent; BOLD and ASL MRI acquisition) was measured (supplementary material for MRI parameters).

MRI analyses

All data analyses were blinded and completed by separate investigators. Please see *supplementary material* for details regarding methodology for MRI analyses. In short, to measure blood flow in the right and left internal carotid and basilar arteries, phase contrast images were analysed using Segment (version 1.9, Medviso, Sweden)[21]. Total cerebral blood flow was estimated as the sum of blood flow in these vessels and scaled for parenchymal tissue volumes. Cerebral vascular resistance was calculated as the brachial mean arterial pressure (measured during the phase contrast acquisition) divided by average flow in each vessel. This method assumes that intra-cranial pressure and venous pressure is normal and similar between groups, and therefore that mean arterial pressure is an accurate estimation of cerebral perfusion pressure in different groups. The method has been used in multiple studies to calculate cerebral vascular resistance [22, 23]. Regional cerebral perfusion was measured from the PCASL images using the standard Buxton model [24]. Cerebral vascular reactivity to hypercapnia (5% CO_2) was calculated as the change in total cerebral blood flow (calculated as the sum of blood flow in the internal carotid and basilar arteries, measured using phase contrast MRI) from the normocapnic condition. Blood flow was scaled for changes in end tidal CO_2 and blood pressure. Finally, positive and negative changes in cerebral blood flow and BOLD signal, in response to the flashing checkerboard stimulus, were measured in the visual cortex.

Statistical analyses

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

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

Results

Retrospective study

Anatomical variations in the cerebral vasculature

Patient characteristics are outlined in the Supplementary Table 1. Fishers exact test showed that VAH and an incomplete *posterior* CoW were highly prevalent in the hypertensive population (hypertensive vs. normotensive[15, 18]: 53% vs. 27% and 64% vs. 36% respectively; $P<0.0001$, Figure 1). The odds ratios indicated that individuals with VAH or those with an incomplete 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 have hypertension. There were no differences in the prevalence of an incomplete *anterior* CoW between our hypertensive cohort and that reported in a healthy control population[18] (32% vs. 25%, respectively, $P=0.26$).

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

Case-control study

Participant characteristics

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

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

Anatomical variants in the posterior cerebral vasculature are more prevalent in humans with hypertension

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

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

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

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

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

The contralateral vertebral artery does not compensate for the hypoplastic artery in hypertensive patients

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

Assessing cause and effect: Cerebral vascular resistance, blood flow and muscle sympathetic nerve activity

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

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

Is cerebral vascular resistance a good predictor of hypertension?

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

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

Cerebrovascular vascular reactivity, hypertension and anatomical variants

We found no difference in total cerebral vascular reactivity to CO_2 (expressed as per % rise in end tidal CO_2 and scaled for changes in mean arterial pressure; MAP) between the hypertensive (n=29) and normotensive groups (n = 22, 5.6 ± 0.6 vs. 4.5 ± 0.7 mL/100mL/min/mmHg/%; *P*=0.21, ANCOVA, Supplementary Figure 1). Additionally, when the groups were split into participants with (n=19) and without VAH plus an incomplete CoW (n = 32; split regardless of hypertensive status), there was no difference in cerebral blood flow reactivity to CO_2 (4.7 ± 0.4 vs. 5.6 ± 0.7 mL/100mL/min/mmHg/%; *P*=0.41, Supplementary Figure 1).

We next assessed the cerebral vascular reactivity to a strong visual stimulus (Figure 4A shows example acquisition). The visual stimulus caused a similar increase in cerebral blood flow in normotensive (n=28) and hypertensive (n=36) subgroups in an activation mask within the occipital lobe, consisting of a union of significantly activated voxels in the BOLD and ASL time-series (Figure 4B). In all participants, negative BOLD and cerebral blood flow signals were also detected within the occipital lobe and surrounding the visual cortex (Figure 4, panel A for example of cerebral perfusion). Despite these similar changes in blood flow, the hypertensive group exhibited a greater increase in BP during the visual stimulus (figure 4B, *P*=0.02, ANCOVA) suggesting that hypertensive men and women rely on increasing perfusion pressure to maintain cerebral blood flow than local vasodilatatory mechanisms. In a group with both VAH and an incomplete CoW, however, data indicated a difference in cerebrovascular reactivity. We found a blunted increase in BOLD signal along with a trend towards a blunted increase in cerebral blood flow response to the visual stimulus (Figure 4C). Moreover, linear regression analyses suggested that for participants with both VAH and an incomplete posterior CoW, the positive and negative BOLD responses have a stronger inverse relationship than for participants without VAH and incomplete posterior CoW (β_1=-0.17; *P*<0.05 vs. β_1 = 0.65; *P*<0.05, respectively; ANOVA, Supplementary Figure 2). This implies that for a larger positive increase in BOLD signal the hypertensive group rely on a blood flow steal from other adjacent tissue. However, this needs to be interpreted with caution since the BOLD response is a result of neurovascular coupling [25], which is a mechanism that does not solely depend on regional cerebral blood flow.

Discussion

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

It is accepted that cerebral arteries and arterioles are remodelled in hypertension, thereby increasing resistance to blood flow [26]. Narrowing of the vessel lumen and an increased wall/lumen ratio are typically demonstrated in animal models [8, 27, 28] and humans with hypertension [9, 29]. Furthermore, cerebral blood flow is attenuated in elderly patients with hypertension [30, 31] and is related to white matter lesions[32] and small vessel disease [33], a finding which is contradictory to studies indicating that cerebral autoregulation is intact in hypertensive patients [34]. Our data are the first to show that in middle-aged hypertensive humans without cerebral stenotic disease, *tot*al arterial cerebral blood flow (Table 1) and cerebral perfusion in all brain regions measured (Table 3) are lower compared to age-matched normotensive participants. This may help to explain why patients with hypertension have an increased risk of developing vascular dementia [14]. Traditionally, cerebral vessel remodelling and cerebral hypoperfusion were thought to be a *consequence* of high blood pressure. Evidence in animals and humans now suggest that this theory may be incorrect with the reverse true; cerebral artery remodelling and hypoperfusion may precede hypertension as found herein [10, 11].

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

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

BP (<120 mmHg) was associated with adverse events, such as syncope and orthostatic intolerance. Although trials, such as the SPRINT[38] and Secondary Prevention of Small Subcortical Strokes[39] indicate decreased incidence stroke with lower BP targets (<120 and <130 mmHg, respectively), these changes were non-significant. The long-term effect of intensive BP lowering on cognitive health and the rate of dementia has yet to be assessed.

If cerebral hypoperfusion causes sympathoexcitation and hypertension then the brain must sense hypoxemia. The highly vascularized regions of the brainstem[40] that regulate the autonomic control of BP could potentially be such sites. In rodents, neurons in areas including the nucleus tractus solitarius and rostral ventrolateral medulla (RVLM) are directly sensitive to hypoxia and cause sympathoexcitation and augmented BP [41 42]. Moreover, Marina et al. [13] showed that hypoxia-induced activation of the RVLM in spontaneously hypertensive rats could be supressed by adenosine triphosphate antagonists or a glycogenesis inhibitor. These data indicate that metabolic by-products, which are increased during hypoxemia, can activate the neurons directly controlling sympathetic outflow.

Exactly what causes elevated cerebral vascular resistance in hypertension is unclear. In the cerebral circulation, larger arteries predominantly regulate cerebral vascular resistance to blood flow, rather than the smaller arterioles [43, 44]. Alterations in the structure of the large feeder arteries and collateral vessels are, therefore, likely contributors to increased cerebral vascular resistance predisposing individuals to hypertension. For the first time, we present interesting evidence that the prevalence of congenital cerebral variants confined to the posterior circulation (VAH and an incomplete posterior CoW) is greater in hypertensive patients compared to controls. This supports the concept proposed by Dickinson [9], that vertebral artery narrowing triggers brainstem hypoperfusion and hypertension. We report that hypertensive participants with VAH (and those with both VAH plus an incomplete posterior CoW) had lower cerebral perfusion and elevated cerebral vascular resistance. VAH and an incomplete posterior CoW have both been individually linked to increased risk of posterior territory stroke [45 46] and may provide an explanation as to why hypertension is a specific risk factor for posterior circulation infarcts [47]. We show that VAH is linked to a higher proportion of lacunar type infarcts in our cohort of hypertensive patients. Additionally, congenital variants in the cerebral circulation may help to explain a proportion of the estimated inheritance of hypertension (30-68% [4]). However, if these variants are indeed congenital, then it is perplexing why hypertension develops with age rather than during childhood development. Potentially, VAH and/or an incomplete posterior CoW might predispose individuals to cerebrovascular disease, since these smaller vessels may be prone to pro-thrombotic/atherosclerotic damage, increasing the risk of stenosis or occlusion in the hypoplastic vessel[15]. However, this needs further research. Intriguingly, we show that normotensive patients who exhibit these anatomical variants do not have elevated cerebral vascular resistance, and have a normal cerebral perfusion suggesting adequate remodelling has compensated. Exactly what prevents an increase in cerebral vascular resistance in these patients is unclear but may include: compensation from the other vertebral artery, collateral vessel formation to maintain cerebral perfusion and/or lower rates of cerebral atherosclerotic disease. The exact mechanism(s) might provide therapeutic insight.

In hypertensive patients without VAH, cerebral blood flow remained lower than that measured in aged matched normotensives with normal vertebral anatomy. This might be explained by the increased incidence of cerebral small vessel disease in hypertension, which may develop before the onset of high BP [33]. Although basal blood flow is important, cerebral vascular reactivity to changes in metabolic demand are also crucial for cerebral health and is impacted by cerebral vessel disease. We used a visual task to assess regional changes in cerebral blood flow in hypertensives and normotensives. Whilst there were no differences in blood flow responses

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

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

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

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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			
White matter (%)		38.61	38.33
Grey matter (%)		40.49	41.74 **
Grey/white matter ratio		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 ****

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

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 ± 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 al[15]. ** 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 ± 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.